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AUTOIMMUNE NEUROLOGY AND MS

S101K: Early Treatment Effects and Lesion Microstructural Subtypes Across the Multiple Sclerosis Disease Spectrum: A Diffusion Basis Spectrum Imaging Study
Presenting Author: *Matthew Brier, MD, PhD, Washington University in St. Louis*
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S102: Trends and Disparities in Multiple Sclerosis Disease-Related Mortality in Postmenopausal Women from 1999-2024, with Forecasts to 2035: A Nationwide Study
Presenting Author: *Mehra Abdul Nazer, MBBS, Omaha, NE*
Co-Authors: *Saad Arsalan Wasti, MBBS, King Edward Medical University, Pakistan Lahore, Punjab, Mehra Abdul Nazer, MBBS, Omaha, NE, Mohammad Omar Faheem, MBBS, National University of Medical Sciences, Rawalpindi, Pakistan Rawalpindi, Sindh, Areesha Wasti, MBBS Continental Medical College Lahore, Punjab, Fiza Shaikh, MBBS, Peoples University of Medical and Health Sciences, Pakistan Nawabshah, Sindh, Muhammad Moiz Javed, MD, Department of Neurology, Geisinger Wyoming Valley Medical Center, Wilkes-Barre, USA Wilkes-Barre, PA*

S103: Bridging the Imaging Gap: A Novel Hybrid Approach for External Imaging Acquisition
Presenting Author: *Ashna Aggarwal, MD, Department of Neurology, Hospital of the University of Pennsylvania Philadelphia*
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S104: Hyponatremia is Associated with Accelerated Hippocampal Atrophy and Delayed Clinical Recovery in LGI1 Encephalitis
Presenting Author: *Soo Hyun Ahn, MD, Korea, Republic of Korea*
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S105: Efgartigimod Is a Unique Neonatal Fc Receptor Blocker That Allows Immunoglobulin G Reduction Without Broad Inhibition of Immune Responses
Presenting Author: *Zohreh Akhavan Aghdam, Medical Science Liaison, argenx, Ghent, Belgium*
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S106: Anti-IgLON5 Disease Presenting as a Convergence of Multiple Clinical Subtypes Including Prominent Cerebellar Ataxia, Painful Axial Spasms, and Encephalopathy: A Case Report
Primary Author: *Sara Muhammad, MD, Department of Neurology, Westchester Medical Center, Valhalla, NY*
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S107: Clinical Heterogeneity of Suspected Transverse Myelitis in VAERS: Insights from Narrative-Based Unsupervised Analysis

Presenting Author: *Jascha Anagaran Tolentino, MD, Premier Clinical and Research Neuromuscular Institute Westfield, NJ*

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S108: The Fatal Triad: A Systematic Review of Immune Checkpoint Inhibitor-Induced Myocarditis, Myositis, and Myasthenia Gravis (Triple M) Overlap Syndrome

Presenting Author: *Aymen Arain, MS, Monroe, LA*

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S109: Utility of the Antibody Prevalence in Epilepsy and Encephalopathy (APE2) Score as a Diagnostic Tool for Autoimmune Encephalitis

Presenting Author: *Bijoya Basu, Case Western Reserve University School of Medicine Cleveland, OH*

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S110*: Protein Kinase Signaling as a Downstream Target of Human Anti-NMDA Receptor Antibodies

Presenting Author: *David Benavides, MD, PhD, University of Maryland School of Medicine Baltimore, MD*

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S111: From Fragmentation to Standardization: Developing an Outpatient Autoimmune Neurology Clinic

Presenting Author: *David Benavides, MD, PhD, Baltimore, MD*

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S112: Endothelial Cell Proteins as Biomarkers in Susac Syndrome

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S113: Minimal Symptom Expression with Claseprubart, an Active C1S Inhibitor, in Patients with Generalized Myasthenia Gravis

Presenting Author: *Aji Nair, PhD, Dianthus Therapeutics, New York, NY*

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S114: Riliprubart in CIDP: Time and Magnitude of Response Analysis from a Phase 2 Trial
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S115*: Safety and Efficacy of Riliprubart in CIDP: 76-week Phase 2 Trial Results
Presenting Author: *Mona Smith, PhD, Sanofi, Cambridge, MA*
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S116: Tracking TREC: Investigations into a Biomarker with Prognostic Potential for PML
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S117: T-Cell-Mediated Molecular Mimicry Between SARS-CoV-2 and GAD65: Immunoinformatic Evidence that SARS-CoV-2 can trigger or worsen GAD-positive Stiff Person Syndrome
Presenting Author: *Shandon Coffman, MD, Philadelphia, PA*
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S118*: Miv-cel CD19 CAR T-Cell Therapy in Stiff Person Syndrome (SPS) in a Pivotal, Multicenter, Phase 2 Study (KYSA-8): Efficacy and Biomarker Analysis of Patients With ≥6 Months of Follow-up
Presenting Author: *Marinos Dalakas, MD, Thomas Jefferson University, Philadelphia, PA*
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S119: HLA-DRB1*03 and HLA-DRB1*03:01 in Neuromyelitis Optica Spectrum Disorder Susceptibility: A Systematic Review and Dual Meta-Analysis of Case-control Studies
Presenting Author: *Daniel de Siqueira Lima, MD, Brazil*
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S120: Tuberculosis and Disease-Modifying Therapies in Multiple Sclerosis: A Retrospective Case Series
Presenting Author: *Daniel de Siqueira Lima, MD, Caruaru, CA*

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S121: Deciphering patterns of Functional Neurological Disorder (FND) in patients referred for Stiff-Person syndrome (SPS)
Presenting Author: *Kathryn Dent, MD, Philadelphia, PA*
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S122: Enterovirus-associated Acute Flaccid Myelitis In A Person With Multiple Sclerosis On Anti-CD 20 Therapy: A Case Report
Presenting Author: *Mostafa Deraz, MD, Thomas Jefferson University Philadelphia, PA*
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S123: Characteristics of Movement Disorders in Susac syndrome
Presenting Author: *Mahmoud Elkhooly, SIU School of Medicine Springfield, IL, USA*
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S124: Isolated Sixth Nerve Palsy as the Initial Presentation of Multisystem IgG4-Related Disease: A Diagnostic Challenge
Presenting Author: *Rithvik Gundlapalli, University of Virginia School of Medicine Charlottesville, VA*
Co-Authors: *Mathura Ravishankar, MD, MSc, INOVA Health Fairfax, VA*

S125*: Post anti-CD19 CAR-T Cell Therapy Immune Response in Treatment Refractory Multiple Sclerosis
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S126: Permissive Central Tolerance and Defective Peripheral Tolerance as Sequential Steps to License CASPR2-directed Pathology
Presenting Author: *Sarosh Irani, Ponte Vedra Beach, FL*

S127: State-Level Variation in Medicaid Coverage and Utilization of High-Efficacy Therapies for Multiple Sclerosis
Presenting Author: *Mihir Kakara, NYU Grossman School of Medicine New York, NY*

S128: Functional Neurological Disorder Mimicking AIDP: Anchoring Bias and Iatrogenic Risk in a Reversible Diagnostic Error
Presenting Author: *Soroush Kakawand, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States*

S129: Rare Case of Multiple Sclerosis (MS) and Coexisting Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) - Showcasing Diagnostic Insight From Markedly Elevated Cerebrospinal Fluid (CSF) Protein
Presenting Author: *Shaweta Khosa, MBBS, Olive View-UCLA Medical Center Sylmar, CA*
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S130: Extracellular Vesicles Derived from Normal Neurons Regulate Transcriptional Responses in Microglia to Reinforce a Homeostatic, Non-inflammatory State
Presenting Author: *Albert La Spada, Irvine, CA*
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S131: Multiple Sclerosis Patients Treated with Ocrelizumab, Aged 70 and Older: A Retrospective Cohort Study
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S132: Comparative Efficacy and Safety of FDA-Approved Advanced Therapies for Generalized Myasthenia Gravis: A Network Meta-Analysis Incorporating CD19, FcRn, and Complement Inhibition
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S133: Prevalence and Diagnostic Significance of the Trident Sign in Spinal Neurosarcoidosis: A Systematic Review and Meta-Analysis
Presenting Author: *Camila D. Lopez,Universidad San Francisco de Quito Quito, Ecuador*
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S134-LB*: Neurosarcoidosis in a Tuberculosis-Endemic Region: Clinical Spectrum, Diagnostic Challenges, and Treatment Outcomes
Presenting Author: *Abhinav Maddipati, MBBS, Kochi, Kerala*
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S135: Beyond the Brain: In Vivo Imaging of Spinal Cord Atrophy in Progressive Multifocal Leukoencephalopathy
Presenting Author: *Andra Mutu, BS, Experimental Immunotherapeutics Unit, NINDS, NIH Bethesda, MD*
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S136: A Rare Convergence of Cryptococcal Meningitis and Anti-NMDA Receptor Antibodies in an Elderly Adult: Case Report
Presenting Author: *Sriya Parchuri, McGovern Medical School at UTHealth Houston, Houston, TX*
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S137: Natalizumab-Associated Acute Liver Injury with Autoimmune Features in Relapsing-Remitting Multiple Sclerosis: A Case Report
Presenting Author: *Farley Reis Rodrigues, Federal University of Viçosa, Viçosa, Minas Gerais*
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S138: Clinical Efficacy and Safety of Tolebrutinib in Multiple Sclerosis: A Systematic Review, Meta-Analysis and Narrative Synthesis of Phase 3 Trials
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S139: Progression of Optic Neuritis to Multiple Sclerosis, Neuromyelitis Optica Spectrum Disorder, and MOG Antibody Disease: A Real-World Retrospective Cohort Study Using TriNetX
Presenting Author: *Astha Sahoo, Philadelphia, PA*
Co-Authors: *Anika Khandekar, Philadelphia, PA, Robert Shin, Charlottesville, VA*

S140*: Proteomic Age Acceleration in Multiple Sclerosis Precedes Symptom Onset and Associates with Disease Severity
Presenting Author: *Fatemeh Siavoshi, Johns Hopkins University School of Medicine, Baltimore, MD*
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S141*: Thyroid Disorders as a Risk Factor for Neurodegenerative Proteinopathies: A Large-Scale Propensity Score-Matched Analysis
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S142: Inpatient Severity, Resource Utilization, and Discharge Outcomes in Neuromyelitis Optica Spectrum Disorder Versus Multiple Sclerosis: A National Inpatient Sample Analysis
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S143-LB: Comparative Effectiveness of Immunotherapies in Immune Checkpoint Inhibitor-Associated Autoimmune Encephalitis: A Case Report-Based Narrative Analysis
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S144: The Association Between Thalamic Atrophy and Fatigue Severity in Multiple Sclerosis: A Systematic Review and Meta-analysis
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S145: OCT Based Criteria for MS Diagnosis; Percentile Analysis of Retinal Layer Thickness Improves Accuracy When Combined With Inter-eye Differences
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S146: Real-World Impact of CSF Metagenomic Sequencing in Suspected CNS Infections: Early Diagnostic and Management Insights from a Tertiary Care Center
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S147: Establishing Age Specific Reference Intervals for Serum Neurofilament Light Chain in a Healthy Indian Cohort
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S148: Clinical Spectrum and Treatment Outcomes in LGI1 Antibody Encephalitis: A Retrospective Cohort from South India
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S149: Upstream Versus Downstream Complement Blockade: Potential Mechanistic Advantages of aC1s Targeting in Myasthenia Gravis

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S150: Sustained Safety and Efficacy of Active C1s Inhibitor Claseprubart in Patients with Generalized Myasthenia Gravis: Results from the MaGic Study Open-Label Extension

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S151: Assessing the Relationship between Focal Neurodegeneration and Chronic Inflammation in Early Multiple Sclerosis

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CEREBROVASCULAR DISEASE

S153: Chronic Kidney Disease Predicts Intracerebral Hemorrhage Mortality Independent of ICH Score

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S154: Persistent Vestibular Dysfunction After Neurologic Decompression Sickness in an Experienced Diver with Patent Foramen Ovale and Atrial Septal Defect and Chronic Topiramate Use

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S155: Racial and Ethnic Disparities in Stroke Among Hypertensive Adults by Antihypertensive Medication Use

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S156-LB: Clinical and Procedural Outcomes of IVUS-Guided versus Angiography-Guided Carotid Artery Stenting (CAS): A Systematic Review and Meta-Analysis

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S157: Bilateral Cerebellar Infarcts Associated with Combined Testosterone Replacement, Finasteride, and Anastrozole Use
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S159: VZV CNS-Vasculitis Causing Sequential Bilateral Pontine Strokes, a case report
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S160: Trends in Mortality from Thromboembolism and Cerebrovascular Diseases Among U.S. Adults Aged ≥65 Years, 1999–2034
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S161: Beyond the Cranium: Lumbar Spinal Subdural Hematoma as a Rare Cause of Intractable Headache
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S162: Regional Balance of Monocyte-Derived Cells and Microglia in Ischemic Stroke Injury and Recovery is Regulated by NR4A1
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S163: A Conserved Developmental Axonal Growth Program in Adult Cortical Neurons After Stroke
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S164: Geographic and Risk-Factor Entrenchment of Intracerebral Hemorrhage in the United States: A GBD 2023 Analysis of 33-Year Trends and Sex Disparities
Presenting Author: *Ahar Bhatt, MBBS, SMT. NHL Municipal Medical College Ahmedabad, India*
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S165: The Stalled Progress of Ischemic Stroke in the U.S.: A GBD 2023 Analysis of Geographic, Sex, and Metabolic Risk Disparities, 1990–2023
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S166: Indobufen Versus Aspirin in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis
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S167: A Novel Autoinflammatory Disorder as an Unusual Cause of Stroke: A Case Report on the Cerebrovascular Complications of VEXAS Syndrome Before and After Transplant
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S168: The Gut Microbiome and Ischemic Stroke Outcomes: A Scoping Review
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S169: Ischemic Stroke Following Oocyte Retrieval in Young Patients Without Known Risk Factors: A Case Series
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S170: Stroke Savvy: A Multidisciplinary Bedside Game Series to Enhance Resident Teaching and Patient Understanding in Acute Stroke Care
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S171: Structural Brain Changes in Adult Patients with Type 2 Diabetes Mellitus in the Dominican Republic: A Case-Control Study
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S172-LB: Clinical Spectrum and Hemorrhagic Risk of Diffusion-Weighted Imaging-Negative Cases After Intravenous Thrombolysis in Acute Ischemic Stroke
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S173: Proximal Internal Carotid Artery Occlusion with Atypical Multifocal Infarcts: A Case Report
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S174: Effect of Statin Therapy on Clinical Outcomes in Patients with Embolic Stroke of Undetermined Source
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S175-LB: Surfer's Myelopathy: Is it time to call it Spinal Hyperextension Stroke?
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S176*: Gut Microbiome–Related Metabolites as Mediators of Environmental Risk of Ischemic Stroke: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study
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S177: Conventional and Interaction-Informed Polygenic Risk Scores Reveal Environment-Dependent Genetic Effects on Ischemic Stroke Risk

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S178: Trends in Mortality Involving Stroke and Falls Among Older Adults in the United States from 2000 to 2023: A Nationwide Retrospective Analysis

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S179: Scrambler Therapy to Reduce Central Post-Stroke Pain: A Pilot Suggesting Evidence of Cortical and Network Reorganization Using Magnetoencephalography

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S180: Intrinsic Vulnerability of the Deep White Matter to Hypoxic–Ischemic Injury Due to Watershed Physiology

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S181: Deficits in Executive Function Selectively Contribute to Upper Extremity Motor Impairment After Stroke

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S182: Comparative Effectiveness and Safety of Prasugrel Versus Clopidogrel in Ischemic Stroke: A Systematic Review and Meta-Analysis of Randomized Trials

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S183: GLP-1 Receptor Agonists for Post-Stroke Recovery and Secondary Prevention: A Systematic Review and Meta-Analysis

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S184: Community-Engaged Stroke Prevention Interventions Addressing Health Disparities in the United States: A Systematic Scoping Review

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S185: Thrombolysis in the Delayed Treatment Window for Acute Ischemic Stroke: Updated Systematic Review and Meta-analysis
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S186: Unilateral Ptosis as a Presenting Manifestation of Carotid Cavernous Fistula
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S187-K: Deletion of Astrocyte-Specific Toll-Like Receptor 4 Signaling is Cerebroprotective following Focal Cerebral Ischemia
Presenting Author: *Bolanle Famakin, MD, University of Wisconsin, Madison, WI*
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S188-LB*: Long-Term Neuropsychiatric Outcomes After Subarachnoid Hemorrhage: The Amplifying Role of Delayed Cerebral Ischemia in Dementia, Epilepsy, and Mood Disorders : A 5-Year Cohort Study
Presenting Author: *Mina Ghayour, BS, UT Health, San Antonio, TX*
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S190: Mental Health Disparities Among U.S. Adults With Stroke History: A Cross-Sectional Analysis of Depression and Anxiety by Ethnicity
Presenting Author: *Adriana Gomez Cardona, Canovanas, PR*
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S191: Migraine-Associated Risk of Cervical Artery Dissection: A Systematic Review and Meta-Analysis
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S193: Multi-lumen Vascular Profiles (MVPs): A Cross-species Microvascular Architecture in Human Aging Linked to Altered Cortical Blood Flow in a Model of Cerebral Small Vessel Disease
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S194: Association of Retrieval Attempts and Procedure Time with Functional Outcomes Following Successful Endovascular Thrombectomy
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S195: Ten-Year Outcomes from a Teleneurology Service Offering Emergent Care to Patients in Community Settings
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S196-K: Single-Cell RNA Sequencing Identifies an Ischemia-Specific Immune Transcriptome in Human Acute Ischemic Stroke due to Large Vessel Occlusion
Presenting Author: *Destiny Hooper, MD, MS | Washington University School of Medicine*
Co-Authors: *Soha Azizi, Washington University School of Medicine, Ricardo D'Oliveira Albanus, PhD, Washington University School of Medicine, Qingli Xiao, PhD, Washington University School of Medicine, Carlos Cruchaga, PhD, Washington University School of Medicine, Daniel Woo, MD, MS, University of Buffalo School of Medicine and Biomedical Sciences, Jin-Moo Lee, MD, PhD, Washington University School of Medicine*

S197: Post-Stroke Mortality and Structural Disadvantage: A NINDS Social Determinants of Health Framework Analysis
Presenting Author: *Fernando Henrique Ibanhes, MD, MS,Los Angeles, CA*
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S198: Incidence, Risk Factors, Clinical Significance, and Management Outcomes of Carotid Stent Fractures: An Updated Systematic Review and Meta-Analysis
Presenting Author: *Venkata Sai Sulekhya Inturu, MBBS, Mamata Medical College, D.No.5, 7-200/8/A, Mamatha Hospital Rd, Manikya Nagar Basti, Khammam,Telangana-507002, India*
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S199: Developmental Venous Anomaly as a Locus of Ischemic Vulnerability: Cocaine-Precipitated Stroke
Presenting Author: *Laiba Iqbal, Baton Rouge, LA*
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S200: Isolated Left Callosal Body Infarction Presenting as Predominant Right Lower-Extremity Weakness
Presenting Author: *Laiba Iqbal, Baton Rouge, LA*
Co-Authors: *Nasser Abdelall, New Orleans, LA*

S201: Acute-Phase Inflammatory Biomarkers and Early Post-Stroke Depression: A Systematic Review
Presenting Author: *Sejal Jain, NSU Dr. Kiran C. Patel College of Osteopathic Medicine Fort Lauderdale, FL*
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S202: Enrollment Trends for Randomized Stroke Trials in the United States
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S203: "I Can See": Anton Syndrome from Sequential Bilateral Occipital Injury in Cerebral Amyloid Angiopathy
Presenting Author: *Soroush Kakawand, Oklahoma City, OK*
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S204: Invasive Versus Transcutaneous Vagus Nerve Stimulation Paired With Rehabilitation for Upper-Extremity Recovery After Stroke: A Systematic Review and Meta-analysis of Randomized Controlled Trials
Presenting Author: *Shradha Kakde, MGM medical college and Hospital Aurangabad, Maharashtra*
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S205: Endovascular Thrombectomy for Large-Core Ischemic Stroke: A Systematic Review and Meta-analysis of Randomized Controlled Trials with Imaging-Paradigm and Core-Severity Subgroup Analyses
Presenting Author: *Shradha Kakde, MGM medical college and Hospital, Aurangabad, Maharashtra*
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S206: 30-Day Ischemic Stroke Following Transient Ischemic Attack: A National Study of Social and Clinical Determinants of Health
Presenting Author: *Daniel Kamyab, MPH, SUNY Downstate, Brooklyn, NY*
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S207: Bilateral Cerebellar Infarcts Associated with Combined Testosterone Replacement, Finasteride, and Anastrozole Use
Presenting Author: *Muhammad Alvi, West Virginia University, Morgantown, WV*
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S208: FACTORS AFFECTING POST-DISCHARGE CLINIC ATTENDANCE FOLLOWING STROKE HOSPITALIZATION
Presenting Author: *Ammar Khan, Philadelphia, PA*

S209: Burden of Cerebrovascular Diseases in Parkinson's Patients in the United States: A CDC WONDER Analysis
Presenting Author: *Zaraq Khan, MBChB, BMedSci, Indiana University School of Medicine Southwest, EVANSVILLE, IN*
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S210: Efficacy Of Priming Strategies for Upper-Limb Motor Recovery After Stroke: A Systematic Review, Meta-Analysis, And Meta-Regression of Randomized Controlled Trials
Presenting Author: *Zaraq Khan, MBChB, BMedSci, Evansville, IN*
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S211: High-Intensity Versus Moderate-Intensity Statin Therapy After Acute Ischemic Stroke: A Multicenteric Cohort of Hemorrhagic Transformation and Short-Term Mortality
Presenting Author: *Yugant Khand, Kathmandu, Bagmati*
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S212: Pre-Stroke Glucagon-Like Peptide-1 Receptor Agonist Use And Outcomes After Acute Ischemic Stroke: A Propensity Score-Matched Retrospective Cohort Study
Presenting Author: *Yugant Khand, Nepalese Army Institute of Health Sciences Kathmandu, Nepal*
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S213: Basilar Artery Hemodynamics Predict Impaired Cerebrovascular Reserve and Metabolic Alterations in Anterior Circulation Steno-Occlusive Disease
Presenting Author: *Seondeuk Kim, Neurology specialist, Seoul National University Hospital Seoul, Seoul*
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S214: Interpretable Actigraphy-Derived Features Improve Prediction of Post-Stroke Functional Outcomes
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S215: Determining the Impact of Cardiac Function on Cerebral Perfusion Imaging Measures in Patients with Acute Large Vessel Occlusion Stroke
Presenting Author: *Sandra Kong, Wichita Falls, TX*
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S217: Paroxysmal Nocturnal Hemoglobinuria Presenting as Ischemic Stroke: A Case Report
Presenting Author: *Asma Akbar Ladak, Department of Neurology, University of Pennsylvania, Philadelphia, PA*
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S218: Carotid Revascularization is Associated with Reduced Recurrence in Symptomatic Carotid Web
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S219-K: Impact of Cerebral Acid-Base Status on Spreading Depolarization
Presenting Author: *Britta Lindquist, MD, PhD, University of California, San Francisco*

S220: Minocycline Transforms Acute Ischemic Stroke Care: A 2,428-Patient Meta-analysis of a Low-Cost Neuroprotective Strategy
Presenting Author: *Mario Lira, Fellow, Faculty of Medcine and Nutrition, Universidad Juarez del Estado de Durango, Durango, Durango*
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S221-LB: Bilateral Cerebellar Peduncle Lesions with Concurrent Psychosis and Disinhibition
Presenting Author: *Victor Lomachinsky-Torres, MD, Cleveland, OH*
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S222: Peripheral Methylation Status Recover in Young but not Aged Animals after Photothrombotic Stroke
Presenting Author: *Miguel Madeira, Nesconset, NY*
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S223: Primary CNS Vasculitis in Patients with Stroke and Conventional Risk Factors
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S224: Polycythemia Vera as a Cause of Multifocal Intracranial Stenosis and Recurrent Strokes: A Case Report
Presenting Author: *Maya Murzello, Jacksonville, FL*
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S225: Neurostimulation Improves Specific Cognitive Functions by Targeting Individual Neural Networks
Presenting Author: *Julia Myers, Moon Twp, PA*
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S226: Postpartum Internal Carotid Artery Dissection Presenting as Tandem ICA-MCA Occlusion With Progressive Flow-Limiting Stenosis Despite Anticoagulation
Presenting Author: *Suhrud Panchawagh, MD, Phoenix, AZ*
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S227: Does IV Thrombolysis Produce Net Lifetime Benefit Over DAPT in Mild Ischemic Stroke? A Decision-Analytic Model
Presenting Author: *Xhoni Pashaj, Huntingdon Valley, PA*
Co-Authors: *Ramin Zand, Hummelstown, PA*

S228: Shaping Tobacco Reduction Policies for U.S Population in Rural Counties Based on Risk of Vascular Diseases
Presenting Author: *Nazli Radfar, MD, Department of Neurology, College of Medicine, The Pennsylvania State University, Hershey, PA*
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S229: Development of NEXUS (Neurology EXposure for Undergraduate Students): A Structured Inpatient Neurology Shadowing Program During the Preclinical Curriculum
Presenting Author: *Hemangi Rajpal, Valhalla, NY*
Co-Authors: *Adam Karp, Fair Lawn, NJ*

S230: A NOVEL LARGE LANGUAGE MODEL-BASED AUTOGRADER FOR EVALUATING PERFORMANCE ON PEDAGOGICAL STROKE ALERT SIMULATIONS
Presenting Author: *Harika Rayala, MD, MSJ, University of Virginia Department of Neurology, Charlottesville, VA*
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S231: Secondary CNS Vasculitis Associated with Sjögren Syndrome
Presenting Author: *Nicholas Reish, Chicago, IL*

S232*: Characterization of a Pragmatic Transcranial Doppler Biomarker of No-Reflow Phenomenon After Large Vessel Occlusion Stroke
Presenting Author: *Lucas Rios Rocha, MD, University of Pittsburgh, Pittsburgh, PA*
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S233: Incidence and Predictors of Early Neurological Deterioration in Minor Ischemic Stroke: A Systematic Review
Presenting Author: *Carlos Rodriguez-Alarcon, University of Miami/Jackson Health System, Miami, FL*
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S234*: Plasma-derived Extracellular Vesicles from Humans with Silent Stroke and a Mouse Model of Silent Stroke Stimulate a Senescence-associated Secretory Phenotype at the Blood-brain Barrier
Presenting Author: *Mohd Salman, Indiana University School of Medicine, Indianapolis, IN*
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S235: Real-World Outcomes of Low-Dose Intravenous Heparin in Aneurysmal Subarachnoid Hemorrhage: A retrospective cohort study
Presenting Author: *Sandra Sanchez, MA, PMP, Scripps Health La Jolla, CA*
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S236-LB: Multimodal MRI Assessment of Blood-Brain Barrier Permeability in Cerebral Small Vessel Disease: Insights from ASL-MRI, DSC-MRI, and DCE-MRI
Presenting Author: *Sarvin Sasannia, MD, Johns Hopkins University, Baltimore, MD*

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S237: The Post-Stroke Spatiotemporal Dynamics of Myeloid Cells are Reciprocally Mediated and Independent of Infarct Topology

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S238: Higher Current Density of Non-invasive Brain-Stimulation Together with Occupational Therapy Leads to Stronger Behavioral and Imaging Changes in Recovering Stroke Patients

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S239: Single-cell RNA Sequencing Analyses Revealed Integrated Vascular Reactions in Promoting Angiogenesis after Chronic Cerebral Hypoperfusion

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S240: *Prognostic and Diagnostic Value of Troponin in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

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S241: Hematological Disorders as Stroke Risk Factors: CDC WONDER Analysis

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S242: Lung Cancer-Associated Acute Ischemic Stroke: A Systematic Review and Meta-Analysis of Coagulation Profile, Lesion Characteristics and Clinical Outcomes

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S243: Delayed Diagnosis of Adult-Onset Moyamoya Syndrome: A Case of Recurrent Stroke-Like Symptoms Despite Initially Normal Imaging

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S244: Comparative Effectiveness of Single Versus Dual Antiplatelet Therapy following Intravenous Thrombolysis for Acute Ischemic Stroke

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S245: Sex Differences in the Association Between 20-year Trajectories of Inflammation and White Matter Lesion Volume in Aging Adults

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S246: Persistent Rise and Disparities in Stroke and Atherosclerosis Mortality: A 25-Year U.S. Retrospective Analysis (1999-2024)

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S247: Feasibility of Clinical Quality Bedside Multimodal Brain Imaging

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S248: FDG-PET Uptake in Concurrent Cranial and Large Vessel Giant Cell Arteritis

Presenting Author: *Sylvia Tawiah-Eshun, Salt Lake City, UT*

S249: Stroke Severity, Mild Cognitive Impairment and Motoric Cognitive Risk, and Post-Stroke Dementia

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S250: Perceived Insurance Adequacy as a Primary Correlate of Unmet Rehabilitation Need After Stroke: Implications for Health Services Research in Post-Stroke Care

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S252: Venous Sinus Stenting Versus Cerebrospinal Fluid Diversion in the Setting of Medically Refractory Idiopathic Intracranial Hypertension: A Systematic Review and Meta-Analysis

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S253: Diabetic Retinopathy and Blood Biomarkers of Neurodegenerative Disease in Type II Diabetes Mellitus
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S254: Health-Related Social Needs Screening Among Hospitalized Patients who had a Stroke or Transient Ischemic Attack Across 11 Hospitals
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S255: Beyond the Lesion: Bilateral Cerebrovascular Disruption Revealed by Perfusion–Diffusion Dissociation after Intracerebral Hemorrhage
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S256: Trends in Racial and Socioeconomic Disparities in Reperfusion Therapy Utilization for Acute Ischemic Stroke in the United States, 2011–2022
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S257: *Clinical Outcomes and Cost of Reperfusion Treatments for Acute Ischemic Stroke in the United States: Estimates from the NIS 2011-2022
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S258: Stroke Risk with Dual vs Triple Antithrombotic Therapy After PCI in Atrial Fibrillation: A Systematic Review and Meta Analysis
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S259: Revascularization Versus Optimized Medical Therapy, and Stenting Versus Endarterectomy, for Carotid Stenosis: A Network Meta-analysis of Randomized Trials
Presenting Author: *Forough Yazdanian, Boston, Massachusetts*
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S260: Hypertension is Protective for Dementia-Related Outcomes in Asymptomatic Carotid Disease Populations - A Multi Cohort Study
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S261: Mapping Ischemic Stroke with Speech-Language Features: A Machine Learning Analysis of Multimodal Picture Description Data
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S262: Gait Speed as a Predictor of Stroke Recurrence in Acute Ischemic Stroke Patients: A Nationwide Multi-Center Registry Study
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EPILEPSY

S263: Refractory Status Epilepticus in a Patient with Parry-Romberg Syndrome: A Case Report
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S264*: The Invisible Storm: A Cutaneously Silent Multi-Organ Lamotrigine Toxicity Phenotype
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S265: Excitatory Dysfunction and Phenotypic Rescue in a Human Neuronal Model of SCN2A-Related Disorders
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S266*: Leiomodin-1 Antibody and Clinical Outcomes in Cryptogenic New-Onset Refractory Status Epilepticus: A Cohort Study
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S267: Functional Seizures after Autoimmune Encephalitis: Temporal Phenotypes and One-Year Clinical Trajectories
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S268: Bone Metabolism Markers and Adult-Onset Seizure Risk: A Retrospective Cohort Analysis of 43,256 Adults in the All of Us Research Program
Presenting Author: *Mehreen Ali, Carle Illinois College of Medicine, University of Illinois Urbana-Champaign Villa Park, ILLINOIS*

S269*: The Bone Toll of Epilepsy Treatment: Antiepileptic Drugs, Incident Bone Disease, and a Population-Level Vitamin D Supplementation Gap in 16,769 Adults
Presenting Author: *Mehreen Ali, Carle Illinois College of Medicine, University of Illinois Urbana-Champaign Villa Park, Illinois*

S270-K: Altered Sleep Microarchitecture in Epilepsy: Spindles, Slow Oscillations and Phase Precession of Spindle-SO Coupling Authors: Alex Bender, MD, PhD, Massachusetts General Hospital
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S271: When Dacrystic Seizures Wear the Face of Panic attacks -A Case of Delayed but Definitive Diagnosis
Presenting Author: *Sushmita Bhandari, University of Alabama at Birmingham, Birmingham, AL*
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S272: Altered EEG Microstate Dynamics of the Ictal Hemisphere Reflect Depressive Symptoms in Temporal Lobe Epilepsy
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S273: Evaluation of a Machine Learning Model (3D-ResNet-18) in Differentiating Epileptic and Non-Epileptic Motor Events in Clinical Settings Using Video Only
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S274-K: Hippocampal-cortical Mechanisms of Altered Memory Consolidation in Epilepsy
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S275-LB: Pre-Ictal Assessment of Autonomic Function Using Heart Rate Variability and Baroreflex Sensitivity from a Wearable Continuous Blood Pressure Sensor
Presenting Author: *David Clymer, M.Sc., University of California, Irvine, Irvine, CA*
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S276-K: The Effects of Single Pulse Electrical Stimulation on Intracranial EEG Monitoring
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S278: Single-Cell Protein Analyses of mTORopathies: Ex vivo Tissue and Organoid Models Reveal Novel Mechanistic Insights
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S279: Case of anti-NMDA Receptor Encephalitis Secondary to Ovarian Teratoma: The Effect of Bias and Delayed Diagnosis in Hispanic Populations in a Tertiary Care Center
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S280: Levetiracetam Versus Phenobarbital as First-Line Therapy for Neonatal Seizures: A Meta-analysis of Randomized Controlled Trials
Presenting Author: *ANA FORNARI CAPRARA, MD, Cooper University Hospital, CAMDEN, NJ*
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S281*: Cell Type-Resolved Multiomics Reveal Signatures of Homeostatic Circuit Reorganization in Focal Epilepsy of Unknown Etiology
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S282-K: Multisite Resting-State fMRI Reveals Network Segregation Loss and Lateralized Connectivity Changes in Epilepsy
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S283: Small Current, Big Impact: Rapid Seizure Reduction with Low-Dose Bilateral Centromedian Nuclei Responsive Neurostimulation
Presenting Author: *Rithvik Gundlapalli, University of Virginia School of Medicine, Charlottesville, VA*

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Co-Authors: *Syeda Amrah Hashmi, MD, University of Virginia Health, Department of Neurology, Charlottesville, VA; Howard Goodkin, University of Virginia Health, Department of Neurology, Charlottesville, VA; Donald Crammond, PhD, University of Pittsburgh Medical Center, Department of Neurosurgery, Pittsburgh, PA; Thandar Aung, MD, OSF Illinois Neurological Institute, Peoria, IL; Jorge Gonzalez-Martinez, MD, PhD, University of Pittsburgh Medical Center, Department of Neurosurgery, Pittsburgh, PA; Ifrah Zawar, University of Virginia Health, Department of Neurology, Charlottesville, VA* multifocal, non-localizable drug-resistant epilepsy. However, prospective randomized controlled trials are needed to better define patient selection criteria, optimize stimulation parameters, and expand therapeutic options for patients with otherwise limited treatment pathways.

S284: EpiScalp™: A Novel Software Tool for Enhancing Diagnostic Precision in First-Time Seizure Evaluations
Presenting Author: *Mark Hays, PhD, Neurologic Solutions, McLean, VA*
Co-Authors: *Golnoosh Kamali, PhD, Neurologic Solutions, McLean, VA; Andrew Gotshalk, BS, Neurologic Solutions, McLean, VA; Khalil Husari, MD, Johns Hopkins Hospital, Baltimore, MD; Jennifer Hopp, MD, University of Maryland Epilepsy Center, Baltimore, MD; Michael Sperling, MD, Thomas Jefferson University, Philadelphia, PA; Jorge Gonzalez-Martinez, MD, PhD, University of Pittsburgh Medical Center, Department of Neurosurgery, Pittsburgh, PA; Sridevi Sarma, PhD, Johns Hopkins University, Baltimore, MD*

S285: Elevated plasma p-tau217 in older adults with epilepsy and cognitive impairment: A pilot study
Presenting Author: *L. Brian Hickman, Los Angeles, CA*
Co-Authors: *Haley Willem, BS, University of California, Los Angeles, Los Angeles, CA; Bhavya Pandey, BS, University of California, Los Angeles, Los Angeles, CA; John Stern, N/A, Los Angeles, CA; Keith Vossel, MD, MSc, University of California, Los Angeles, Los Angeles, CA*

S286-K: Single Nucleus Transcriptomics Identifies an Epilepsy-Associated Microglial Population in the Pilocarpine Model of Temporal Lobe Epilepsy
Presenting Author: *Victoria Ho, MD, PhD, University of California, Los Angeles*
Co-Authors: *Ruth Tjondropurnomo, BS, University of California, Los Angeles, Jennifer Nguyen, BS, University of California, Los Angeles, Eszter Balko, PhD, University of Veterinary Medicine Budapest, Samantha Depew, BS, University of California, Los Angeles, Xing Chen, BS, University of California, Los Angeles, Radhika Singh, BS, University of California, Los Angeles, J Edward Van Veen, PhD, University of California, Los Angeles, Bence Racz, PhD, University of Veterinary Medicine Budapest, Peyman Golshan, MD, PhD, University of California, Los Angeles*

S287-K: Callosal Conduction Velocity Determines Bilateral Synchrony and Epilepsy Severity
Presenting Author: *Juliet Knowles, MD, PhD, Stanford University School of Medicine*
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S289: Trends, Demographic Characteristics, Risk Factors, and Outcomes of Epileptic Spasm Hospitalizations: A U.S. Population-Based Analysis (2016–2022)
Presenting Author: *Snigdha Kosuri, MPH, Medical College of Wisconsin, Wauwatosa, WI*
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S290-K: Striatal Interneuron Dysfunction as a Novel Mechanism for Autism Related Features in Dravet Syndrome
Presenting Author: *Laura McGarry, MD, PhD, Children's Hospital of Philadelphia*
Co-Authors: *Zachary P. Rosenthal, MD PhD, The University of Pennsylvania Perelman School of Medicine, Ala Somarowthu, PhD, Children's Hospital of Philadelphia, Marc V. Fuccillo, MD, PhD, The University of Pennsylvania Perelman School of Medicine, Ethan M. Goldberg, MD, PhD, Children's Hospital of Philadelphia, The University of Pennsylvania Perelman School of Medicine*

S291: Polygenic Risk Predicts Seizure Control in Drug-resistant Focal Epilepsy
Presenting Author: *Christopher McGraw Northwestern University Chicago, IL*
Co-Authors: *Marisha Dhakal, MA, Northwestern University, Chicago, IL; Muhammed Cagri Bayraktutan, MD, Boston Children's Hospital, Boston, MA; Chun Yin William Leung, MD, Massachusetts General Hospital, Cambridge, MA; Nivedita Jha, MBBS, Massachusetts General Hospital, Cambridge, MA; Hyunyong Koh, Baylor College of Medicine, Houston, TX; Emory Peng, BA, Massachusetts General Hospital, Boston, MA; Andrew Cole, Massachusetts General Hospital, Cambridge, MA*

S292: Benchmarking AI-Driven Epilepsy History-Taking Through LLM-Based Virtual Standardized Patients and Interviewers
Presenting Author: *Christopher McGraw, Northwestern University, Chicago, IL*

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S293-K: Quantitative EEG Biomarkers to Support Clinical Trial Readiness in SYNGAP1-Related Disorders
Presenting Author: *Jillian McKee, MD, PhD, Children's Hospital of Philadelphia*
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S294-K: Semi-Self-Supervised Representation Learning of Spike Waveforms Reveals Emergent Excitatory-Inhibitory Organization
Presenting Author: *Andrew Michalak, MD, MS, New York University Grossman School of Medicine*
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S295: TSC-Associated SEGA in the Era of Everolimus: A Case Series on Variable Epilepsy Outcomes
Presenting Author: *Garima Misra, MBBS, Hyderabad, Telangana*
Co-Authors: *Sakshi Solanki, Dr, Kalyan West, NC; Lokesh Lingappa, Dr, Yashoda Hospital, Hyderabad, Telangana; Bhoomika Sharma, Dr, Yashoda Hospital, Hyderabad, Telangana, Hyderabad, Telangana; Mohammad Anas, Dr, Yashoda Hospital, Hyderabad, Telangana, Hyderabad, Telangana; Apoorva Gupta, Dr, Rainbow Children's Hospital, Hyderabad, Telangana*

S296: Biological Biomarkers of Post-Stroke Seizures After Ischemic Stroke: A Systematic Review and Meta-Analysis
Presenting Author: *Soheil Mohammadi Yazdi, MD, Pediatric Critical Care, Baylor College of Medicine Houston, TX*
Co-Authors: *Claudia Robertson, MD, Department of Neurosurgery, Baylor College of Medicine, Houston, TX, Spyridoula Tsetsou, MD, Department of Neurology and Neurosurgery, Baylor College of Medicine, Houston, TX*

S297: Medication Affordability and Seizure Control in U.S. Adults With Active Epilepsy: A Nationally Representative Cross-Sectional Analysis
Presenting Author: *Soheil Mohammadi Yazdi, MD, Division of Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX*
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S298-K: Frequency-Specific Thalamocortical Network Dynamics During Focal Seizures in Humans
Presenting Author: *Hiroki Nariai, MD, PhD, University of California, Los Angeles*
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S299: Development of an On-demand Preclinical Model of the Postictal State
Presenting Author: *Anam Noor, BS Candidate, Canton, MI*
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S300-K: Optimizing Sleep Architechture and Cognitive Function in New-Onset Temporal Lobe Epilepsy
Presenting Author: *Temitayo Oyegbile-Chidi, MD, PhD, University of California Davis*
Co-Authors: *Cameron Carter, MD, University of California, Irvine, Phyllis Zee, MD, PhD, Northwestern Memorial Hospital, Jack J Lin, MD, University of California, Davis, Danielle Harvey, PhD, University of California, Davis, Amy Brooks-Kayal, MD, University of California, Davis*

S301: Can Large Language Models Assist in Differentiating Epileptic from Non-Epileptic Events in Epilepsy Monitoring Unit (EMU) Videos?
Presenting Author: *Anshum Patel, M.B.B.S, Mayo Clinic, Jacksonville, FL*
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S302-LB: Outcomes of Laser Ablation in Drug-Resistant Focal Epilepsy Among Older Adults
Presenting Author: *Faiza Qureshi, MD, University of Virginia, Charlottesville, Virginia*
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S303: Neurologic Spectrum and Outcomes in GPI-Anchor Deficiency related Congenital Disorders of Glycosylation: Insights from the Natural History Study from Frontiers in CDG Consortium
Presenting Author: *Jai Kumar Rajavoor Muniswamy, MBBS, Mayo Clinic, Jacksonville, FL*
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S304: Medical Cannabis in Pediatric Epilepsy: An Ethical Analysis of Consent, Access, and Long-Term Safety
Presenting Author: *Sarah Razzaq, BS, New Hyde Park, NY*
Co-Authors: *Bernadette Riley, DO, MS, FACOFP, FILM, DABFM, NYITCOM, Glen Head, NY*

S305*: Thalamic Network Involvement Reshapes Treatment Selection in Drug-Resistant Epilepsy: Evidence from 104 Patients with Intracranial Thalamic Recordings
Presenting Author: *Mark Richardson, MD, PhD, Massachusetts General Hospital; Harvard Medical School, Boston, MA*
Co-Authors: *Catherine Chu, Cambridge, MA, Sydney Cash, Boston, MA*

S306: A Novel Synonymous Splicing Variant in KCNQ2 Leading to Neonatal Epilepsy
Presenting Author: *Jessica Roberts, Washington University School of Medicine, Saint Louis, MO*
Co-Authors: *Judith Weisenberg, MD, Washington University School of Medicine, Saint Louis, MO; Rejean Guerriero, DO, Washington University School of Medicine, Saint Louis, MO; Kevin Bowling, PhD, Washington University School of Medicine, Saint Louis, MO; Xinming Zhuo, PhD, Washington University School of Medicine, Saint Louis, MO; Fumihiko Urano, MD, PhD, Washington University School of Medicine, St. Louis, MO; Saumel Ahmadi, MD, PhD, Washington University School of Medicine, Saint Louis, MO*

S307: The Risk of Remote Symptomatic Seizures Associated with Cerebral Microbleeds and Hemorrhagic Transformations in Patients with Ischemic Stroke
Presenting Author: *Zachary Shuckrow, BS, Penn State College of Medicine, Hershey, PA*
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S308-K: Microbleed Burden Predicts Cognitive Impairment in Older Adults with Epilepsy
Presenting Author: *Alena Stasenko, PhD, University of California San Diego*
Co-Authors: *McKenna Williams, PhD, University of California, San Diego, Anny Reyes, PhD, Cleveland Clinic, Ifrah Zawar, MD, University of Virginia, Taha Gholipour, MD, University of California, San Diego, Carrie R. McDonald, PhD, University of California, San Diego*

S309: Seizure Remission in Focal Cortical Dysplasia: Clinical Factors versus Treatment Modality in a Multicenter Real-World Cohort of 495 Patients
Presenting Author: *Jun-Sang Sunwoo, Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine Seoul, Korea, Republic of*
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S310-K: Profiling and Engineering the Ion Channel Transcriptome
Presenting Author: *Sheng Tang, MD, PhD, Northwestern University*
Co-Authors: *Gemma Carvill, PhD, Northwestern University*

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S311: Cenobamate and Epilepsy Surgery
Presenting Author: *William Theodore, Bethesda, MD*
Co-Authors: *Nakeyia Rhodes, RN, NIH, NINDS, Bethesda, MD, Aaliyah Hamidullah Thiam, MA, NIH, NINDS, Bethesda, MD, Ejaz Shamim, MD, NIH, NINDS, Bethesda, MD, Yung-Tian Gau, MD, NIH, NINDS, Bethesda, MD, Tilman Rosales, MD, NIH, NINDS, Bethesda, MD, Yasser Tajali, MD, NIH, NINDS, Bethesda, MD, sara Inati, MD, NIH, NINDS, Bethesda, MD*

S312*: Efficacy of Open-Loop versus Closed-Loop Stimulation in a Rat Model of Infantile Epileptic Spasms Syndrome
Presenting Author: *Kayla Vieira, MS, New York Medical College, Valhalla, NY*
Co-Authors: *Antonia Schonwald, MS, New York Medical College, Valhalla, NY, Chian-ru Chern, PhD, New York Medical College, Valhalla, NY, Jana Veliskova, MD/PhD, New York Medical College, Valhalla, NY, Libor Velisek, MD/PhD, New York Medical College, Valhalla, NY*

S313: Bilateral Mesial Temporal Lobe Epilepsy in a Patient with Gaucher Type III Disease
Presenting Author: *Paul Wang, Case Western Reserve University / University Hospitals, Cleveland, OH*
Co-Authors: *Rui Tang, MD, Case Western Reserve University / University Hospitals, Cleveland, OH; Persen Sukpornchairak, MD, Case Western Reserve University / University Hospitals, Cleveland, OH; Mahmoud Omar, MD, Case Western Reserve University / University Hospitals, Cleveland, OH; Wassim Malak, MD, Case Western Reserve University / University Hospitals, Cleveland, OH; Guadalupe Fernadez-Baca Vaca, MD, Case Western Reserve University / University Hospitals, Cleveland, OH; Rupin Singh, MD, Case Western Reserve University / University Hospitals, Cleveland, OH*
Conclusion: Herein, we report the first case of GD3 with drug-resistant bilateral mesial temporal lobe epilepsy. The diagnosis of GD3 was confirmed by WGS which found GBA p.Leu483Pro mutation. MRI brain was non-lesional and stereo EEG confirmed bilateral independent mesial temporal lobe seizures. We provide detailed clinical features of this case and expand the phenotypic spectrum of epilepsies associated with GD3 to include bilateral mesial temporal lobe epilepsy.

S314: Educational Gaps in Long-Term Video-EEG Monitoring: Convergent Perspectives from Patients and Multidisciplinary Clinical Staff
Presenting Author: *Jonathan Williams, Washington University in St Louis, St. Louis, MO*
Co-Authors: *Shanita Navies, RN, BJC Saint Louis, MO, Brittiny Cross, R EEG Tech, BJC, Saint Louis, MO*

S316-LB: Sex-Specific Differences in Seizure-Associated Cognitive Decline in Older Adults: A Longitudinal Multicenter Study
Presenting Author: *Ifrah Zawar, Charlottesville, VA*
Co-Authors: *Emily Johnson, Baltimore, MD, Jagan Pillai, MD, PhD, Cleveland Clinic, Cleveland, OH, Mark Quigg, Charlottesville, VA, Jaideep Kapur, Charlottesville, VA*

S317-K: Parvalbumin-positive Interneuron Density and Intrinsic Property Alterations in a Mouse Model of Pcdh19 Clustering Epilepsy
Presenting Author: Julie Ziobro, MD, PhD, University of Michigan
Co-Authors: *Noor Daddo, BS, University of Michigan, Joy Huang, BS, University of Michigan, Kira Jonatzke, BS, University of Michigan, Yukun Yuan, PhD, University of Michigan, Lori L. Isom, PhD, University of Michigan, Jack M. Parent, MD, University of Michiganz*

S318: Diagnostic Accuracy of Multi-modal Deep Learning Models for Epileptogenic Zone Localization in Drug-Resistant Focal Epilepsy: A Systematic Review and Descriptive Analysis
Presenting Author: *Amel Hanan Zehra, MBBS, Medstar Harbor Hospital, Baltimore, MD*
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GLOBAL NEUROLOGY

S320: Educational Interventions to Address Neurophobia in Medical Training: A Scoping Review
Presenting Author: *Hemanth Kumar Arumugam, Department of Neurology, University of Minnesota, Minneapolis, MN*
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S321: Early CSF and Serum Biomarker Dynamics Are Associated with Functional Recovery in Tuberculous Meningitis: Insights from the ALTER Trial
Presenting Author: *Alexander Junxiang Chen, University of California, San Francisco School of Medicine, San Francisco, CA, USA*
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School of Hygiene and Tropical Medicine, London, UK; Felicia Chow, University of California, San Francisco School of Medicine, San Francisco, CA, USA

S322: Socioeconomic and Regional Disparities of Neurocognitive Disorder and Multimorbidity Among Peruvian Younger and Older Adults
Presenting Author: *Lesley A. Guareña, B.S. University of Arizona Tucson, AZ*
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S323: Significant Decline in Stroke Mortality Emerging After the Early 2010s in the Dominican Republic, 2000–2018
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S324-K: Predictors of Caregiver Burden and Depression Among Zambian Caregivers of Older Adults with Neurologic Disease
Presenting Author: *Melissa Elafros, MD, PhD, University of Michigan/Ciheb Zambia*
Co-Authors: *Lisa Kalungwana, MS, Ciheb Zambia, Nicholas Heaton, MS, University of Michigan, Mataa M. Mataa, MBChB, Ministry of Health, Linah Mwango, MPH, Ciheb Zambia, Lottie M. Hachaambwa, MBChB, University of Maryland/Ciheb Zambia*,

S325: Pediatric Neurological Care in Sub-Saharan Africa: Current Status and Future Directions
Presenting Author: *Mabel Frimpong, Bryn Mawr College, Bryn Mawr, PA*
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S326: Building a Brain in Cambodia: From Concept to Validation of a Novel, Structured Clay-Based Neuroanatomy Teaching Tool in a Low-Resource Global Context
Presenting Author: *Fernando Henrique Ibanhes, MD, MS, University of Southern California, Los Angeles, CA*
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S327: Diagnosis of Multiple Sclerosis Before MRI: Clinical Approaches from the Pre-Imaging Era
Presenting Author: *Shaweta Khosa, MBBS, Olive View-UCLA Medical Center, Sylmar, CA*
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S328: Hippocampus and Amygdaloid Nuclei - The Brain Structures Most Resistant to Volume Decrease in Physiological Aging: MR Volumetric Study
Presenting Author: *Dusko Kozic, - Novi Sad, Serbia*

S329: Integrating Neurodivergent Panel-Based Education and Innovative Reflection in a Neuroscience Medical Student Curriculum
Presenting Author: *Kristy Y Lin, BS, Carle Illinois College of Medicine, Urbana, IL*
Co-Authors: *Lauren Sekiguchi, MS, Carle Illinois College of Medicine, Urbana, IL, Rachael Rubin, PhD, Carle Illinois College of Medicine, Urbana, IL, Grace Lee Park, MD, MEHP, Carle Illinois College of Medicine, Urbana, IL*

S330: Mortality Trends in Traumatic Brain Injury Complicated by Sepsis in the United States: A Population-Based Analysis, 1999-2024
Presenting Author: *Sushma Chowdary Kanakamedala, MD, St Martinus University, Visakapatnam, Andhrapradesh*
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S331: Results of a Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Bezisterim (NE3107) in Long COVID (ADDRESS-LC)
Presenting Author: *Penelope Markham, PhD, BioVie Inc., Carson City, NV*
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S333: Melkersson–Rosenthal Syndrome in Three Affected Siblings: A Familial Case Series Suggesting Possible Genetic Predisposition
Presenting Author: *Mazin Mohamed Ali, Researcher, Flint, MI*

S334: The Challenges of Utilizing Electrodiagnostic Studies in Resource-Limited Settings: Lessons From Cambodia
Presenting Author: *Yaesshna Pillay, MD, Keck School of Medicine, University of Southern California, Los Angeles, CA*
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S335*: Responsible AI in Neurology Patient Care: A Systematic Review of Clinical AI Algorithm (2020–2025)
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S336: Rapid Whole-Genome Sequencing in Hospitalized Adults with Complex Unexplained Acute Neurologic Conditions: Diagnostic Yield and Clinical Impact
Presenting Author: *Jai Kumar Rajavoor Muniswamy, MBBS, Mayo Clinic, Jacksonville, FL*
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S338: Temporal Trends in Mortality Due to Intracranial, Intraspinal Abscess and Sepsis in the United States: A CDC WONDER Analysis 1999-2024
Presenting Author: *Sushma Chowdary Kanakamedala, MD, St Martinus University, faculty of medicine, Visakapatnam, Andhrapradesh*
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S339: Improving Inpatient Length of Stay Among Neurology and Medicine Services, While Maintaining Provider Autonomy: A Discharge Prediction Tool on Hospital Throughput
Presenting Author: *Melissa Reider-Demer, DNP, MSN, CNP, FAAN, Los Angeles, CA*

S341: Trends in the Neurology Physician Training Pipeline: A Retrospective Observational Study
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S342: Perceived Severity of Common Neurological Symptoms of Multiple Sclerosis Among Healthy Women in Zambia: A Community-Based Participatory Study
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S343: Neurological Disorders in an Indigenous Amazonian Population: A Community-Based Study of Shawi Adults in Peru

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S344: MRNA Cytokine Profiling in Tuberculous Meningitis-associated Infarctions

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S346: Robotic-Assisted Versus Fluoroscopic-Guided Surgery on the Accuracy of Spine Pedicle Screw Placement: A Systematic Review and Updated Meta-Analysis

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S347: Adjunct Corticosteroid Use in Pediatric Herpes Simplex Virus Encephalitis and Post-Infectious Autoimmune Encephalitis: A Case Report

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S348: Video-Based Artificial Intelligence for Neurological Diagnosis: A Systematic Review of Diagnostic Performance and Clinical Applicability

Presenting Author: *Caroline Tatit, M.D, research trainee, FL*

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S349: Door-to-CT Intervals in Acute Stroke Care in Sub-Saharan Africa: A Scoping Review Protocol with Preliminary Findings

Presenting Author: *William Tembo, M.D, University of Zambia Lusaka, Lusaka*

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S350: Low Utilization and Barriers to Physiotherapy After Stroke in Zambia: A Tertiary Hospital Cohort Study

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S351: Social Needs Screening in Neurologic Transition of Care: A Mixed Methods Initiative

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HEALTH SERVICES AND HEALTH EQUITY RESEARCH

S352-K: A Trauma-Informed Cognitive Rehabilitation Program for Refugees with Traumatic Brain Injury and Cognitive Impairment: An Open Pilot Study
Presenting Author: *Altaf Saadi, MD, MSc, Massachusetts General Hospital, Harvard Medical School*
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NEUROCRITICAL CARE AND TRAUMATIC BRAIN INJURY

S353-K: Time-Dependent Remodeling of the Choroid Plexus Promotes Neutrophil Recruitment After Traumatic Brain Injury
Presenting Author: *Prajwal Ciryam, MD, PhD, University of Maryland School of Medicine*
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S354-K: Distinct Cytokine Trends are Associated with Outcome after Aneurysmal Subarachnoid Hemorrhage
Presenting Author: *Jessica Magid-Bernstein, MD, PhD, Yale University*
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355-K: REducing Sympathetic Hyperactivity After Traumatic Brain Injury Using Transcutaneous Auricular Vagus Nerve Stimulation (REST-VNS): A Literature Review, Rationale, And Clinical Trial Protocol
Presenting Author: *Jamie Podell, MD, University of Maryland School of Medicine*
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S356-K: Impaired Cerebral Autoregulation is Associated with Carbon Dioxide Levels in Pediatric ECMO Patients
Presenting Author: *Ethan Sanford, MD, FAAP, University of Texas Southwestern*
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S357-K: Hemoglobin Metabolites and Mitochondrial Dysfunction in Traumatic Brain Injury
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S358-K: Cardiac Arrest Stakeholders' Views on Measuring Prognostication Quality in Post-cardiac Arrest Patients: A Concept Mapping Study
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S361: Temporal Trends in Mortality Attributable to Sepsis-associated Encephalopathy in the United States from 1999–2023
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S363: Comparative Effects of Volatile Sedation and Total Intravenous Anesthesia on Neurologic Outcomes After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-analysis

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S364: Impact of Older Age and Biological Sex on Axonal Survival within the Spinal Cord White Matter After Acute Spinal Cord Injury

Presenting Author: *Julio Furlan, KITE Research Institute, University Health Network, and University of Toronto, Toronto, ON*

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S365: Conventional-therapy & FES-therapy In-Veritas Effects Study (C-FIVE Study): Neuromodulation in the Rehabilitation for Persistent C5 Palsy After Surgery in Individuals with Cervical Myelopathy

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S366: Readability of Online Patient Education Materials in Traumatic Brain Injury: A Quantitative, Descriptive Assessment Across Source Types

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S367: Atypical Cervicomedullary Involvement in HSV-2 Myelitis with Delayed Inflammatory Progression in an Immunocompetent Patient

Presenting Author: *Rithvik Gundlapalli, University of Virginia School of Medicine, Charlottesville, VA*

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S368: Quantitative EEG Features and Time to Recovery of Command-Following in Moderate-to-Severe Traumatic Brain Injury: An Exploratory Analysis

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S369-LB: Exploratory Analysis of Effects of Context-dependent Hypothermia in Two High Acuity Clinical Groups – Patients in Aortic Arch Repair Surgery and Patients with Acute Heart, Brain or Polytrauma

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S370: Decompressive Craniectomy by Multiple Dural Stabs Versus Open Dural Flap for the Evacuation of Acute Subdural Hematoma
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S371: Early versus Delayed Surgical Decompression in Spinal Cord Injury: A Systematic Review and Updated Meta-Analysis
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S372: Comparing the Use of Subgaleal and Subdural Drains in Non-acute Subdural Hematomas: A Systematic Review and Updated Meta-Analysis
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S373: Mortality Trends in Traumatic Brain Injury Among Adults Aged ≥25 Years in the United States: A CDC WONDER Population-Based Analysis (1999-2024)
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S374: Drains Drains Versus No Drain After Burr Hole Craniotomy for Chronic Subdural Hematoma: A Systematic Review and Meta-Analysis
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S375: Assessment of Stakeholders' Perceptions of Outcomes After Subarachnoid Hemorrhage: A Single-center Prospective Study
Presenting Author: *Skylar Lewis, BA, Providence, RI*
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S376: Multimodal Neuromonitoring of Neurovascular Coupling may Prognosticate Neurological Outcome after Anoxic Brain Injury
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S377: Not Just a Snore: When Stridor Signals Something Sinister in the ICU
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S378: Sex Differences in Metacognitive Awareness and Cognitive Screening in a Post-Mild TBI Clinic

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S379: Mapping the Social Exposome in Traumatic Brain Injury with a Machine Learning Approach to Identify Latent Social-Exposure Clusters

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S380: Operationalizing the Neural Exposome in Mild TBI: Feasibility and Directional Trends of a Three-Domain Framework on Cognitive Trajectories using Principal Component Analysis

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S381: Efficacy and Safety of Hypertonic Saline Versus Mannitol for Intraoperative Brain Relaxation in Supratentorial Craniotomies: A GRADE Assessed Systematic Review and Updated Meta-Analysis

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S382: Changes in Cerebral Glucose Metabolism Following Hemicontusive Cervical Spinal Cord Injury in Mice: A Whole-Brain Autoradiographic Study
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S383: Efficacy of Intravenous 20% Mannitol vs 3% Hypertonic Saline in Reducing Intracranial Pressure in Nontraumatic Brain Injury: A systematic Review and Updated Metanalysis of RCTs
Presenting Author: *Kashan Shahid, Mr., University of Nevada, Las Vegas, Las Vegas, NV*
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S384: Outcomes of Decompressive Craniectomy in Severe Traumatic Brain Injury: A Retrospective Cohort Study (2003–2021)
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S385: Rising Mortality of Brain Herniation in the United States: Insights from 25 Years of Data from CDC-WONDER
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S386: Disparities In Mortality Trends Due To Encephalopathy And Sepsis; A CDC-WONDER Based Retrospective Analysis of 25 Years Data
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S387-LB: Long-Term Multidisciplinary Follow-Up in Pediatric TBI: Accidental vs. Abusive Head Trauma
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S388: SAH Survivorship Through the Patient Lens: Early Feasibility of a Patient-Centered PROM Battery and Photovoice Methodology
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S389: Low Preoperative Seizure Rate in Infants with Congenital Heart Disease Undergoing Surgery with Cardiopulmonary Bypass
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S390: Cross-Domain Neural Exposome Burden is Associated with Worse-Than-Expected Cognitive Recovery After Mild TBI: An Unsupervised Dimension-Reduction Approach
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S391: Mild Traumatic Brain Injury Facilitates Development of Anterior Insula Hyperactivation to Fearful Stimuli in Trauma Survivors with Post-Traumatic Stress Disorder
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S392: NITE RN: Feasibility and Preliminary Educational Outcomes of a Night-Shift Neurology Resident-Led Teaching Initiative for Registered Nurses in the Neurological ICU
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NEUROGENETICS AND GENE THERAPY

S393-K: Longitudinal Sway and Gait Changes and Discrimination of Fall Risk in Adults With X-Linked Adrenoleukodystrophy
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S394-K: Allele-Specific Antisense Oligonucleotide with Enhanced Specificity for Timothy Syndrome Type 1
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S395-K: Development of Antisense-Oligonucleotide Therapy for Histone 3.3-Related Bryant-Li-Bhoj Syndrome
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NEUROINFLAMMATION AND NEUROINFECTION

S396-K: Allogenic Engineered T Cell Receptor Therapy for Progressive Multifocal Leukoencephalopathy
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SLEEP DISORDERS AND CIRCADIAN RHYTHMS

S398-LB: Circadian and Non-Circadian Sleep Disorders as Predictors of Neurodegenerative Diagnosis: Evidence from Three Retrospective Cohorts
Presenting Author: *Nicole Ash, M.A.S, Clinical Research, San Diego, CA*

S399-LB: Diurnal Variation in Brain Diffusion MRI in a Large Preadolescent Cohort
Presenting Author: *Linda Chang, University of Maryland School of Medicine Baltimore, Maryland*
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S400:Sleep Apnea in Paralympic Ontario-Resident aThletes with Spinal Cord Injury (SPORTS) Study: A Prospective Study
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S401: AUTONOMIC REGULATION VIA DERMAL VIBROTACTILE TRIGGERING OF PIEZOELECTRIC CHANNELS: AN EMERGING NONMEDICATION APPROACH TO SYMPTOM RELIEF
Presenting Author: *Peter Hurwitz, BS, Narragansett, RI*
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S402*: Clinical Predictors of Phenoconversion in Isolated REM Sleep Behavior Disorder
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S403: Pre–Shift Work Sleep Quality Predicts Early-Career Turnover in Newly Hired Nurses: A Prospective Cohort Study
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BEHAVIORAL NEUROLOGY & DEMENTIA

M100-K: Interrogating Amygdala-predominant Lewy Body Disease with Spatial Proteomics
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M101-K: Neural Replay Events Emerge During Periods of Cortical Beta Suppression
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M102-K: β-Amyloid Induces Microglial Expression GPC4 And APOE Leading to Increased Neuronal Tau Pathology and Toxicity
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M104: Trends in Fracture-Associated Mortality Among Individuals with Mental and Behavioral Disorders in the United States (1999-2019)
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M105: Methamphetamine-Driven Dopaminergic Signaling Enhances Microglial HIV Infection in Human Brain Organoids
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M106*: Association Between Generative AI Integration and Perceived Cognitive Failures Among Healthcare Professionals: Implications for Workforce Cognitive Load
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M109: The Shifting Hierarchy of Death: A 25-Year Analysis of Neurodegenerative, Cancer, and Ischemic Heart Disease Mortality in the United States (1999–2023)
Presenting Author: *Muhammad Alvi, West Virginia University, Morgantown, WV*
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M110: Sepsis-Related Mortality Among Older Adults with Alzheimer's Disease in the United States, 1999–2023: A CDC WONDER Population-Based Analysis of Demographic and Regional Disparities
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M111: An Escalating Crisis: A 25-Year CDC WONDER Analysis of Fall-Related Mortality in Older Adults with Neurodegenerative Diseases (1999–2023)
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M112: Trends, Disparities and Shifting Patterns of Mortality in Alzheimer's Disease with Mental Health in the United States: a CDC WONDER Analysis
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M113-LB: Auditory Cortex Connectivity Disruption in Behavioral Variant Frontotemporal Dementia
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M114: Effects of Non-Invasive Cervical Vagus Nerve Stimulation on Neuroinflammation, Brain Oxygenation, and Behavior in Alzheimer's Transgenic Mice
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M115: Low levels of Insulin Signaling proteins in HIV Brains are Associated with Neurocognitive Impairment and CSF Viral Load
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M117: Interpretable Mathematical Foundations for Reliable Event-Based Modeling of Alzheimer's Disease Progression
Presenting Author: *David Camacho, BS, Utah State University, Provo, UT*
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M118: Redox-Mediated Regulation of Neuroinflammatory STING Pathway via Protein S-Nitrosylation Contributes to Damage in Alzheimer's Disease Brain
Presenting Author: *Lauren Carnevale, Del Mar, CA*
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M119: Nonalcoholic Fatty Liver Disease, ApoE Genotype, and Neurocognitive Function in Middle-Aged Adults in the Dominican Republic: The HIGACOGNI Study
Presenting Author: *Gelanys Castro, Neurology resident, Westchester Medical Center, Hawthorne, NY*
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M120: Gut Microbiota Alterations in Alzheimer's Disease and Mild Cognitive Impaired Patients in the Dominican Republic: A Translational Study
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M121*: Neurodegeneration Meets Infection: A Population-based Analysis of Sepsis Mortality in Alzheimer's Disease (CDC WONDER 1999-2024)
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M122: Temporal Trends in Respiratory Failure Contributing Mortality Among Parkinson's Disease Decedents in the United States, 1999–2024: A CDC WONDER Population Based Analysis
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M123: Distinct Patterns of Mnemonic Similarity Task Performance in Alzheimer's Disease Variants: lvPPA and MCI/AD
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M124-LB: Modeling Amyloid and Tau Biomarker Trajectories Across the 2024 NIA-AA Clinical Staging of Alzheimer's Disease in ADNI
Presenting Author: *Kieffer Christianson, MA, University of Nevada, Reno, Reno, NV*
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M125: Trends in Dementia-Associated Mortality Among Diabetes Mellitus Patients in the United States (1999–2023): A Retrospective Analysis
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M126: Alzheimer's Disease–Related Mortality in the United States (1968-2023): A CDC WONDER Database Study
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M127: National Trends and Disparities in Mortality among U.S. Older Adults, with Coexisting Alzheimer's Disease and Hypertension, 1999-2023
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M128: Temporal Trends in Mortality Among U.S. Adults With Coexisting Dementia and Sepsis, 1999–2023

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M129: National Trends and Disparities in Mortality Involving Chronic Obstructive Pulmonary Disease and Dementia in the United States, 1999-2023

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M130: When Psychiatry Masks Neurodegeneration: Sex-Specific Diagnostic Pathways in Frontotemporal Dementia

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M131: Structural Abnormalities Of Perivascular Spaces By Brain Free Water Imaging In People with HIV

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M132: Effect Modification by Demographics in the Relationship between Midlife Adiposity and Late-life Brain Amyloid: The Atherosclerosis Risk in Communities (ARIC) Study

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M133-LB: Association of Midlife Obesity and Adiposity Measures with Late-life Changes on Brain MRI: The Atherosclerosis Risk in Communities (ARIC) Study
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M134-LB: Functional Differences in Primary Human Microglia Across Alzheimer's Disease and SuperAgers
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M135: How Much Brain Atrophy Is Too Much? It Depends on Who You Are – Normative Brain Volume Z-Scores Predict 5-Year Transition To Mild Cognitive Impairment/Alzheimer's Disease In Cognitively Normal Adults
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M136: Investigating Speech Behaviors in Mild Cognitive Impairment Using Human-Computer Interaction: A Comparative Study of Speech Tasks in Chinese Context
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M138: Diagnostic Performance of CSF Protein 14-3-3 For Prion Disease In The Modern Era
Presenting Author: *Anas Elgenidi, Jacksonville, FL*
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Background: CSF protein 14-3-3 has been incorporated into diagnostic criteria for Creutzfeldt–Jakob disease for decades. Advances in MRI and RT-QuIC enable detection of prion disease at earlier symptomatic stages, when neuronal injury biomarkers such as 14-3-3 may be below detection. To improve sensitivity, the US National Prion Disease Pathology Surveillance Center (NPDPSC) lowered the positivity threshold from >4,000 to >2,000 AU/mL. The impact of this change on diagnostic performance remains uncertain.

M139: Creutzfeldt–Jakob Disease Initially Misdiagnosed as Alzheimer's Disease: Lessons From Reported Cases
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M140: Neurodegenerative Disease Mechanisms: Predicting Antioxidant Therapeutic Potential in Alzheimer's and Parkinson's Diseases
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M141: Associations between Midlife Alcohol Use and Dementia: The Atherosclerosis Risk in Communities Study
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M142: Practical Factors Influencing the Use of Confirmatory Blood-Based Biomarkers in Alzheimer's Care
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M143: From First Visit to Disclosure: How Confirmatory Blood-Based Biomarkers Are Changing Diagnostic Timing in Alzheimer's Disease
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M144: Noninvasive, Brain-Specific Inhibition of BMP Signaling For The Prevention Of Tauopathy
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M145*: Heterotypic Co-Assembly of α-Synuclein and Tau Drives Pathology in Synucleinopathies: Implications for Therapeutic Targeting
Presenting Author: *Satkarjeet Gill, MBBS, Tomball, TX*

M146-LB: Pediatric Acute-onset Neuropsychiatric Syndrome in Children With Autism Spectrum Disorder
Presenting Author: *Brian Gomringer, BS, Portland, OR*

M148: Novel platform to study gut-microbiome dysbiosis in Brain Injury Associated Fatigue and Altered Cognition
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M149: Planetary Health Diet Adherence and Domain-Specific Cognitive Function in Older Adults: Evidence from NHANES 2003–2010
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M150: Case Report of Wernicke's Encephalopathy Mimicking Autoimmune and Psychiatric Encephalopathy in a Non-Alcoholic Female
Presenting Author: *Khai Harris,Atlanta, GA*
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M151: Cognition More Closely Linked to Liver Dysfunction than Age in Cirrhosis and Liver Transplant: A Pilot Study of Cirrhosis-Associated Cognitive Impairment
Presenting Author: *Sloane Heller, New York, NY*
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M152*: Plasma p-tau217/Aβ42 Ratio vs. Amyloid PET for Detecting Autopsy-Confirmed Amyloid Plaques
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M154: Imaging Changes Prior to Symptom Onset in Semantic Variant Primary Progressive Aphasia: A Case Report
Presenting Author: *Emily Iannopollo, MD, Washington University, St Louis, MO*
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M155: Progressive Changes in Innate Immune Responses, Post-Synaptic Dynamics, and Secretory Pathways in Virally Suppressed People with HIV
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M156: Predicting Amyloid PET Positivity with Cognitive Impairment Phenotyping
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M157*: Genetically Determined Resilience to Alzheimer's Disease Is Independent of Genetic Risk and Gated by Cardiovascular Comorbidity
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M158: Adiposity-Related Structural Brain Changes Across Midlife and Late-Life in the Dallas Heart Study
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M159*: Wearable-Derived Physical Activity Trajectories and Incident Neurological Disease: A Prospective Cohort Study of 22,518 Adults from the NIH All of Us Research Program
Presenting Author: *Meet Popatbhai Kachhadia, MD, Boca Raton, FL*

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M160: Efficacy and Safety of Anti-Amyloid Monoclonal Antibodies in Early Alzheimer Disease: A Systematic Review of Randomized Controlled Trials
Presenting Author: *Shradha Kakde, MGM medical college and Hospital, Aurangabad, Maharashtra*
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M161: Telehealth Music Therapy for Neuropsychiatric Symptoms in Amnestic Mild Cognitive Impairment: Exploring Behavioral and Brain Network Changes
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M162: Carboxy-terminal blockade of sortilin binding enhances progranulin gene therapy, a potential treatment for frontotemporal dementia
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M163: Prospective and Consecutive Evaluation of Anti-Amyloid Therapy in Patients with Alzheimer's Pathology
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M164: Low-Field MRI Detects CD8-Associated White Matter Hyperintensity in Long-Treated Adults With HIV
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M165: Dual Burden of Parkinson's and Alzheimer's Disease: A CDC WONDER Analysis
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M166: ZCCHC17 - A Novel Mechanism of Alzheimer's Disease Pathophysiology
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M169: Association of a Proteomic-based Biological Age Clock with Delirium in Older Adults with Acute Hip Fracture
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M171: Predicting Language Recovery at 12 Months from Acute Stroke Data: Machine Learning Identifies Shared and Distinct Neural Predictors
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M172: The Impact of the Trajectory of Insurance Coverage on Cognitive Function at Midlife
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M174: Efficacy and Safety of Dexmedetomidine for Prevention of Postoperative Delirium in Adult Surgical Patients - A Systematic Review and Meta-Analysis
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M175: One Year Maintenance Acoustic Neuromodulation versus Initial Neuromodulation alone for Perceived Stress in Healthcare Workers: A Randomized, Controlled Trial
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M177: Heart Rate Variability in Schizophrenia During Baseline Eyes-Open Resting State Compared to Healthy Controls
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M178: A Novel Neuroprotective Mechanism of Hexaraphane (6 MSITC) Derived from Wasabi
Presenting Author: *Isao Okunishi, Dr, Nagoya, Aichi*

M181-LB: The Cognitive Effects of Creatine Supplementation in Older Adults and Preclinical Models of Dementia: A Scoping Review
Presenting Author: *Aidan Pech, BS, New York Medical College, Amityville, NY*
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M182: Frontline Perspectives on the Real-World Use of Blood-Based Biomarkers in Alzheimer's Disease
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M184: Sex-Based Outcomes of Lecanemab in Early Alzheimer's Disease: A Comprehensive Multicenter, Real-World, Retrospective Study (LEADER)

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M185: GWAS Identifies Single-Nucleotide Polymorphisms in the SRPK1 Gene Linked To Diverse Neurological Traits

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M186: The Montreal Cognitive Assessment (MoCA) Memory Index Score (MIS) Classification Accuracy for Delayed Memory Performance Across Neuropsychological Measures

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M187: A Three-year Update of Lecanemab Use in Early Alzheimer's Disease: A Comprehensive Multicenter, Real-World, Retrospective Study (LEADER)

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M188-LB: Altered Resting-State Connectivity of the Auditory Cortex in Alzheimer's Disease

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M189: Utility of CSF Biomarkers in Patients with Suspected Alzheimer's Disease : A Tertiary Care Center Experience from India

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M190: Age at Onset Influences the Frequency and Etiology of Rapidly Progressive Alzheimer Disease and Related Dementias

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M191: Same Tau, Different Story: The Effect of Assay Choice on Prion Disease Detection

Presenting Author: *Nihal Satyadev, Jacksonville, FL*

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M192: A Novel Neurological Divide: IgG Subclass-Dependent CNS Safety, Neuropsychiatric Outcomes, and Survival Across PCSK9 Inhibitors, A Real-World Propensity-Matched Analysis
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M193*: Circulating Microbial DNA Signatures Associated with Cognitive Impairment in People with HIV
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M194: Clinical and Comorbidity Correlates of Discordant Plasma p-tau217
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M194-B: Eligibility for Anti-Amyloid Therapies in Biomarker-Confirmed Atypical Alzheimer's Disease Phenotypes
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M195: National Trends in Alzheimer's Disease and Arrhythmia Mortality Among Older Adults in the United States, 1999–2025
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M196: Differences in Functional Connectivity of the Basal Ganglia between Parkinson's Disease and Dementia with Lewy Bodies
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M197: Young Cerebrospinal Fluid Induces Oligodendrocyte-Associated Transcriptomic Remodeling with Relevance to Alzheimer's Disease
Presenting Author: *Maxwell Tran, Student, Corona del Mar High School, Newport Beach, CA*

M198: Interim Results from a Phase I Clinical Trial of AAV2-BDNF Gene Therapy in Alzheimer's Disease and Mild Cognitive Impairment
Presenting Author: *Mark Tuszynski, UC San Diego, La Jolla, CA*
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M199: Targeting Menopause Hormone Treatment (MHT) for the Brain
Presenting Author: *Rhonda Voskuhl, University of California, Los Angeles, Los Angeles, CA*
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M200: COVID-19 and Socioeconomic Disparities in Developmental Abnormalities Among US Children: Changes in Preexisting Trends
Presenting Author: *Anthony Wickett, BS in Psychology, Westwood, MA*
Co-Author(s): *Charles Wells, 1st Year MD Student, Valhalla, NY, Christopher Wu, BA, Valhalla, NY, Mill Etienne, Valhalla, NY*

M201*: 12-Month Results of a Randomized, Blinded Placebo-Controlled Trial of Shunting for Idiopathic NPH (PENS Trial)
Presenting Author: *Michael Williams, MD, University of Washington School of Medicine, Seattle, WA*
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M202: Secondary Progression in Alzheimer Dementia after Achieving Treatment-Related Amyloid Clearance - A Case Report
Presenting Author: *Chuang-Kuo Wu, Providence, RI*

HEADACHE AND PAIN

M203-K: Clinical and Network Predictors of Response to Motor Cortex repetitive Transcranial Magnetic Stimulation (rTMS) for Trigeminal Neuropathic Pain: A Randomized Controlled Trial
Presenting Author: *Julian Motzkin, MD, PhD, University of California, San Francisco*
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M204: Prevalence and Clinical Correlates of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in Adults with Celiac Disease: A Cross-Sectional Study
Presenting Author: *Layan Abu Ali, Dr, Faculty of Medicine, Yarmouk University, Amman, Jordan*
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M205: Burden of Migraine and Its Impact on Quality of Life in Adults with Celiac Disease: A Cross-Sectional Study
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M206: Safety and Efficacy of Atogepant for Migraine Prophylaxis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Presenting Author: *Muhammad Alvi, West Virginia University, Morgantown, WV*
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M207-LB: Neuralgia due to Bifid Mandibular Condyle: a Rare Condition Caused by an Extremely Rare Disorder
Presenting Author: *Hossein Ansari, La Jolla, CA*

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M208-LB*: Patient-Similarity Graph Neural Networks Stratify Treatment Escalation in Pediatric Headache
Presenting Author: *Astrid Geraldine Carrión Cuellar, Miss, Universitat Autònoma de Barcelona, Barcelona, Catalunya*
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M209: Systematic Review of Post-Surgical Opioid-Induced Hyperalgesia: Neurological Consequences of Persistent Opioid Prescriptions
Presenting Author: *Raymond Chiang, BS, ScM, Elk Grove, CA*
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M210: Psychiatric and Functional Burden of Neuropathic Pain Components in Chronic Low Back Pain: A Registry-Based Analysis
Presenting Author: *Ridhi Choragudi, BS, University of Pittsburgh School of Medicine, Pittsburgh, PA*
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M211: Safety and Efficacy of Atogepant for Migraine Prophylaxis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
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M212: Crisugabalin for Neuropathic Pain in Neuromyelitis Optica Spectrum Disorders: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial (TERMINATOR)
Presenting Author: *Wenyan Zhao, MD, Tangdu Hospital, Fourth Military Medical University, Xi'an, China*
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M214: GLP-1 Receptor Agonists in Migraine: Differential Clinical Response in an Expanded Single-Center Retrospective Cohort
Presenting Author: *Bianca Hoang-Dang, Oregon Health & Science (OHSU) Medical Scientist Training Program (MSTP) Portland, Oregon*
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M215: Enlarged Virchow-Robin Spaces and Lacunar Pathology: Mechanistic Insights into Neurovascular Dysfunction
Presenting Author: *Dr. Muhammad Mashood Iqbal, MBBS, MPH, Boston University, Boston, MA*

M217: Hydrocephalus as a Delayed Complication of Post-Transpedicular Fixation Meningitis: A Diagnostic & Therapeutic Challenge
Presenting Author: *Haris Malik, MBBS, PAF Hospital, Islamabad Capital Territory, Islamabad, Pakistan*
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M218: AI-Driven Closed-Loop Neuromodulation for Chronic Pain: A Pilot Evaluation of a Digital Self-Management Platform
Presenting Author: *Siva Krothapalli, Saint Louis University School of Medicine, Plainfield, Illinois*
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M219: Interventional Pain Exposure in Neurology Residents: A Observational Cohort Study
Presenting Author: *Gauri Patil, MD, New York City, NY*
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M220: Chronic Pain in Ehlers-Danlos Syndrome Patients: Prevalence, Pathophysiology, and Management
Presenting Author: *Sarah Razzaq, BS, NYITCOM, New Hyde Park, NY*
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M222: Treatment Of Chronic Nausea with Proposed Left Vagal Afferent Nerve Blocks
Primary Author(s): *John Schmidt, MD, FAHA, FAAN, Maguire Neuropsychiatric Institute, Oroville Hospital Oroville, CA, California Northstate University College of Medicine, Elk Grove, California*
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M223: Safety, Efficacy and Impact of Patient-Specific Moderators on CGRP Monoclonal Antibodies for Migraine Prevention: A Systematic Review and Meta-Analysis with Meta-Regression
Presenting Author: *Nikitha Settipally, Medical Graduate Prathima Institute of Medical Sciences Karimnagar, Telangana, Shoubhit P A Nair, MBBS Student, All India Institute Of Medical Sciences, Nagpur, Nagpur, India*
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M224: Opioid Deprescribing in Neurology: Trends Among U.S. Neurologists From 2013 to 2023
Presenting Author: *Noah Slobodin, University of Rochester School of Medicine and Dentistry, Rochester, NY*
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M226-LB: Insurance-Mandated Delays in OnabotulinumtoxinA Treatment for Chronic Migraine: Functional Consequences of Administrative Barriers
Presenting Author: *Michelle Temby, BS, Tucson, AZ*

M227-LB*: The Endometriosis-Migraine Visibility Gap: A 13-Million Patient Meta-Analysis of Shared Neuro-Gynecological Biology
Presenting Author: *Yohannes Woubishet Woldeamanuel, Phoenix, AZ*
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M229: Identification of Acute Pain Signatures in Healthy Adults Using Time-Domain Near-Infrared Spectroscopy
Presenting Author: *Audrey Zhang, University of California Irvine School of Medicine, Department of Neurology Irvine, CA,*
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MOVEMENT DISORDERS

M231: Plasma Proteomics Profile in Atypical Parkinsonism Syndromes Reveals Shared and Unique Molecular Signatures
Presenting Author: *Boluwatife Adewale, National Institute of Neurological Disorders and Stroke, Bethesda, MD*
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M232: Expanding the Therapeutic Window in DBS: A Comparison of Pseudomonopolar and Monopolar Configurations
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M233: Suspected Lifelong POLR3A-Related Disorder with Late-Emerging Levodopa-Responsive Parkinsonism and Pyramidal Signs: A Video Case Report
Presenting Author: *Saif Ahmed, University of Kentucky, Lexington, KY*
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M234: Integrated multi-omics identifies convergent dysregulation of Fam107b and Tph2 as potential therapeutic targets in SCA7
Presenting Author: *Soo Hyun Ahn, MD, Korea, Republic of*
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M235*: Developmental Failure of Cortical Inhibition in Huntington's Disease: Implications for Early Therapeutic Intervention
Presenting Author: *Yagiz Altun, MD, PhD, Bronx, NY*
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M236: Severe Holmes Tremor Associated with Autosomal Recessive Spinocerebellar Ataxia Type 16 (SCAR16)
Presenting Author: *Stephanie Anakwe, New York, New York*
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M237*: In vivo screen of Parkinson's disease GWAS risk genes identifies ARIH2 as a novel regulator of α-synuclein toxicity in dopaminergic neurons
Presenting Author: *Maria Armakola, Chicago, IL*
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M238: The Rising Burden of Alzheimer's Disease and Respiratory Failure Mortality among Older Adults (1999-2025): a CDC WONDER Analysis
Presenting Author: *Hafiz Sohail Ashraf, MBBS, MD, University of Illinois, Champaign, IL*
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M239: Late-Onset Ataxia-Telangiectasia in a 75-Year-Old Woman: A Rare Diagnostic Insight from Whole Exome Sequencing
Presenting Author: *Dhruv Bansal, MRCP, MD, Baylor College of Medicine, PDCMDC, Houston, TX*
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M240: When Dopa-Responsive Dystonia Is Not So Dopa-Responsive: An Atypical G
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M241-K: Mechanistic Cross-talk Between LRRK2 and GBA1 in Regulating Lysosomal Function and Inflammatory Activity in Microglia
Presenting Author: *Sarah Brooker, MD, PhD, Northwestern University Feinberg School of Medicine*

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M242: Machine Learning Identifies GBA1 and LRRK2 Molecular signatures in Sporadic Parkinson's Disease Patients Beyond Clinical Phenotypes
Presenting Author: *Bernabe Bustos, Chicago, IL*
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M243: Patients Taking Once-Daily Valbenazine Report Improved Quality of Life/Functionality and Experience Remission of Tardive Dyskinesia Symptoms: Findings From the KINECT-PRO™ Trial
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M244: Once-Daily Valbenazine Demonstrates Greater and More Predictable Pharmacokinetic Exposure and VMAT2 Target Occupancy in the Brain Than Deutetrabenazine Extended-Release: A PET Study
Presenting Author: *Precious Cagungun, PharmD Neurocrine Biosciences, Inc,. San Diego, CA*
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M245: Multi-locus Genetic Dosage Shapes Cognitive Disease Progression in Parkinson's: 15-year Meta-analysis of 24 Cohorts
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M246: Patterns of Use and Clinical Utility of Alpha-Synuclein Skin Biopsy at a Rural Tertiary Neurology Center
Presenting Author: *Patrick Callaghan, MD, Geisinger Medical Center, Bloomsburg, PA*
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M247: Non-Motor Medication Trajectories in Early Parkinson's Disease by Dopaminergic Therapy Status
Presenting Author: *Jun Ha Chang, Omaha, NE*
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M248: Integrative Medicine Use in Parkinson's Disease: A Mixed-Methods Study of the UCLA Center for East-West Medicine
Presenting Author: *Tiffany Chen, Los Angeles, CA*
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M249-K: Robust and multi-mechanistic Enhancement of Neuronal Autophagy to Rescue Parkinson Disease
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M250: Identifying Proteins of Mitochondria-lysosome Contact Sites with a Proximity-labling Approach
Presenting Author: *Robert Coukos, Northwestern University - Feinberg School of Medicine, Chicago, IL*

M252*: Low Density Lipoprotein Receptor-related Protein 1 (LRP1) Regulates Microglial Uptake of Alpha-synuclein
Presenting Author: *Albert Davis, Washington University, St. Louis, MO*
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M253: Neuroinflammation in REM Sleep Behavior Disorder
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M254: Boosting Education and Awareness Together for people with Parkinson's Disease (BEATs-PD): Results to Inform a Community Centered Parkinson's Dance and Music Program
Presenting Author: *Kerry Devlin, Johns Hopkins University School of Medicine, Baltimore, MD*
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M255: Patient Experiences and Perspectives During a One-Week Dopaminergic Medication Washout in Early-Stage Parkinson's Disease: A Qualitative Study
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M256: Neural Correlates of Limb-Kinetic Apraxia in Parkinson's Disease: A Scoping Review
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M257: Deep Learning Networks to Predict Phenoconversion in Individuals with Isolated REM Sleep Behavior Disorder
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M258: Long-term Wildfire Smoke Exposure and Parkinson Disease Diagnoses

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M259: One day accelerated 10 Hz rTMS for Focal Hand Dystonia: A Phase II Clinical Trial

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M260-LB: Levodopa Response as a Defining Axis of Freezing of Gait in Parkinson's disease: Convergent Evidence from Clinical Testing, Fluid Biomarkers and NET-PET Imaging

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M262: Safety Profile of Deep Brain Stimulation for Essential Tremor: A Large-Scale Retrospective Database Study

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M264: Long-Term Safety and Efficacy of Once-Daily INGREZZA® (Valbenazine) in Huntington's Disease Chorea: Results From the 5-Year KINECT®-HD2 Study

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M265*: Continued Evaluation of Participants With Parkinson's Disease Through 4 Years After Bemdaneprocel Administration
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M266: Differential Functions of FIG4 and PIKfyve in PAS Complex Regulation of Peripheral Myelination
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M268-K: Somatosensory Gating Impairment in Adults with Chronic Tic Disorder
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M269: Atypical Parkinsonian Disorders Differential Diagnosis: A Survey of Movement Disorders Specialists
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M270: Case Series of Creutzfeldt Jakob Disease presenting as Progressive Supranuclear Palsy
Presenting Author: *Nicholas Kaliss, San Francisco, CA*
Co-Author(s): Maria Noelle Florendo, MD, University of California Davis, Sacramento, CA, Alexandra Duffy, DO, University of California Davis, Sacramento, CA

M271: Mortality Trends and Demographic Disparities in Progressive Supranuclear Palsy in the United States: A CDC WONDER-Based Analysis (2014-2020)
Presenting Author: *Sushma Chowdary Kanakamedala, MD, St Martinus University, Visakhapatnam, Andhrapradesh*
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M272: Anxiety as a Primary Predictor of Pain Severity in Parkinson's Disease: A Cross-Sectional Study Using the King's Parkinson's Disease Pain Scale in a Georgian Population
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M273: Cognitive and Neuropsychiatric Effects of Home-based, Remotely Supervised Strength Exercise Combined with Guideline-based Aerobic Physical Activity Modification in Parkinson's Disease
Presenting Author: *Ryul Kim, MD, SMG-SNU Boramae Medical Center, Seoul*
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M274: *Staged, Bilateral Magnetic Resonance-guided Focused Ultrasound Pallidothalamic Tractotomy in Advanced Parkinson's Disease
Presenting Author: *Lindsay Knight, PhD, Insightec, Miami, FL*

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M275: Understanding Individual Challenges in Treating and Living with Essential Tremor: Results from a Lived-Experience Focus Group
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M276: Long-Term Safety of MR-Guided Focused Ultrasound Thalamotomy in Essential Tremor and Parkinson's Disease: Updated Evidence from Clinical Trials and Real-World Data
Presenting Author: *Lindsay Knight, PhD, Insightec, Miami, FL*
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M277: Tubulin modulation as a potential mechanism for toxicity of the Parkinson's Disease-associated pesticide trifluralin in iPSC-derived models
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M278: Living with Parkinson's: Development and Planned Evaluation of an Immersive Virtual Reality Simulation for Empathy and Education
Presenting Author: *Henry Lewis, Undergraduate Student, University of California, Los Angeles, Daniel Island, SC*

M279: Alteration of Myelin Polarity as an Early Detection of Myelin Abnormalities in a HNPP model
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M280: Peripheral Administration of a Novel Stabilized Fc-GDNF Protein Protected Against the Loss of Dopaminergic Neurons in an MPTP Model of Parkinson's Disease
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M281: Parkinson's Dyskinesia-Hyperpyrexia Syndrome in a Patient with Newly Prescribed Foscarbidopa/ Foslevodopa Infusion Pump
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M282-LB: *DT-216P2, a Gene-Targeted Small Molecule, Produces Rapid Dose-Dependent Clinical Improvements and Comprehensive Frataxin Biomarker Activity in Friedreich Ataxia: RESTORE-FA 4-week IV Cohorts Results
Presenting Author: *David Lynch, Philadelphia, PA*
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M283: Long-Read Genome Sequencing for Cerebellar Ataxia
Presenting Author: *Niki Maki, MD, UCI, Irvine, CA*

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M284-K: Dissecting Neural Circuits Regulating Sleep State Transitions in a Mouse Model of Parkinson's Disease
Presenting Author: *Pamela Marcott, MD, PhD, University of California San Francisco*
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M285: Metabolic Approach to Understanding Microglial Dysfunction in Parkinson's Disease
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M286*: VPS39 Variants Cause a Spectrum of Neurological Disorders Through Impaired Lysosomal Function and Autophagy
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M287-K: Dissecting the Mechanisms of BORCS5-related Lysosomal Dysfunction
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M289: The Silence of the Aqueduct: Web and Stenosis Masquerading as Neurodegeneration
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M290: Are Lower-Limb Tasks Underrepresented? Dopaminergic Responsiveness Across Digital and Clinical Bradykinesia Measures in Early PD
Presenting Author: *Han Nguyen, Vanderbilt University Medical Center, Casselberry, FL*
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M291: Clinical Characteristics and Insurance-Based Disparities in Huntington's Disease Care at an HDSA Center of Excellence: A 12-Year Retrospective Analysis
Presenting Author: *Derrick Okine, David Geffen School of Medicine, UCLA, Los Angeles, CA*

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M292: Bezisterim (NE3107) in Early Parkinson's Disease (SUNRISE-PD): Initial Results and Observations from a Phase 2 Hybrid Design Trial
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M294: Caregiver Networks, Social Programs, and Care Delivery for Aging Individuals with Huntington's Disease
Presenting Author: *Paola Perez, BS, Neurology, David Geffen School of Medicine, UCLA, Los Angeles, CA*
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M295: Deferiprone in Parkinson's Disease: Motor, Imaging, and Safety Outcomes Across Randomized Trials
Presenting Author: *Jamir Pitton Rissardo, MD, Cooper University Hospital, Camden, NJ*
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M297: Staged Bilateral MR-Guided Focused Ultrasound in Essential Tremor: Safety, Efficacy, and Rising Adoption of Second-Side Treatment
Presenting Author: *Kaite Gant, Insightec, Miami, FL*
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M298: Alien Limb Syndrome as a Manifestation of Intracranial Hemorrhage: A Case Report
Presenting Author: *Sheharyar Raashid, MD, Department of Neurology, Marshall University, Huntington, WV*
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M299: Determinants of Psychiatric Care Utilization in Huntington's Disease: A Cross-Sectional Analysis
Presenting Author: *Angie Roman Ramirez, Undergraduate Student, University of California, Los Angeles, Los Angeles, CA*
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M300*: Heterogeneity of alpha-Synuclein Seed Amplification Assay Time-to-threshold Across Diseases: A Cross-sectional Study
Presenting Author: *Eshita Shah, MD, University of California, San Diego, La Jolla, CA*
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M301: Delayed Recognition of Oromandibular Dystonia: A Systematic Review of Misdiagnosis as Temporomandibular Disorder
Presenting Author: *Fahima Akter Shammi, Research Associate, University of Toledo College of Medicine and Life Sciences, Toledo, OH*
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M302: Temporal and Demographic Trends in Mortality from Parkinson's Disease and Sepsis in U.S. Older Adults From 1999 to 2025
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M303: Dorsal and Ventral STN Exhibits Opposing Dynamics Between Spiking Synchrony, Beta Power, and LFP Coherence in Parkinson's Disease
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M304: Multi-Nodal Measures of Network Oscillatory Activity Associated with Longitudinal Deep Brain Stimulation Therapy for Dystonia

Presenting Author: *Noah Slobodin, University of Rochester School of Medicine and Dentistry, Rochester, NY*

Co-Author(s): *Abigail Alpers, MS, University of Rochester School of Medicine and Dentistry, Rochester, NY, Angela Hewitt, MD, PhD, University of Rochester School of Medicine and Dentistry, Rochester, NY*

M305-LB: PDCP Expression Correlates with Domain-Specific Cognitive Performance Following One-Week Dopaminergic Washout in Early-Stage Parkinson's Disease

Presenting Author: *Ella Tobias, High School Diploma, Scottsdale, AZ*

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M307: HISHS-3001 Treatment Preserves the Nigrostriatal Dopaminergic Pathway by Restoring Striatal and SNpc Dopamine and Maintaining Tyrosine Hydroxylase Immunoreactivity In 6-OHDA-Induced PD Model in Rats

Presenting Author: *Rajamannar Thennati, MSc, PhD, High Impact Innovations – Sustainable Health Solutions (HISHS), Sun Pharmaceutical Industries Limited, Vadodara, Gujarat*

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M308: Cerebrospinal Fluid Biomarkers in Autoimmune Atypical Parkinsonism: A Prospective Case-Control Study

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M309: PDCP Expression Correlates with Domain-Specific Cognitive Performance Following One Week Dopaminergic Washout in Early-Stage Parkinson's Disease

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M310: Fmnl2 Splice Mutation Prevents Motor System Development By Overpromoting Actin Polymerization in Cellular Migration Structures
Presenting Author: *Joyce Tran, La Jolla, CA*

M311: Generalized Chorea in an Older Adult: A Neuronal Intermediate Filament Antibody–Associated Paraneoplastic Syndrome
Presenting Author: *Ricardo Vivanco Menoscal, Lexington, KY*
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M312: Reversible Carbamazepine Induced Episodic Ataxia Without Cerebellar Atrophy
Presenting Author: *Ricardo Vivanco Menoscal, Lexington, KY*
Co-Author(s): *Andrew Welleford, MD, PhD, University of Kentucky, Lexington, KY, Tarek Ali, Lexington, KY*

M313-K: Projections from Hippocampal CA1 to Striatum are Biased Toward Either the Striosome or Matrix Compartments
Presenting Author: *Jeff Waugh, MD, PhD, University of Texas Southwestern*
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M315*: Mechanisms of α-Synuclein mediated circuit dysfunction in prefrontal and posterior cortical circuits
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M317: Visualizing the Developing Brain: Accelerated Golgi Staining Optimization for Early Postnatal Mice
Presenting Author: *Kevin Zheng, BS, Fresh Meadows, NY*
Co-Author(s): *Siyu Yan, MS, New Rochelle, NY, Yagiz Altun, MD, PhD, Albert Einstein College of Medicine, Bronx, NY, Aldrin Molero, MD, PhD, Albert Einstein College of Medicine, Bronx, NY*

M318: Patient-reported Botulinum Toxin Response Scale (BTRS) for Cervical Dystonia: A Patient Experience and Perspective Study
Presenting Author: *Cole Zweber, Robert Larner MD College of Medicine at the University of Vermont, Burlington, VT*
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NEURODEGENERATION AND CELL DEATH

M320-K: Diffusion Tensor Imaging as a Data-Driven Classifier of Early Cerebral Adrenoleukodystrophy
Presenting Author: *Elizabeth Pierpont, PhD, University of Minnesota*
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NEUROMUSCULAR DISEASE

M322-LB: Association of Use of Prescription Medications with Neuromuscular Adverse Effects with Frailty and Mobility Limitations Among Older Adults in the U.S
Presenting Author: *Sinan Abusalah, Undergraduate Student, University of Illinois Urbana-Champaign, Grainger College of Engineering, Oak Brook, IL*

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M323: Beyond the Triad: An Atypical GQ1b-Positive Miller Fisher Syndrome
Presenting Author: *Thomas Annesi, Glen Oaks, NY*
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M324-K: NEIMY-Associated KIF5A Mutation Impairs Trak-Mediated Mitochondrial Transport
Presenting Author: *Jonathan Brent, MD, PhD, University of Pittsburgh*
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M325*: Towards a Digital Twin for Myasthenia Gravis
Presenting Author: *Charles Carpenter, MS3, Washington, DC*
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M326-K: Long-Read Amplicon Sequencing Method to Measure CTG Repeat Length and Mosaicism for Correlation to Disease Severity in Myotonic Dystrophy Type 1
Presenting Author: *Samuel Carrell, MD, PhD, Virginia Commonwealth University/ Myotonic Dystrophy Clinical Research Network (DMCRN)*
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M327: Dual Neuromuscular Decline: A Case Report on Comorbid Myasthenia Gravis and AMSAN variant of Guillain-Barré Syndrome
Presenting Author: *Meagan Carter, BS, UTMB, Galveston, TX*
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M328: Every neuron counts: Presymptomatic disease manifests as degraded computational flexibility in a mouse model of SOD1-ALS
Primary Author(s): *Ravi Chopra, Washington University in St. Louis, St. Louis, MO*
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M329*: Efficacy and Safety of Intravenous Immunoglobulin after One Year of Treatment in Post-Polio Syndrome: Results from the FORCE Trial
Presenting Author: *Marinos Dalakas, MD, Thomas Jefferson University, Philadelphia, PA*
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M330: Assessment of the Burden of Constipation in Amyotrophic Lateral Sclerosis and its Relationship to Dysautonomia
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M331: Clinical Characteristics of Late-Onset Pompe Disease: A 15-Year Single-Center Experience
Presenting Author: *Isabella Dunn, BS, Hummelstown, PA*
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M332: Sporadic Late-Onset Nemaline Myopathy: A Diagnostic Challenge in Adult-Onset Myopathy
Presenting Author: *Isabella Dunn, BS, Hummelstown, PA*
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M333: Guillain-Barré Syndrome: A Complication of Metapneumovirus Infection
Presenting Author: *Mahmoud Elkhooly, Department of Neurology SIU School of Medicine, Springfield, IL*
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M334: Decades in Disguise: Bulbar-Onset Spinal and Bulbar Muscular Atrophy Misdiagnosed as Parkinsonism
Presenting Author: *Johny Tran, MD, UCLA, Corona, CA*
Co-Author(s): *Joshua Fernandez, MD, Corona, CA, Bhavesh Trikamji, MD, UCLA, Corona, CA*

M335: Stepping into Rarity: Late-Onset Distal Myopathy Revealing PHKA1-Related Glycogen Storage Disease IXd
Presenting Author: *Johny Tran, MD, UCLA, Corona, CA*
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M336: Social Vulnerability Is Associated With Reduced Use of First-Line Therapy in Amyotrophic Lateral Sclerosis: A Real-World EMR Cohort Study
Presenting Author: *Alexander Fish, Santa Monica, CA*
Co-Author(s): *Cara Siegel, MD, Ronald Reagan UCLA Medical Center, Los Angeles, CA*

M337: Sex-Specific Genetic Architecture and Liability Thresholds in Amyotrophic Lateral Sclerosis
Presenting Author: *Maurizio Grassano, National Institute of Neurological Diseases and Stroke (NINDS); University of Turin Bethesda, MD; Torino, Italy*
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M338: Motor Neuron Disease Preceded by Facial Sensory Deficits: A Case Report Highlighting Diagnostic Challenges in Amyotrophic Lateral Sclerosis Spectrum Variants
Presenting Author: *Ryan Gross, BSc, St. George's University School of Medicine, St. George's Grenada*
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M339: Prognostic Value of Anti-Ganglioside Antibodies in Guillain-Barré Syndrome: A Systematic Review and Meta-Analysis
Presenting Author: *Devansh Gupta, MD, Jefferson Einstein Hospital, Philadelphia, PA*
Co-Author(s): *Aparna Prabhu, MD, Jefferson Einstein Hospital, Philadelphia, PA, Marzieh Hassanijirdehi, MD, Jefferson Einstein Hospital, Philadelphia, PA*
Conclusion: Anti-GM1 antibodies confer two-fold increased odds of poor walking recovery in GBS with zero heterogeneity across 33 years of international evidence. A biologically coherent dissociation emerged: anti-GM1 (concentrated on limb motor neurons) predicts motor disability but not respiratory failure, while anti-GQ1b (cranial nerve distribution) predicts ventilation requirement. These findings support incorporating antibody specificity into GBS prognostic models, though the absence of poolable adjusted estimates warrants cautious causal interpretation.

M340: A Comparative Systematic Review and Meta-Analysis of Unilateral Biportal Endoscopic Procedure Versus Micro-Endoscopic Discectomy in Lumbar Spinal Stenosis and Related Neuromuscular Dysfunction
Presenting Author: *Khai Harris, Philadelphia College of Osteopathic Medicine, Atlanta, GA*
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M341*: A Motor Neuron-Intrinsic MTMR5/SBF1 Dysfunction Drives Early Lysosomal Trafficking Defects and Mitochondrial Stress in CMT4B3
Presenting Author: *Annabelle Huang, Baltimore, MD*
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M342: ANCA-Associated Vasculitic Neuropathy Mimicking Aggressive Axonal GBS: A Case of MPO-Positive Microscopic Polyangiitis
Presenting Author: *Laiba Iqbal, Baton Rouge, LA*
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M345: Synthetic VHH-TRIM21 RING Degraders Reduce TDP-43 C-terminal Domain Aggregates While Preserving an Endogenous TDP-43 Functional Readout
Presenting Author: *Hesan Jelodari Mamaghani, MD, UT Southwestern Medical Center, Dallas, TX Dallas, TX*
Co-Author(s): *Grigorii Sultanakhmetov, PhD, UT Southwestern Medical Center, Dallas, TX, Ankit Gupta, PhD, UT Southwestern Medical Center, Dallas, TX, Skyler Taylor, N/A, UT Southwestern Medical Center, Dallas, TX, Andrea Bennici, PhD, UT Southwestern Medical Center, Dallas, TX, Jaime Vaquer-Alicea, PhD, UT Southwestern, Dallas, TX, David Sanders, PhD, UT Southwestern Medical Center, Dallas, TX, Marc Diamond, MD, UT Southwestern, Dallas, TX*

M346: From Clinical Observation to Neuromuscular Junction Disorder: The Early European Development of Myasthenia Gravis
Presenting Author: *Shaweta Khosa, MBBS, Olive View-UCLA Medical Center, Sylmar, CA*
Co-Author(s): *Robert Freundlich, MD, Olive View-UCLA Medical Center, Sylmar, CA Subsequent use of longer-acting agents, including neostigmine, demonstrated reproducible clinical improvement, reinforcing role of impaired synaptic transmission. This further propelled understanding and identification of specific receptors in NMJ, ultimately leading to recognition of autoimmune mechanisms targeting acetylcholine receptor in MG.*

M347*: Alternative polyadenylation determines Ataxin-3 deubiquitinase-mediated TDP-43 cleavage and aggregation to modify ALS/FTD disease risk and can be modulated by polyadenylation site blocking ASOs
Presenting Author: *Albert La Spada, Irvine, CA*
Co-Author(s): *Frederick Arnold, PhD, Washington University at St. Louis, St. Louis, MO*

M348: Dietary Nutrients Associated with Odds and Progression of Amyotrophic Lateral Sclerosis
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M349: Efficacy and Safety of Efgartigimod Treatment for Patients with Myasthenia Gravis: A Systematic Review and Meta-analysis
Presenting Author: *Michael Lee, Kirk Kerkorian School, Las Vegas, Nevada*
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M350-K: Characterizing Energy Metabolism Among People With ALS And Pathogenic Gene Carriers
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M351: Machine-Learning Triage of Suspected Guillain-Barré Syndrome Reports in VAERS Using Physician-Adjudicated Data
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M352*: AI-Assisted Classification and Phenotyping of Guillain-Barré Syndrome Reports in VAERS: Implications for Neuromuscular Surveillance

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M353: Timing Matters: Patient, Caregiver, and Clinician Perspectives on Optimizing Palliative Care in ALS

Presenting Author: *Lina Lew, Medical Student, UC San Francisco (UCSF), San Francisco, CA*

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M355: A Rare Case of Late-Onset Myotonia

Presenting Author: *Vibha Murthy, University of Louisville School of Medicine, Louisville, KY*

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M356: A Slowly Progressive MYOT-Related Myofibrillar Myopathy Misdiagnosed as Multilevel Radiculopathy: A 66-Year-Old Woman with Long-Standing Distal Weakness

Presenting Author: *Shaida Omid, MD*

Co-Author(s): *Mona Rezaei, MD, Assistant professor, Irvine, CA*

M357: Homozygous RFC1 AAGGG Repeat Expansions Are Common in Idiopathic Peripheral Neuropathy

Presenting Author: *Sinem Ovunc, Virginia Commonwealth University, Health Richmond, VA*

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M358: Feasibility Study of Non-Invasive Assessment of Emotional Responsiveness in Patients with ALS

Presenting Author: *Gülşen Öztosun, MD, George Washington University School of Medicine & Health Sciences, Department of Neurology, Washington, DC*

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M359*: Sex-Dependent Remodeling of Langerhans Cell Morphology and Transcriptional Profiles in Painful Diabetic Neuropathy

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M360*: Brain Structure, Cognition, and Fluid Biomarkers in Myotonic Dystrophy Type 2: A Multimodal Analysis

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M361-LB: Development of Quantitative Muscle Imaging as a Biomarker of Disease Endpoints in Myotonic Dystrophy (DeQoDE-DM)

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M362: Refractory Chronic Cough as an Early Prodrome of Cerebellar Ataxia-Neuropathy-Vestibular Areflexia Syndrome (CANVAS): A Case Report

Presenting Author: *Goran Rakocevic, Philadelphia, PA*

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M363: Nanopore Long-read Sequencing for Profiling Genomic Rearrangements in Neuromuscular Disorders: A Resource For AllAllAllM363: Nanopore Long-read Sequencing for profiling genomic rearrangements in neuromuscular disorders: a resource for all

Presenting Author: *Memoona Rasheed, PhD, National Institute on Aging, NIH, Bethesda, MD*

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M364: Artifact-Aware AI-Assisted Identification of Myasthenia Gravis-Consistent Reports in VAERS Using Physician-Adjudicated Anomaly Detection

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M365: Beyond Demographics: Narrative-Based Phenotyping of Suspected Guillain-Barré Syndrome Reports in VAERS Recovers Physician-Adjudicated Diagnostic Structure

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M366: Age-Dependent Vulnerability in TDP-43 Pathology: Investigating Immunological and Molecular Determinants of Early Mortality in Mice Models

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M367: Optimizing Treatment Strategy for Onasemnogene Abeparvovec in Spinal Muscular Atrophy: A Meta-Analysis

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M368: Cutaneous Stigmata Heralds Calamity: A Case Series on Delayed Presentation of Occult Spinal Dysraphism in Adolescents

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M369: Survival and Cause of Death in Pontocerebellar Hypoplasia: An Individual-Level Meta-analysis to Guide Prognostic Counseling

Presenting Author: *Shriya Singh, Children's National Hospital, Washington, DC*

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M370: Temporal Trends in Amyotrophic Lateral Sclerosis Mortality in the United States,1999-2024: A CDC WONDER Study

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M371: Serum Protein Profile Predicts Antiretroviral Response in Amyotrophic Lateral Sclerosis
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M372: Neuronal Caveolin-1 overexpression preserves motor neuron and neuromuscular junction integrity in female TDP-43 A315T mouse model of Amyotrophic Lateral Sclerosis (ALS)
Presenting Author: *Vinh Ta, UCSD, San Diego, CA*
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M373: Impersonating Congenital Myopathy: A Case of GFPT1-related Congenital Myasthenic Syndrome
Presenting Author: *Payam Soltanzadeh, MD, FAAN, UCLA EMG Laboratory, Los Angeles, CA*
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M374: Acute Flaccid Paralysis Uncovering Novel Mutation in a Paediatric Alkaptonuria
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M375*: System-wide RNA Processing Disruption and Compensation by EXOSC3 p.G191 Variants in Pontocerebellar Hypoplasia 1B Reveal Candidate Therapeutic Targets
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M376: Unmasking Myasthenia Gravis in a Patient with Post-ACDF Horner Syndrome
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Co-Author(s): *Pawan Rawal, MD/MBBS, MHA, Neurology Department, College of Medicine, The University of Tennessee Health Science Center, Memphis, TN*

M377*: Early Intervention with RKER-065 Mitigated Disease Progression in an Amyotrophic Lateral Sclerosis Mouse Model
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NEURO-ONCOLOGY

M378: First Seizure Unmasks Endometrioid Adenocarcinoma Brain Metastases
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M379*: Siglec-15 and PD-1 Checkpoint Blockade in Combination with Oncolytic Zika Virus Infection Confers Protection Against Immune-resistant Gliomas
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M380: ALK-Positive Histiocytosis Presenting with Diffuse Leptomeningeal Disease and
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M381: Geographical and Demographic Disparities in Pediatric Brain Tumor Mortality in the United States from 1999 to 2023: A Nationwide Joinpoint Regression Analysis
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M382: Physical Exercise in Brain Tumor Patients: A Systematic Review
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M383: Intraoperative Stimulation Mapping in Pediatric Supratentorial Brain Tumor Resection: A Systematic Review and Meta-Analysis of Neurological Outcomes and Extent of Resection
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M384: Socioeconomic Predictors of Diagnostic Delay in Nonfunctioning Gonadotroph Adenomas
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M385: Tumor Treating Fields in Glioblastoma: A Systematic Review of Quality of Life and Functional Outcomes Across Randomized and Prospective Studies
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M386: A Novel Case of ARID1A Mutation in Pediatric Choroid Plexus Tumor
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M387: Glioblastoma in Patients with Multiple Sclerosis: A Natural History Analysis of Inflammatomas
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M388: Progressive Multifocal Glioblastoma in a Patient with Multiple Sclerosis: Case report
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M391: Levetiracetam Use and Survival Outcomes in Glioblastoma: A Systematic Review and Meta-Analysis
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M392-LB: Epimedin A Prevents Glioblastoma Growth and Invasion
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M393: Case of Posterior Reversible Encephalopathy Syndrome or Leptomeningeal Disease? Exploring the diagnostic difficulty of AMS in advanced gastrointestinal malignancy
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M394: Pain Outcomes in Patients With/Without Volumetric Tumor Response: Post Hoc from the ReNeu Trial of Mirdametinib in Adults & Children With Neurofibromatosis Type 1-Associated Plexiform Neurofibroma
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M395: Transcriptomic Meta-Analysis and Functional Validation Identify a Long Non-Coding RNA Network that Governs Zika Virus Oncolysis in Glioblastoma Multiforme

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M396: Trends in mortality from Primary Malignant Brain Neoplasms in the United States from 1999-2024: A CDC WONDER analysis

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M397*: Heterogeneity in Tissue Modeling for Tumor Treating Fields Dosimetry: Implications for Field Distribution in the Brain

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M398: The Natural History of Lymphomatosis Cerebri: An Analytical Assessment

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NEUROOPHTHALMOLOGY AND NEUROVESTIBULAR DISEASE

M399: Safety and Efficacy of Intravenous Recombinant Tissue Plasminogen Activator in Acute Central Retinal Artery Occlusion: A Systematic Review and Meta-Analysis

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M400: Peduncular Hallucinosis with Palato-Ocular Myoclonus Secondary to Ponto-Mesencephalic Hemorrhage: A Rare Dual-Pathway Brainstem Syndrome

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M402: Interocular Microvascular Asymmetry Selectively Associates with Verbal Memory Performance

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M403: Type 1 Cryoglobulinemia Presenting with Sequential Bilateral Ophthalmoplegia and Ophthalmic Venous Outflow Obstruction

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AUTOIMMUNE NEUROLOGY AND MS

S101K: Early Treatment Effects and Lesion Microstructural Subtypes Across the Multiple Sclerosis Disease Spectrum: A Diffusion Basis Spectrum Imaging Study

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Background: Conventional MRI cannot resolve the pathological processes coexisting within multiple sclerosis (MS) tissue. Diffusion Basis Spectrum Imaging (DBSI) decomposes the diffusion signal into anisotropic and isotropic compartments, yielding fiber, cell, and hindered ratios indexing axonal integrity, cellularity, and extracellular space. We characterized lesion microstructure across the MS spectrum and early treatment response.

Methods: Thirty-seven participants underwent multi-shell diffusion MRI: 11 healthy controls, 15 treatment-naïve relapsing MS (RMS), and 11 non-relapsing MS (NRMS; ≥10-year duration, ≥3 years inactive). Thirteen RMS were rescanned ~3 months after starting B-cell-depleting or sphingosine-1-phosphate receptor-modulating therapy. DBSI metrics were extracted from normal-appearing gray (NAGM) and white matter (NAWM) and lesions (subdivided into core, rim, and perilesional white matter); Gaussian mixture model clustering identified lesion subtypes.

Results: Treatment-naïve RMS showed reduced NAWM fiber ($p=0.04$) and elevated hindered ratio ($p=0.02$) versus controls. Lesions had lower fiber and cell ratios and higher hindered ratio than within-subject NAWM (all $p<0.001$). After treatment, lesional fiber ratio increased ($p=0.01$) while lesional and NAGM cell ratios declined (both $p=0.02$). Lesional cell ratio was higher in RMS than NRMS at core ($p=0.03$) and rim ($p=0.04$) but not perilesionally; treatment was spatially uniform. Clustering yielded four reproducible subtypes (edematous-hypocellular, moderately cellular, actively inflamed, structurally preserved); the inflamed subtype predominated in RMS and edematous-hypocellular in NRMS.

Conclusions: DBSI resolves microstructural lesion pathology, distinguishes relapsing from non-relapsing MS via lesion-body cellularity, and detects treatment-related changes in fiber and cell compartments. Unsupervised clustering yields reproducible lesion subtypes shifting across the disease spectrum, supporting DBSI as a candidate biomarker for in vivo lesion phenotyping.

S102: Trends and Disparities in Multiple Sclerosis Disease-Related Mortality in Postmenopausal Women from 1999-2024, with Forecasts to 2035: A Nationwide Study

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Background: Menopause significantly affects women with Multiple Sclerosis (MS). Declining estrogen levels during menopause may reduce neuroprotection, contributing to worsening disability, cognitive decline, and functional impairment despite stable or reduced relapse rates. Additionally, menopausal symptoms, such as fatigue, sleep disturbance, mood changes, and cognitive dysfunction, often overlap with MS manifestations, complicating disease management and potentially accelerating progression. Despite these vulnerabilities, population-level mortality trends in postmenopausal women with MS remain incompletely characterized.

Methods: We analyzed death certificates from the CDC WONDER multiple cause of death database from 1999-2024 for postmenopausal women with MS listed as underlying or contributing cause of death. Age-adjusted mortality rates (AAMRs) per 100,000 were calculated and stratified by age, race/ethnicity, region, and urbanization. Temporal trends were assessed using Joinpoint regression to compute annual percent change (APC) and average annual percent change (AAPC). Forecasts through 2035 were generated using ARIMA modeling.

Results: A total of 80,625 MS-related deaths were identified. Most deaths occurred in nursing homes/long-term care (33.4%), followed by home (28.1%) and inpatient settings (25.7%). The overall AAMR increased from 5.6 in 1999 to 8.1 in 2024 (AAPC 1.18; 95% CI 0.87-1.45). Among ages 55-74, mortality remained relatively stable ($P=0.30$). In contrast, women ≥75 years experienced a sustained rise (AAPC 2.95), with AAMR doubling from 5.9 to 12.3. The highest AAMRs were seen among non-Hispanic White women, followed by non-Hispanic Black women. Geographic variation showed higher burdens in the Midwest and the fastest growth in the South (AAPC 2.25). Non-metropolitan

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populations experienced steeper increases than metropolitan areas (AAPC 2.15 versus 1.51). Forecasting predicted stabilization in AAMRs at around 8.1 through 2025-2035.

Conclusion: MS-related mortality among postmenopausal women increased overall from 1999-2024, with a notable rise until 2022 followed by a recent decline till 2024, and projected stabilization through 2035. The burden is highest among women ≥75 years, with stable trends in those aged 55-74. Persistent disparities by race, region, and rurality highlight uneven risk. Despite recent stabilization, targeted efforts are needed to address high-risk populations and geographic inequities.

S103: Bridging the Imaging Gap: A Novel Hybrid Approach for External Imaging Acquisition

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Background: Timely access to imaging is critical for diagnosis, yet obtaining studies from external institutions remains problematic. This gap causes diagnostic delays, duplicate exams, unnecessary return visits, and added burden on physicians, patients, and staff. Existing solutions, such as EPIC Care Everywhere, provide limited image access, and long-term vendor fixes remain years away. An interim workflow is therefore essential.

Methods: Phase 1 consisted of sequential pilots within the multiple sclerosis (MS) division to improve imaging availability at NPVs. Interventions included automated patient text messaging via Penn Medicine's "Switchboard" telecommunications platform, a resource-focused approach with a staff member allocating dedicated time to function as a fake-backend new patient coordinator, and a combined synergistic model. A subsequent pilot tested workflow enhancements such as batching outbound requests. Outcomes included percentage of NPVs with imaging available and time required per patient. In Phase 2, we implemented the pilot-proven synergistic workflow within the MS division and collected data over a 30-week period.

Results: At baseline, fewer than 40% of NPVs had external imaging available, with 22% requiring a return visit solely due to missing studies. Phase 1 demonstrated that the text-based intervention improved availability to 48% (n=21), while a resource-focused approach using a fake-backend coordinator reached 80% (n=15). Combining both strategies yielded 88% availability (n=28). Workflow refinements, including batching and enhanced system access, reduced time per patient from 20 to 17 minutes (n=12). Phase 2 captured outcomes over 30 weeks, showing that for n=401, image availability remained high at 85% and time per patient was dramatically reduced to 3.5 minutes. Ongoing analyses will further expand this sample size to further evaluate scalability and durability of this workflow.

Conclusion: Pilot studies demonstrated that a synergistic workflow integrating patient-focused automation with focused staff involvement via a mock new patient coordinator markedly improved external imaging availability. The workflow yielded sustained improvements in imaging availability. Next steps include stepwise implementation of this model across additional Penn Neurology subspecialties, with successful early adoption in the epilepsy division. This model offers a scalable and broadly applicable model to optimize imaging access.

S104: Hyponatremia is Associated with Accelerated Hippocampal Atrophy and Delayed Clinical Recovery in LGI1 Encephalitis

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Background: Leucine rich glioma inactivated-1 (LGI1) encephalitis is the most common form of autoimmune limbic encephalitis. While hippocampal atrophy and cognitive impairment are well-recognized long-term sequelae, clinical predictors of vulnerability to these outcomes remain unclear. This study aimed to identify early clinical factors associated with longitudinal hippocampal atrophy and cognitive outcomes in patients with LGI1 encephalitis.

Methods: This retrospective cohort study enrolled patients diagnosed with LGI1 encephalitis at Seoul National University Hospital between January 2012 and June 2023. Patients with at least one 3D T1-weighted brain magnetic resonance imaging (MRI) and sufficient clinical data and follow-up period were included. All MRI scans obtained within 2 years from symptom onset were collected, and hippocampal

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volumes were quantified using FreeSurfer. Clinical data including demographics, clinical presentation, laboratory findings, and treatment information were collected. Clinical outcome measures included modified Rankin Scale (mRS), Clinical Assessment Scale in Autoimmune Encephalitis (CASE), and Clinical Dementia Rating (CDR) scores assessed up to 2 years.

Results: A total of 57 patients (73.7% male; mean age 61.1 ± 12.1 years) and 173 MRI scans were included in this study. Longitudinal volumetric analysis demonstrated an overall significant decrease in hippocampal volume over 2 years for the entire patient population ($p<0.001$). Hyponatremia was observed in 54.4% (n=31) and was associated with significantly greater hippocampal volume loss after age adjustment compared to normonatremia ($p=0.006$). Treatment variables, including corticosteroid use ($p=0.619$), rituximab ($p=0.053$) were not associated with differences in hippocampal atrophy. Patients with hyponatremia had a higher age at onset (64.4 vs. 57.1 years, $p=0.029$), but other baseline characteristics were comparable. Over a mean follow-up of 56.8 ± 38.3 months, changes in mRS did not differ between groups ($p=0.472$); however, improvement in CASE scores was significantly slower in the hyponatremia group ($p=0.043$). Baseline CDR scores were higher in the hyponatremia group (1.19 vs. 0.96, $p<0.001$), with no difference in longitudinal change ($p=0.221$). Hypothalamic volume change did not differ by hyponatremia status ($p=0.791$).

Exploratory IgG subclass analysis (n=10 per group) showed a trend toward higher IgG1 and lower IgG4 intensity in the hyponatremia group, but did not achieve statistical significance ($p=0.138$ and $p=0.350$, respectively).

Conclusion: Hyponatremia in LGI1 encephalitis is associated with higher baseline cognitive impairment, accelerated hippocampal atrophy, and delayed clinical recovery. These findings suggest that hyponatremia may serve as an early clinical marker of vulnerability to long-term sequelae.

Differences in IgG subclass profiles may represent a potential mechanistic link, warranting further investigation.

S105: Efgartigimod Is a Unique Neonatal Fc Receptor Blocker That Allows Immunoglobulin G Reduction Without Broad Inhibition of Immune Responses

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Background: Treatment with some immunosuppressive and B cell–depleting therapies may lead to increased risk of severe infections in patients and may reduce immunogenicity of vaccines. Previous studies have demonstrated that efgartigimod, a human immunoglobulin (Ig) G1 antibody Fc fragment that reduces levels of IgG (including pathogenic autoantibodies) through neonatal Fc receptor blockade, does not impair cellular and humoral immune responses to antigenic challenges. Rates and severities of severe infections have been similar between efgartigimod- and placebo-treated participants in placebo-controlled studies and have not increased during long-term open-label studies. The objective of this study is to investigate the effect of efgartigimod treatment on immune responses to vaccination.

Methods:A cross several clinical studies in healthy volunteers and in participants with generalized myasthenia gravis, chronic inflammatory demyelinating polyradiculoneuropathy, immune thrombocytopenia, and pemphigus vulgaris, intravenous efgartigimod or subcutaneous efgartigimod PH20 was administered in various dosing regimens. Vaccine-specific IgG titers and cellular immunity were assessed at multiple time points, including prevaccination, ≥4 weeks post-vaccination, and at maximal IgG reduction.

Results: In participants receiving efgartigimod, antigen-specific IgG titers increased from prevaccination to post-vaccination, even during maximal IgG reduction. Additional data demonstrating preservation of cellular immune responses during efgartigimod treatment will be presented.

Conclusion: Efgartigimod's unique structure as an Fc fragment selectively reduces IgG antibodies and autoantibodies while preserving the ability to mount antigen-specific responses to immunization. This mechanism avoids both broader impacts on immunity and increased risk of infections observed with some immunosuppressive and B cell–depleting therapies.

S106: Anti-IgLON5 Disease Presenting as a Convergence of Multiple Clinical Subtypes Including Prominent Cerebellar Ataxia, Painful Axial Spasms, and Encephalopathy: A Case Report

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Background: Anti-IgLON5 disease is a rare autoimmune encephalopathy characterized by four clinical subtypes: sleep disorder with parasomnia, bulbar syndrome, PSP-like syndrome, and cognitive decline. Simultaneous expression of multiple subtypes alongside appendicular cerebellar signs, painful axial spasms, and encephalopathy has rarely been described. We present such a case with a relapsing-remitting course.

Methods: Case: An 87-year-old male was evaluated for a six-month history of painful axial spasms involving the chest, epigastrium, and interscapular region, upper extremity jerking, intermittent diplopia, encephalopathy with cognitive decline and functional deterioration, conversational sleep-

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talking consistent with REM sleep behavior disorder, and bilateral impairment of horizontal and vertical optokinetic nystagmus (OKN). Serum IgLON5 antibody titer was markedly elevated at 1:384, confirming the diagnosis. MRI brain with contrast showed only chronic white matter changes without abnormal enhancement. He was initiated on IV methylprednisolone, a prolonged prednisone taper, and five-day IVIG, with monthly IVIG maintenance thereafter. Three months later, the patient re-presented with an exacerbation marked by recurrence of sleep-talking, worsening dysphagia, dysarthria, and new finger-to-nose dysmetria, which improved substantially following repeat IVIG. He subsequently experienced a second exacerbation during which examination demonstrated encephalopathy with lethargy and disorientation, dysarthria, recurrence of OKN impairment, and appendicular dysmetria. Repeat MRI brain with contrast again revealed only chronic white matter changes with no abnormal enhancement. Given progression despite first-line immunotherapy, rituximab was administered.

Results: This case is notable for the simultaneous convergence of all four established subtypes from initial presentation. Encephalopathy, conversational parasomnia, and bilateral OKN impairment each resolved with treatment and recurred with subsequent exacerbations, tracking closely with disease activity. Finger-to-nose dysmetria represented overt appendicular cerebellar involvement, infrequent in the literature despite neuropathological evidence of tau deposition in the cerebellar cortex. Painful axial spasms - distinct from the cervical dystonic spasms in prior reports - remain poorly characterized and may represent an underrecognized manifestation. Consistently negative MRI with contrast despite significant clinical severity reinforces that a negative MRI should not dissuade clinicians from pursuing antibody testing.

Conclusion: Anti-IgLON5 disease can simultaneously express features of all recognized subtypes from initial presentation, with painful axial spasms, appendicular cerebellar dysmetria, and encephalopathy representing underreported manifestations. This case underscores the phenotypic heterogeneity of the disease, broadens its recognized clinical spectrum.

S107: Clinical Heterogeneity of Suspected Transverse Myelitis in VAERS: Insights from Narrative-Based Unsupervised Analysis

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Background: Suspected transverse myelitis (TM) reports in VAERS are clinically heterogeneous and often lack standardized documentation, complicating interpretation. Whether latent structure exists within these narratives, and whether it aligns with established clinical patterns, remains unclear.

Methods: From 1,296 screened reports, 332 underwent physician adjudication using criteria aligned with the Transverse Myelitis Consortium Working Group framework. Free-text narratives were encoded using BioClinicalBERT embeddings (768 dimensions), reduced via UMAP, and clustered with HDBSCAN without prespecified cluster number. Diagnostic labels were not used during clustering. Cluster quality was assessed using silhouette score and bootstrap stability (median adjusted Rand index [ARI]). Clusters were characterized using clinical variables and TM-consistency labels.

Results: Seven clusters were identified, with 8 reports (2.4%) classified as noise. Separation was moderate (silhouette 0.616) and stability moderate (ARI 0.672). Cluster composition was dominated by age: two pediatric-predominant clusters (median age 0.2 and 4.0 years; n=26 and 104) showed near-zero TM-consistent rates (0.0% and 1.0%), whereas three adult-predominant clusters (median age 19–23 years; n=42, 34, 53) showed higher TM-consistent proportions (35.3–40.5%). Two intermediate clusters (n=29, 36) showed mixed profiles.

Conclusion: Unsupervised narrative analysis recovers a clinically interpretable axis: pediatric mimics versus adult inflammatory myelopathy without using diagnostic labels, providing construct validation for narrative-based representations. These findings highlight demographic structure as a dominant driver of apparent clustering, with implications for distinguishing likely inflammatory myelopathy from common mimics in surveillance data. Further work is needed to assess robustness and define utility for pharmacovigilance applications.

S108: The Fatal Triad: A Systematic Review of Immune Checkpoint Inhibitor-Induced Myocarditis, Myositis, and Myasthenia Gravis (Triple M) Overlap Syndrome

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Background: Immune checkpoint inhibitors (ICIs) have transformed neuro-oncology and solid tumor therapy but cause severe immune-related adverse events. The "Triple M" (MMM) overlap syndrome is the most severe neurological outcome, defined by myocarditis, myositis, and myasthenia gravis occurring together, and a mortality rate of nearly 50%. The use of ICIs and rescue therapies has grown, even though early evaluations reported initial cases. This systematic review aims to improve on previous incidence reports by quantifying mortality determinants, identifying high-risk subgroups, and evaluating the survival efficacy of novel targeted rescue therapies for MMM syndrome up to April 2026 in patients with advanced malignancies such as melanoma, lung cancer, and urothelial carcinoma.

Methods: A systematic review was conducted following PRISMA guidelines and searched PubMed, EBSCO/MEDLINE, and ScienceDirect until April 2026. The search required all three Triple M components and ICI terms to be present together. Two examiners screened titles, abstracts, and full texts after deduplication. We excluded non-human research and meta-analyses. Data extraction focused on mortality outcomes, rescue therapies, high-risk characteristics, and ICI regimens. Quality assessment was performed using the JBI Critical Appraisal Checklist for case reports and case series.

Results: The initial search found 780 records; 97 primary studies met full eligibility after screening, forming the largest MMM cohort analyzed to date, representing over 300 individual patients. Notably, 33 studies (34%) were published in 2025–2026, showing a rise in clinical encounters. Most cases (31/50) involved PD-1 inhibitors (pembrolizumab, nivolumab) in the 50 unique case reports/series. However, mortality was highest for combination therapy (PD-1 + CTLA-4), with an observed case fatality rate of at least 18% across case reports, rising substantially in combination ICI cases. Pre-existing thymoma was identified as uniquely lethal, with a 100% case fatality rate in published reports with PD-1 inhibitors. Six recent cases (12%) used novel, steroid-sparing targeted therapies: FcRn blockade (efgartigimod), complement inhibition (eculizumab), and CTLA-4-Ig (abatacept). These demonstrated significant survival benefits for refractory, impending-crisis patients.

Conclusion: Cases of MMM syndrome surged in 2025–2026. Combined ICI therapy and pre-existing thymoma mainly predict mortality, even though PD-1 monotherapy causes most cases. Increasing FcRn blockade and complement inhibition suggest that early targeted therapies may reduce triad mortality more effectively than prolonged reliance on corticosteroids.

S109: Utility of the Antibody Prevalence in Epilepsy and Encephalopathy (APE2) Score as a Diagnostic Tool for Autoimmune Encephalitis

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Background: Diagnosis of autoimmune encephalitis (AE), particularly in antibody-negative cases, remains challenging and depends on clinical criteria and supportive investigations. We compared the diagnostic performance of the Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score to the Graus criteria for autoimmune encephalitis (AE), identified pragmatic APE2 cutoffs for clinical use, and explored whether a modified seizure-and movement-weighted score (APE2SM) improves discrimination.

Methods: We conducted a retrospective study of consecutive referrals to a tertiary neuroimmunology clinic (January 2017–May 2023). AE diagnosis was determined by expert consensus based on clinical features, investigations, exclusion of alternative diagnoses, and immunotherapy response. APE2 scores, Graus categories, and the exploratory APE2SM model were assigned retrospectively. Diagnostic performance was assessed using ROC analysis and contingency tables, and logistic regression modeled the probability of AE across scores.

Results: Eighty-five patients were included (56.5% female; mean age 53.8 years). Fifty-nine (69.4%) had AE (34 antibody-positive). APE2 outperformed Graus in the full cohort (AUC 0.894 vs 0.804) and in antibody-negative patients (AUC 0.905 vs 0.850). In both models, an APE2 cutoff ≥4 balanced sensitivity and specificity near or above 80%, whereas in the full patient cohort no Graus threshold achieved a similar balance. Probability modeling showed APE2 ≥4 crossed 80% in all patients and 60% in antibody-negative patients. Exploratory analyses showed that APE2SM achieved the highest overall AUC.

Conclusion: APE2 score provides strong diagnostic discrimination and supports a practical cutoff of ≥4 for AE screening. Incorporating seizure and movement disorder weighting may further enhance sensitivity, particularly in antibody-negative cases, enabling earlier recognition and treatment.

S110*: Protein Kinase Signaling as a Downstream Target of Human Anti-NMDA Receptor Antibodies

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Background: The most common form of autoimmune encephalitis is associated with antibodies that target N-methyl-D-aspartic acid receptors (NMDARs). NMDARs play a pivotal role in neurotransmission and synaptic plasticity. Mounting evidence has shown that antibody targeting of the NMDAR GluN1 subunit, as in anti-NMDAR encephalitis, leads to NMDAR cross-linking and receptor internalization. However, the underlying signaling pathways affected by antibodies targeting NMDARs remain to be explored. We previously demonstrated that a human GluN1 monoclonal antibody 5F5 (GluN1 mAb 5F5) rapidly localizes to and regulates synaptic NMDAR function at native synapses of primary hippocampal neurons (Dean et al. Front Mol Neurosci 2022). Here, we sought to explore signaling targets of GluN1 mAb 5F5 in primary cortical neurons of either sex using biochemistry, subcellular fractionation, and label-free quantitative phosphoproteomics.

Methods: We employed subcellular fractionation of primary cortical neurons to generate synaptoneurosomes (SNs), enriched in presynaptic and postsynaptic elements, and postsynaptic density (PSD) fractions. We isolated SNs or PSD fractions after GluN1 mAb or Control mAb exposure to explore changes in synaptic signaling pathways.This approach enabled us to focus on GluN1 antibody-mediated synaptic pathology. A quantitative phosphoproteomic analysis using mass spectrometry identified kinase signaling cascades regulated by GluN1 mAbs compared to Controls mAb in SNs.

Results: Phosphoproteomic analyses by mass spectrometry demonstrate that GluN1 mAb 5F5 alters protein phosphorylation in SN fractions and regulates numerous synapse-related biological processes and protein kinase activities. Bioinformatic analyses suggest that these phosphoproteomic proteomic changes are positively correlated with NMDAR activation and negatively correlated with NMDAR inhibition. Together, these data suggest that GluN1 mAb 5F5 alters intracellular kinase signaling pathways in primary cortical neurons, likely by activating the NMDAR.

Conclusion: Anti-NMDAR encephalitis is the most common form of autoimmune encephalitis. The pathophysiology of this clinical syndrome remains poorly defined but is currently thought to involve pathogenic antibodies that crosslink and internalize NMDARs. We identify intracellular signaling pathways targeted by human NMDAR antibodies in primary cortical neurons. Our key findings are obtained using specific, patient-derived human monoclonal antibodies with high affinity to the GluN1 subunit of NMDARs, which have been shown to induce key pathogenic effects of anti-NMDAR encephalitis. These studies expand the underlying pathophysiological molecular mechanisms involved in anti-NMDAR encephalitis.

S111: From Fragmentation to Standardization: Developing an Outpatient Autoimmune Neurology Clinic

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Background: Clinical care for patients with suspected autoimmune encephalitis (AIE) and paraneoplastic neurological syndromes (PNS) is often fragmented, leading to delayed diagnosis, unnecessary testing, and inconsistent use of validated diagnostic frameworks. Dedicated subspecialty clinics may improve efficiency and diagnostic accuracy, but practical models and implementation strategies remain underreported.

Methods: We describe the development of an outpatient autoimmune neurology clinic and evaluate its role in standardizing diagnostic approaches to suspected AIE and PNS. We established a specialized outpatient autoimmune neurology clinic using a structured referral, triage, and evaluation model. Standardized workflows incorporated phenotype-based templates, centralized record acquisition, and systematic application of validated clinical scores to guide diagnostic testing and antibody interpretation. We performed a retrospective analysis of the first 50 consecutive patients evaluated, including demographics, referral patterns, time to evaluation, prior testing, antibody panel utilization, need for repeat testing, and concordance between referral and final diagnoses.

Results: Fifty patients were evaluated following screening of 77 referrals. Patients were predominantly female with a mean age in the mid-50s. Most had extensive prior workup, including neuroimaging and neuroglial antibody testing. A substantial proportion of externally obtained antibody panels required repeat testing to meet gold-standard criteria. Application of validated clinical scores improved stratification of patients undergoing antibody evaluation and supported more targeted diagnostic pathways. The clinic model reduced time to key diagnostic studies through coordinated workflows and enabled systematic reinterpretation of prior results.

Referral diagnoses were frequently revised following standardized evaluation.

Conclusion: A structured autoimmune neurology clinic model enables standardized, high-value evaluation of suspected AIE and PNS. Integration of clinical scoring systems, centralized data review, and coordinated diagnostic workflows improves consistency in neuroglial antibody testing and diagnostic decision-making. This

model provides a framework for other centers seeking to develop subspecialty outpatient autoimmune neurology programs.

S112: Endothelial Cell Proteins as Biomarkers in Susac Syndrome

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Background: Susac syndrome (SS) is a rare immune-mediated microangiopathy affecting the brain, retina, and auditory labyrinth. Endothelial injury mediated by $CD8^+$ T cels is thought to be a central mechanism; however, no circulating disease biomarkers are known. We performed targeted serum proteomic profiling to identify circulating proteins with known endothelial cell associations as candidate biomarkers in SS.

Methods: Serum samples from four patients with definite or probable SS and eight neurologic controls were analyzed using data-independent acquisition mass spectrometry on a high-resolution Orbitrap platform. To enhance biological relevance and reduce multiple-testing burden, analyses were restricted to a predefined, biologically curated panel of endothelial cell surface– and membrane-associated proteins with evidence of expression in brain, retinal, and labyrinthine microvasculature. Proteomic data were analyzed using a two-stage framework. Detection frequency was assessed using Fisher's exact test to account for non-random missingness, and quantitative differences in protein abundance were evaluated using probabilistic dropout analysis, which models intensity-dependent missing values. Results were integrated for prioritization of candidate biomarkers.

Results: Following endothelial-focused filtering of the global proteomic dataset, 59 endothelial-associated proteins were quantified in serum. Detection-based analysis did not identify differences in protein presence between SS and control samples. Quantitative analysis identified six endothelial-associated proteins with nominal differences in abundance in SS ($p < 0.05$, unadjusted). Low-density lipoprotein receptor–related protein 1 (LRP1) was increased ($\log_2$ fold change $= +2.19$, $p = 0.0059$), whereas nectin cell adhesion molecule 2 (NECTIN2), melanoma cell adhesion molecule (MCAM), solute carrier family 27 member 4 (SLC27A4), P-selectin (SELP), and interleukin-6 signal transducer (IL6ST) were decreased ($\log_2$ fold change -1.38 to -1.89; all $p < 0.05$). These proteins are involved in endothelial barrier integrity, leukocyte–endothelial interactions, and inflammatory signaling pathways.

Conclusion: This exploratory study identifies a set of circulating endothelial-associated proteins that differ between SS and controls and are biologically consistent with endothelial dysfunction in SS. Although these findings did not meet significance after multiple testing correction and require validation, their functional coherence supports their potential relevance as biomarkers of disease-related vascular injury. Future studies incorporating larger cohorts, treatment-naïve sampling, and longitudinal analysis across disease stages will be critical to establish diagnostic and mechanistic utility.

S113: Minimal Symptom Expression with Claseprubart, an Active C1S Inhibitor, in Patients with Generalized Myasthenia Gravis

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Background: The classical complement pathway plays a significant role in generalized myasthenia gravis (gMG) pathology. Claseprubart is a potent monoclonal antibody that selectively targets the classical pathway by inhibiting active C1s (aC1s). Remission is a key goal in gMG and achieving minimal symptom expression (MSE) with claseprubart is a key treatment objective.

Methods: MaGic (NCT06282159), is a global Phase 2, randomized, double-blind, placebo-controlled trial. Patients treated with claseprubart (300mg, Q2W) were evaluated for MSE (MG-ADL ≤1 or QMG ≤3) compared with placebo p-values were one-sided and nominal significance was assessed at an alpha= 0.1. Outcomes include proportion of patients achieving MSE at Week 13 and anytime during the study, earliest timepoint of MSE achievement, and durability defined as sustained MSE for at least 6 weeks.

Results: At Week 13, 37% of claseprubart treated patients achieved MG-ADL-MSE versus 14% with placebo (OR 3.81; p=0.0550). 43% achieved MG-ADL-MSE at least once during the study versus 14% of placebo (OR: 4.72; p=0.0231). This effect was observed as early as Week 1 (median time to response was Week 3). Sustained remission-like states (for at least 6 weeks) were seen in all patients who achieved MSE. Similar results were observed using QMG minimum symptom expression threshold.

Conclusion: Claseprubart patients were more than four times more likely to achieve MSE than placebo patients and MSE was observed as early as week 1. Patients who achieved MSE maintained responses for at least 6 weeks. These results highlight the therapeutic potential of aC1s inhibition in AChR+ gMG.

S114: Riliprubart in CIDP: Time and Magnitude of Response Analysis from a Phase 2 Trial

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Background: Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s

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in classical complement pathway and can be self-administered subcutaneously via auto-injector. In Phase-2 trial (NCT04658472), riliprubart demonstrated favorable safety and encouraging efficacy in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Here, we present time and magnitude of response analyses to characterize clinical benefits.

Methods: The open-label Phase-2 trial evaluated riliprubart across three groups: Standard-of-care (SoC)-Treated, SoC-Refractory, and SoC-Naïve. Participants received 24-week treatment (Part-A), followed by an optional 52-week treatment-extension (Part-B). Primary endpoint (Part-A) evaluated percentage of participants relapsing in SoC-Treated (≥1-point increase in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability score) and percentage of participants responding in SoC-Refractory/Naïve groups (≥1-point decrease in adjusted INCAT score). This post hoc analysis focused on INCAT responders (≥1-point decrease) in Part-A, and evaluated time-to-first-response, and proportion of participants with deep response (≥2-point decrease), overall, and by baseline INCAT score (3–4 versus ≥5).

Results: Among 43 INCAT responders in Part-A, first INCAT response was observed as early as Week-2 with ≥44% of first responses achieved by Week-4, and ≥89% by Week-12 in all three groups. At the last INCAT assessment through Week-24, 44% (19/43) responders achieved deep response with higher rates in participants with severe baseline impairment (INCAT ≥5: 69% [11/16]) versus moderate impairment (INCAT 3–4: 38% [8/21]).

Conclusion: Riliprubart provided rapid and substantial improvement in INCAT score with majority of responders achieving first response by Week-12 and nearly half of responders achieving deep response (≥2-point decrease); supporting Phase-3 development of riliprubart as a potential treatment for people with CIDP.

S115*: Safety and Efficacy of Riliprubart in CIDP: 76-week Phase 2 Trial Results

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Background: Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated C1s in the classical complement pathway and can be self-administered subcutaneously via an auto-injector. Preliminary results from an ongoing Phase-2 trial (NCT04658472) evaluating riliprubart in participants with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) suggested encouraging clinical benefits and safety profile up to 48 weeks. Here, we report efficacy and safety results of riliprubart at Week-76.

Methods: This open-label, Phase-2 trial evaluates riliprubart across three groups: Standard-of-care (SoC)-Treated, SoC-Refractory, and SoC-Naïve. Participants undergo 24-week treatment (Part-A), followed by an optional treatment extension (Part-B: 52 weeks). Primary endpoint (Part-A) is % of participants relapsing (SoC-Treated) or responding (SoC-Refractory/Naïve), defined as ≥1-point change in adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. Part-B evaluates safety and efficacy-durability based on % relapse-free participants (SoC-Treated) or with sustained response (SoC-Refractory/Naïve), defined as no increase in adjusted INCAT score ≥2-points at Week-76 relative to Week-24. Exploratory endpoints include additional efficacy measures (INCAT, IRODS, MRC-SS, grip-strength), change in total-complement, and plasma neurofilament-light chain levels.

Results: At Week-24, Part-A pre-specified interim analysis showed 87% (N=42/48) SoC-Treated participants improved/remained stable (improved: 52%; N=25/48) after directly switching from SoC to riliprubart. 50% (N=9/18) SoC-Refractory, and 75% (N=9/12) SoC-Naïve participants responded to riliprubart. As of August 2024, in SoC-Treated group, 81.3% (N=39/48) participants entered Part-B, including 47.9% (N=23/48) completed Part-B treatment period (ongoing: 27.1%; discontinued: 6.3%). In SoC-Refractory and SoC-Naïve groups, 72.2% (N=13/18) and 50% (N=6/12) participants, respectively, entered Part-B, including 61.1% (N=11/18) in SoC-Refractory (ongoing: 0%; discontinued: 11.1%) and 16.7% (N=2/12) in SoC-Naïve group (ongoing: 8.3%; discontinued: 25%) completing Part-B treatment-period. Updated full Part-B efficacy and safety data up to Week-76 will be presented at meeting.

Conclusion: Mature Week-76 results may suggest potential for riliprubart to demonstrate sustained clinical effect in participants who experience failure/inadequate response or residual disability despite SoC therapy, supporting its development in Phase-3, and potentially offering a new treatment option for people with CIDP.

S116: Tracking TREC: Investigations into a Biomarker with Prognostic Potential for PML

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Background: Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic infection of the central nervous system (CNS) with high mortality. PML occurs in the setting of profound immune suppression, such as HIV infection, primary immunodeficiencies, or immunomodulatory medications administered to manage immune dysregulation. There is currently no approved treatment for PML, so therapeutic strategies are rooted in facilitating immune reconstitution. In patients with severe and pervasive immune dysregulation, absolute lymphocyte counts often do not accurately reflect ability to control infection. Measurement of T-cell receptor excision circles (TRECs) in blood, a proxy for thymic function, has been identified as a potentially valuable biomarker for predicting immune recovery and survival after initiation of combination antiretroviral therapy in HIV patients and after hematopoietic stem cell transplant. We hypothesize that TREC measurements may likewise be useful in predicting potential for immune reconstitution in patients with PML.

Methods: DNA was isolated from peripheral blood mononuclear cells of a cohort of 22 patients using the QIAamp® DNA Blood Mini Kit. TREC levels were quantified by ddPCR using a Bio-Rad® QX200 Droplet Digital PCR System and normalized to T-cell receptor alpha constant (TRAC) gene expression levels to determine TREC frequency relative to lymphocyte count. Statistical analysis was performed using Microsoft® Excel and Graphpad Prism for macOS.

Results: While absolute lymphocyte counts were not significantly different between survivors and non-survivors, Mann-Whitney U tests revealed that survivors of PML had significantly higher initial lymphocyte-normalized TREC levels ($p = 0.0180$) and maximal rate of increase in TRECs ($p = 0.0025$) over the course of their treatment than non-survivors. Initial TREC and TREC rates of change were not significantly different between patients who experienced immune reconstitution inflammatory syndrome (IRIS) and those who did not. TREC levels were weakly negatively correlated with JCV copy number in cerebrospinal fluid at each timepoint (Spearman's $\rho = -0.2499$, $p = 0.0306$), and moderately negatively correlated with change in JCV copy number over treatment course (Spearman's $\rho = -0.5018$, $= 0.0418$). TREC levels were not found to be significantly correlated with CD4 or CD8 antiviral response, but the small sample size limited statistical power.

Conclusion: Baseline TREC measurement shows promise as a prognostic biomarker of patients with PML with greater potential to control infection. Furthermore, change in TREC over clinical course may be a valuable blood biomarker for tracking immune reconstitution. These preliminary data support further development and validation in larger cohorts.

S117: T-Cell-Mediated Molecular Mimicry Between SARS-CoV-2 and GAD65: Immunoinformatic Evidence that SARS-CoV-2 can trigger or worsen GAD-positive Stiff Person Syndrome

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Background: Stiff person syndrome (SPS) is a neuroimmunological disorder characterized by impaired GABAergic inhibitory neurotransmission and high-titer GAD65 antibodies against linear GAD epitopes. Because GAD is an intracellular antigen and GAD-antibodies do not correlate with disease severity, their pathogenic role remains unclear. Although convergent evidence supports a T-cell-mediated mechanism driven by GAD65-reactive T cells, it is uncertain what breaks tolerance and leads to T-cell activation and SPS symptomatology. SPS and GAD65-spectrum disorders have shown temporal associations with viral infections, particularly SARS-CoV-2, paralleling observations in GAD65-positive Type-1 Diabetes (T1D), suggesting possible molecular mimicry. In a referral-center, among 120 followed GAD-positive SPS patients, a worsening symptomatology was historically triggered or objectively documented after COVID-19 in 10 patients with clear temporal association and steady disease progression in 9 of them. Such a biological plausibility could be however supported only if a COVID-19 viral epitope shares sufficient linear sequence and TCR-facing homology with a self GAD65 epitope processed and presented by shared HLA alleles.

Methods: We performed a two-phase immunoinformatic analysis to investigate $CD8^+$ T-cell cross-reactivity using 3,248 IEDB-reported SARS-CoV-2 T-cell epitopes and 2,204 predicted HLA class I-binding peptides, with 613 IEDB-reported GAD65 linear epitopes and 1,733 predicted HLA class I-binding peptides. Phase 1 performed epitope screening using: (i) local sequence alignment (Smith-Waterman/BLOSUM62) against GAD65 epitope datasets and full-length GAD65 sequence; (ii) HLA class I binding prediction (NetMHCpan 4.1) across supertypes covering 97% global population; and (iii) processing/presentation filters (NetCTLpan, MHC-flurry 2.0, PRIME v2.1, NetMHCStabPan). Phase 2 integrated TCR-pMHC structural modeling (TCRpMHCmodels-1.0, TCRmodel 2.0) with HLA-matched TCR clonotypes, quantifying geometric and biophysical similarity.

Results: Phase 1 identified 8 epitope pairs with high sequence similarity between SARS-CoV-2 and GAD65; 5 pairs showed allele-concordant HLA class-I presentation and 3 passed all prespecified immunoinformatic criteria. The top-ranked pair, derived from the SARS-CoV-2 Spike glycoprotein, shared a conserved TCR-facing N(L/I)LLQY motif that was predicted to be presented by HLA class I alleles within extended SPS-enriched DR3-DQ2 and T1D-associated DR4-DQ8/DR3-DQ2 haplotypes. The Phase 2 structural modeling for the top-ranked pair supported similar TCR-facing electrostatic topology, consistent with cross-reactive $CD8^+$ T-cell recognition.

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Conclusion: Based on sequence-to-structure analysis, there is computational evidence of T-cell molecular mimicry between SARS-CoV-2 and GAD65 that provides a biologically plausible mechanism linking SARS-CoV-2 exposure to triggering or worsening SPS symptomatology in genetically susceptible individuals; an ex vivo epitope validation can be further confirmatory.

S118*: Miv-cel CD19 CAR T-Cell Therapy in Stiff Person Syndrome (SPS) in a Pivotal, Multicenter, Phase 2 Study (KYSA-8): Efficacy and Biomarker Analysis of Patients With ≥6 Months of Follow-up

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Background: SPS is a progressive, autoimmune neurologic disease characterized by muscle stiffness and painful spasms, leading to substantial disability. Miv-cel (mivocabtagene autoleucel; formerly KYV-101) is a fully human, autologous CD19 CAR T-cell therapy with CD28 costimulation in development for SPS and other autoimmune diseases. In the KYSA-8 primary analysis, a single dose of miv-cel resulted in significant improvement (P=0.0003) in timed 25-foot walk (T25FW) at 16 weeks and immunotherapy-free remissions with a consistent, well-tolerated safety profile in patients with SPS. This analysis evaluated miv-cel in patients from the KYSA-8 primary analysis with ≥6 months of follow-up.

Methods: Adults with SPS with inadequate response to immunomodulatory therapies received lymphodepletion followed by a single infusion of miv-cel. Primary endpoints were the change from baseline to week 16 in the T25FW and safety. Secondary endpoints were modified Rankin scale (mRS), distribution-of-stiffness index (DSI), heightened sensitivity scale (HSS), and Hauser ambulation index (HAI). Exploratory endpoints included biomarker analyses of T- and B-cell populations, cytokines, and GAD65-IgG levels.

Results: Overall, 26 patients were treated. AEs were consistent with those expected from lymphodepletion and CAR T therapy. Grade 1/2 CRS and Grade 1 ICANS occurred in 92.3% and 11.5% of patients, respectively; all resolved without sequalae. Sixteen patients completed the 6-month visit with a median follow-up of 7.5 months (range, 6-12.2). In this subset, significant improvement (P=0.0025) in T25FW of median -5.7 seconds (50.9% median improvement) was observed at week 16 and sustained at month 6 (median -6.0 seconds; 44.4%). mRS, DSI, HSS, and HAI showed significant mean improvements at week 16 of -0.6 (SD, 0.72; P=0.0017), -2.0 (1.67; P=0.0001), -2.5 (1.75; P<0.0001), and -1.9 (1.20; P<0.0001) points, respectively, all of which were sustained at month 6. Deep B-cell depletion was observed, associated with immune reset, with reductions from baseline in GAD65-IgG observed at month 6. Nine of 16 (56%) patients showed B-cell reconstitution by 6 months, with increased naïve B cells and decreased class-switched memory B cells, associated with increase in Tregs.

Improvements in efficacy endpoints were comparable between patients with and without B-cell reconstitution. At last follow-up, all patients remained free of immunomodulatory therapies for SPS.

Conclusion: In this analysis of patients with the longest follow-up in KYSA-8, a single dose of miv-cel resulted in durable immunotherapy-free remissions to 6 months, demonstrating a highly effective therapy with ongoing clinical benefit following B-cell reconstitution. Additional biomarker analyses, including autoantibodies, cytokines, and expanded immunophenotyping will be presented.

S119: HLA-DRB1*03 and HLA-DRB1*03:01 in Neuromyelitis Optica Spectrum Disorder Susceptibility: A Systematic Review and Dual Meta-Analysis of Case-control Studies

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Background: HLA class II alleles have been individually associated with Neuromyelitis Optica Spectrum Disorder (NMOSD) susceptibility, but no meta-analysis has quantified the pooled effect of HLA-DRB1*03 across resolution levels and European, East Asian, admixed, Afro-Caribbean, and South Asian populations. We systematically characterized this association by identifying studies reporting allelic or phenotypic frequencies of HLA-DRB1*03 or HLA-DRB1*03:01 in NMOSD patients compared with healthy controls.

Methods: Following PRISMA guidelines (PROSPERO: CRD420261376834), a systematic search of PubMed, Cochrane, and Embase was conducted. To avoid unit-of-analysis heterogeneity, two separate meta-analyses were performed: a chromosome-level analysis for studies reporting low-resolution HLA-DRB1*03, and a phenotype-level analysis for studies reporting high-resolution HLA-DRB1*03:01. Pooled odds ratios were estimated using R-based random-

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effects models with REML. Heterogeneity was assessed using I^2 and Cochran's Q, with leave-one-out sensitivity analyses.

Results: Thirteen case-control studies (2009-2026) were included, comprising 1,671 NMOSD patients and 10,262 healthy controls. Diagnostic criteria varied between Wingerchuk 2006 and IPND 2015, while AQP4-IgG weighted mean seropositivity was 88.6% (range 44.8-100%). HLA typing was either low or high-resolution, with heterogeneous sample sizes. Six studies were excluded from pooled analyses: four for failing Bonferroni correction for DRB1*03, identifying ethnicity-specific alleles including HLA-DPB1*05:01 and HLA-DQB1*04; one (Zhong, 2021) for reporting HLA-DRB1*16:02 despite surviving correction; and one (Estrada, 2018) for using SNP imputation rather than classical HLA typing. For Alonso (2018), OR was recalculated to phenotypic carrier counts (2.00 [0.71–5.65]) to maintain unit-of-analysis consistency. The remaining seven studies demonstrated significant associations: NMOSD was significantly associated with both low-resolution HLA-DRB1*03 (pooled OR 2.44; 95% CI: 1.66-3.56; $p < 0.0001$) and high-resolution HLA-DRB1*03:01 (pooled OR 3.12; 95% CI: 2.40-4.04; $p < 0.0001$). Both analyses showed no heterogeneity ($I^2 = 0\%$) and remained significant in leave-one-out analyses across diverse ancestries.

Conclusion: Our findings suggest that HLA-DRB1*03 and HLA-DRB1*03:01 are susceptibility alleles for NMOSD across different populations. By separating low and high-resolution analyses, our study provides the first pooled evidence that HLA-DRB1*03:01 may represent the primary risk allele driving the broader DRB1*03 association. These results support the immunogenetic distinction between NMOSD and multiple sclerosis (where DRB1*15:01 predominates), while encouraging future large-scale studies with AQP4-IgG stratification and standardized four-digit HLA typing to further characterize haplotype-specific contributions to seropositive NMOSD risk.

S120: Tuberculosis and Disease-Modifying Therapies in Multiple Sclerosis: A Retrospective Case Series

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Background: Patients with Multiple Sclerosis (MS) receiving Disease-Modifying Therapies (DMTs) may have increased risk of reactivation of latent infections, including Tuberculosis (TB). Although screening before treatment initiation is important, Latent TB Infection (LTBI) and active TB remain poorly characterized in this population, particularly in endemic regions. We described cases of active TB and LTBI among patients with MS followed at a referral center in Paraiba, Brazil.

Methods: This is a retrospective case series based on medical records from the Multiple Sclerosis Reference Center of Paraíba between January 2019 and March 2026. Patients with Relapsing-Remitting MS (RRMS) who developed active TB or LTBI were included. Diagnostic assessment included tuberculin skin testing (PPD, positivity threshold ≥5 mm in immunocompromised patients per Brazilian Ministry of Health guidelines), sputum smear microscopy, and chest radiography. DMT status at TB or LTBI diagnosis was recorded. Treatment regimens were described, including isoniazid alone, isoniazid combined with rifapentine or rifampicin, and a prolonged regimen for active TB.

Results: Among the six included cases, all receiving natalizumab (mean age 30.5 years, range 21–39; three female, three male), 66.7% (n=4) were classified as LTBI and 33.3% (n=2) as active TB. Diagnostic criteria included a positive tuberculin skin test in 83.3% (n=5) and positive sputum smear microscopy in 16.7% (n=1). In 33.3% (n=2), LTBI was identified during initial screening before DMT initiation. In the other 66.7% (n=4), TB-related diagnosis or treatment occurred after DMT initiation, including one patient also receiving immunoglobulin therapy. Treatment included isoniazid alone or combined with rifapentine/rifampicin for LTBI, and one patient required a prolonged regimen due to persistent positive sputum smear microscopy at month three. Regarding outcomes, four patients had documented treatment completion or favorable clinical evolution; two were still undergoing treatment at last assessment. No deaths or recurrences were recorded.

Conclusion: The clustering of TB-related diagnoses in natalizumab-treated patients from an endemic region reinforces the importance of systematic pre-treatment screening and heightened vigilance during treatment. Early LTBI identification and preventive therapy may reduce clinical complexity and support safer outcomes in this population.

S121: Deciphering patterns of Functional Neurological Disorder (FND) in patients referred for Stiff-Person syndrome (SPS)

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Background: SPS is an autoimmune hyperexcitability disorder characterized by muscle stiffness, painful spasms and exaggerated startle responses. Diagnosis relies on clinical findings of truncal and limb stiffness concurrently in agonist/antagonist muscles, hyperlordosis and stiff gait associated with high-GAD-antibody titers. Because symptoms of painful muscle spasms, stiffness, startles and ambulatory dysfunction are not unique to SPS but frequently observed in other neurological diseases, especially FND, such overlapping clinical

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symptomatology results in frequent misdiagnoses necessitating the need for precisely delineating FND among SPS subsets. The objective of this study is to characterize the frequency and clinical features consistent with FND in patients referred for suspected SPS.

Methods: We conducted chart reviews of patients referred to our Center for evaluation of SPS to identify characteristics of patients subsequently re-classified as having FND. Data collected included age at symptom-onset, time to diagnosis, prior neurology evaluations, presenting symptoms, neurological findings, GAD-antibody levels, electrophysiology, and neurologic or psychiatric comorbidities. Patients were included in the cohort if their clinical and laboratory findings were inconsistent with SPS and reclassified as being more consistent with FND. Ambiguous cases were independently reviewed by two neurologists to determine eligibility for inclusion.

Results: Among 119 cases, 16 (13.4%) were reclassified as non-SPS, and mostly FND, with 1 having both SPS and FND. 9 (56%) were females and 7 (44%) males. The average age of symptom onset was 42.5 y/o and time to re-diagnosis 4.78 years; 2 patients had prior confirmed diagnosis of SPS. The main presenting features in all 16 patients were: prominent spasms (n=15); intense muscle pains (n= 11), muscle stiffness (n=10); abnormal movements (uncontrolled jerking, limb contortions, tremors) (n=6); and weakness (n=3). 13/16 had various psychiatric diagnoses and all reported anxiety disorder. The main findings resembling SPS on examination were: paraspinal or abdominal stiffness and brisk reflexes with overactive functional spread (n=5); and unusual patterns of episodic spasms with falls even during the clinic exam or on provided videos. All 16 were GAD-ab-negative except of 2 with low-serum GAD-ab titers and negative CSF; SPS-specific electrophysiology in at least 9 studied patients was normal. 50% had been previously prescribed benzodiazepines with all but one reporting symptomatic improvement.

Conclusion: Among referred patients, distinction between seronegative SPS and FND is challenging requiring comprehensive evaluation due to overlapping clinical features; painful spasms and even mild stiffness do not exclude FND. Atypical patterns of spasmodic falls, normal electrophysiology, inconsistently intense painful spasms and persistent requests for benzodiazepines, provide key diagnostic clues.

S122: Enterovirus-associated Acute Flaccid Myelitis In A Person With Multiple Sclerosis On Anti-CD 20 Therapy: A Case Report

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Background: Acute flaccid myelitis (AFM) is a polio-like neurologic complication associated with non-polio enteroviruses and flaviviruses. AFM is fundamentally distinct from autoimmune multiple sclerosis (MS) myelitis, with underlying grey matter pathophysiology and seasonal occurrence. Although primarily a pediatric disorder, AFM can affect immunocompetent adults and patients on chronic immunosuppressive therapies. The true prevalence of AFM in persons with MS (PwMS) is unknown. Immune therapies may alter innate immunity and increase the risk of neurotropic viral complications. In PwMS, distinguishing a de novo viral CNS infection from an MS relapse poses additional diagnostic challenges, as the prodromal event (e.g., upper respiratory illness) may be subtle or absent, and the pathogenic hallmark of anterior horn cell involvement may be missed and left untreated.

Methods: We describe a 46-year-old male with a 25-year history of MS, stable on anti-CD20 therapy since February 2025, also on hydroxychloroquine and mycophenolate for inflammatory arthropathy, who presented to the ER with a 3-day history of rapid-onset flaccid left arm weakness without sensory deficit, in the setting of preexisting paraparesis and two months of unexplained weight loss. MRI of the brain and cervical cord showed no enhancement or diffusion abnormalities. Malignancy workup was negative. A course of IV methylprednisolone followed by plasma exchange and physical therapy did not result in neurologic improvement. EMG performed two months after the onset of flaccid weakness demonstrated a diffuse lower motor neuron disorder with prominent denervation in bilateral cervical myotomes. CSF revealed an inflammatory profile with protein of 164 mg/dL and elevated neurofilament light chain. Coxsackie A enterovirus was detected in the CSF by PCR.

Results: Rapid development of flaccid limb weakness without sensory deficits, corroborated by EMG findings, inflammatory CSF profile, and enterovirus detection in CSF, supported the diagnosis of virally induced AFM. The presence of preexisting MS paraparesis likely diminished diagnostic sensitivity. Detection of enterovirus more than two months after symptom onset suggests a blunted febrile prodrome and impaired viral clearance in the context of chronic immunosuppression.

Conclusion: This case highlights the importance of recognizing AFM in PwMS receiving chronic immunosuppressive agents who present with rapid-onset flaccid weakness without commensurate sensory involvement or demyelinating radiographic correlate. AFM should remain in the differential diagnosis in this population. Long-term viremia may enhance the pathogenic potential of neurotropic viruses, particularly in patients receiving multiple and prolonged immunomodulatory agents.

S123: Characteristics of Movement Disorders in Susac syndrome

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Background: Susac syndrome is a rare disease characterized by an inflammatory microangiopathy limited to the brain, eye, and ear vessels. Young women are primarily affected. Recent findings support a primitive vasculitis affecting the cerebral, retinal, and cochlear small arteries, although the mechanism remains unclear. The diagnosis is based on the

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identification of the triad: subacute encephalopathy, bilateral occlusion of the retinal arterial branches on fundoscopy, and neurosensorial hearing loss. Movement abnormalities are still underreported in the disease, though. We outline the types and prevalence of movement disorders found in the literature.

Methods: A thorough literature review was conducted using PubMed and Google Scholar, in accordance with PRISMA criteria. Movement disorders, tremors, chorea, dystonia, ataxia, myoclonus, nystagmus, and Susac syndrome are the terms that have been used. We considered ten studies in our analysis.

Results: A total of 189 patients were included, with a mean age of 31 $\pm$ 2.16 years and 72.5% being female. Ataxia was identified in 84.7% of cases (160 out of 189 patients), while eye movement abnormalities, including nystagmus or saccadic ocular pursuit, were present in 15.3% (29 out of 189 patients). Some patients exhibited more than one type of movement disorder.

Conclusion: Among those with Susac syndrome, ataxias are among the most reported movement disorders. Clinicians should be aware of these symptoms to aid in differential diagnosis.

S124: Isolated Sixth Nerve Palsy as the Initial Presentation of Multisystem IgG4-Related Disease: A Diagnostic Challenge

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Background: Immunoglobulin G4-related disease (IgG4-RD) is a rare, chronic, immune-mediated fibroinflammatory disorder characterized by tumefactive lesions and dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells across multiple organ systems[1]. Neuro-ophthalmologic manifestations of IgG4-RD are well-documented, particularly in the setting of orbital inflammation or lacrimal gland involvement[2]; however, these complications are often seen as long-term effects of inflammation and fibrosis[3]. Isolated cranial neuropathies without overt orbital symptoms are not well-documented. Here, we report a case of IgG4-RD presenting initially as isolated binocular diplopia due to sixth cranial nerve dysfunction.

Methods: A 45-year-old woman with no significant past medical history presented with acute onset painless binocular diplopia that progressed over two days. Neurologic examination revealed dysconjugate gaze with impaired abduction of the right eye, without any other cranial nerve, motor, or sensory deficits. Initial CT imaging of the head did not reveal any evidence of hemorrhage or infarct but demonstrated bilateral soft tissue thickening of bilateral globes and the cavernous sinus. MRI confirmed enhancing globe and cavernous sinus fullness, raising suspicion for inflammatory, neoplastic, or infiltrative processes. Further systemic imaging demonstrated diffuse soft tissue thickening surrounding the aorta, bilateral kidneys, and omentum, raising concern for systemic inflammatory or infiltrative disease.

Results: Laboratory studies revealed elevated inflammatory markers but were otherwise nonspecific. Given persistent concern for systemic disease, a perinephric tissue biopsy was obtained. Histopathologic analysis demonstrated dense lymphoplasmacytic infiltrates composed of plasma cells, lymphocytes, eosinophils, and fibroblasts. Immunostaining confirmed increased IgG4-positive plasma cells, supporting the diagnosis of IgG4-RD. The patient was treated with systemic glucocorticoid therapy, resulting in improvement of diplopia.

Conclusion: This case illustrates an unusual presentation of IgG4-RD manifesting as isolated binocular diplopia due to presumed sixth cranial nerve involvement. While IgG4-related orbital disease commonly presents with lacrimal gland enlargement, orbital pseudotumor, or chronic inflammatory features, isolated cranial neuropathy without prominent orbital symptoms is rare. The variable clinical spectrum of IgG4-related disease highlights the need to characterize emerging presentations, enabling clinicians to recognize subtle manifestations earlier and initiate treatment before irreversible fibrosis develops. Recognition of atypical neurologic presentation is essential to facilitate timely diagnosis and treatment of potentially progressive systemic disease. References: 1. Katz G, Stone JH. Clinical Perspectives on IgG4-Related Disease and Its Classification. Annu Rev Med. 2022;73(1):545-562. doi:10.1146/annurev-med-050219-034449 2. Miyabe K, Zen Y, Cornell LD, et al. Gastrointestinal and Extra-Intestinal Manifestations of IgG4–Related Disease. Gastroenterology. 2018;155(4):990-1003.e1. doi:10.1053/j.gastro.2018.06.082 3. Chwalisz BK, Stone JH. Neuro-ophthalmic complications of IgG4-related disease. Current Opinion in Ophthalmology. 2018;29(6):485-494. doi:10.1097/ICU.0000000000000523

S125*: Post anti-CD19 CAR-T Cell Therapy Immune Response in Treatment Refractory Multiple Sclerosis

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Background: Despite the success of B cell depleting therapies in relapsing forms of multiple sclerosis (MS), many patients

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with progressive forms of MS continue to experience worsening disability. This may be due to central nervous system (CNS) resident B cells that are resilient to peripheral B cell depletion by anti-CD20 monoclonal antibodies. CD19-targeted chimeric antigen receptor (CAR)-T cells offers the promise to deplete B cells in the peripheral immune system and within the CNS. We were able to immunologically and proteomically profile longitudinal blood and cerebral spinal fluid (CSF) from 2 participants treated with KYV-101, a fully human autologous second generation CAR-T cell.

Methods: Adult participants with treatment refractory progressive MS, defined as evidence of clinical disability progression within the 2 years prior to inclusion despite at least 1 year of treatment for progressive MS were screened for enrollment. Two participants were treated with 0.33×108 CAR-T cells intravenously after a preconditioning regime of cyclophosphamide and fludarabine. Key study procedures included longitudinal blood and CSF sampling, MRI neuroaxis, and monitoring standard laboratory parameters, neurologic status, surveys, and expanded disability status scale (EDSS) regularly through the follow up period. We analyzed biologic samples via flow, single cell analysis, and proteomics.

Results: Patient 1 (55F, EDSS 6, dosed Aug 2024) had no cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS). CSF CAR-T cells were detected at day 14 with sustained oligoclonal band (OCB) clearance at week 24 and 48 despite peripheral naive B cell reconstitution; immune profiling showed effector predominance and upregulated trafficking markers. A day-32 cutaneous eruption from an endogenous T cell response requiring oral steroids. MRI was stable at week 48; EDSS improved to 4 by week 24 and remained stable at week 48. Patient 2 (63F, EDSS 4.5, dosed Mar 2025) had grade 1 CRS, no ICANS, and CSF CAR-T expansion at day 14. EDSS transiently rose to 5 during her washout, returning to 4.5 by week 24 and remained stable. MRI stable at week 48; proteomics showed mild inflammatory decreases. More in depth analysis in currently ongoing.

Conclusion: This study addresses the unmet need for effective therapies in progressive MS. Early results suggest anti-CD19 CAR-T cell therapy is safe in MS patients and penetrate the CSF effectively. We have further noted stabilization of EDSS scores despite their prior progression and evidence of a deep depletion and less inflammatory background in our 2 participants.

S126: Permissive Central Tolerance and Defective Peripheral Tolerance as Sequential Steps to License CASPR2-directed Pathology

Presenting Author: *Sarosh Irani, Ponte Vedra Beach, FL*

Background: Autoantibody-mediated diseases targeting one autoantigen provide a unique opportunity to comprehensively understand the development of disease-causing B-cells and autoantibodies. In neurology, multiple such diseases exist whereby studying one in detail may offer cross-condition paradigms of immune tolerance and, hence, etiology. Convention suggests such autoreactivities are generated during germinal center reactions. Here, we explore earlier immune checkpoints, focusing on patients with CASPR2-autoantibody encephalitis.

Methods: B cell flow cytometry and sorting, cell culture, recombinant antibody generation and determination of biophysical characteristics including kinetics and cross competition. Recombinant antibodies were test in dissociated neuronal cultures and in vivo injections.

Results: In both disease and health, high (~0.5%) frequencies of unmutated CASPR2-reactive naïve B-cells were identified. By contrast, CASPR2-reactive memory B-cells were exclusive to patients, and their B-cell receptors harbored affinity-enhancing somatic mutations. These mutated B cell receptors showed pathogenic effects in neuronal cultures and mice, including CASPR2 internalization, AMPA receptor dysfunction and spatial memory deficits. The unmutated, precursor memory B-cell receptors often retained binding to CASPR2, suggesting a loss of early tolerance. Further, these CASPR2-binders showed a distinctive balance between strong CASPR2 reactivity and very limited binding across the remaining human proteome, thus identifying a balance between specificity and broad reactivity which may permit select CASPR2-reactive cells to break immune checkpoints.

Conclusion: Our results identify permissive central tolerance, defective peripheral tolerance and autoantigen-specific tolerance thresholds in humans, as sequential steps which license CASPR2-directed pathology. These data provide a roadmap to study autoantibody-mediated conditions. By leveraging the basic immunobiology, we rationally direct tolerance-restoring approaches, with an experimental paradigm applicable across autoimmunity

S127: State-Level Variation in Medicaid Coverage and Utilization of High-Efficacy Therapies for Multiple Sclerosis

Presenting Author: *Mihir Kakara, NYU Grossman School of Medicine New York, NY*

Background: Patients on Medicaid are less likely to receive MS DMTs and experience worse disability outcomes. Early initiation of high-efficacy DMTs (HET) such as anti-CD20 agents and natalizumab improves long-term outcomes, but may delayed by utilization management strategies such as preferred drug lists (PDLs) and prior authorization. Quantifying variation in these policies and their impact on treatment patterns is critical for addressing disparities, as historically marginalized populations are overrepresented in Medicaid. Insurance-driven MS disparities remain understudied, particularly in Medicaid, and understanding how coverage translates into real-world use is key to identifying actionable policy levers. We evaluated state-level variation in Medicaid (i) coverage and (ii) utilization of HETs, and assessed how formulary design influences use.

Methods: We combined data from two complementary analyses. First, we evaluated 462 Medicaid PDLs (412 Managed Care Organization [MCO], 50 Fee-for-Service [FFS]) for 2024 to quantify coverage generosity (≥2 HETs listed as preferred) and consistency across states (≥1 HET listed). Second, we analyzed the 2024 Medicaid State Drug Utilization Data

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for 27 FDA-approved MS therapies to calculate state-level drug-utilization ratios (DURs), standardizing across formulations using a "days of use" approach. Regression models linked PDL generosity to DURs, adjusting for Medicaid expansion, enrollment, and MCO penetration.

Results: Drug formulary analyses revealed substantial variation both across and within states, with clusters of restrictive formularies in the Midwest and South. Overall, 42% of Medicaid plans lacked any HET in their plans, and only 24.7% met our definition of generous plans (≥2 HETs as preferred). Nine states had no plan with any HET as preferred, and thirteen states had no plan with an anti-CD20 drug. A higher proportion of FFS plans had a high-efficacy DMT in their formulary (70%), compared to MCO plans (58.7%). In utilization analyses, there was wide variation in HET use, with some states demonstrating high uptake of HET, while others relied more on lower- or moderate-efficacy DMTs. After adjustment, patients in MCO plans had a 17.9% lower likelihood of HET use ($\beta = -0.178$; 95% CI $= -0.33, -0.02$; $p = 0.026$), compared to FFS plans.

Conclusion: Significant variability in Medicaid drug formularies and real-world utilization of high-efficacy MS therapies across and within states. These findings suggest that payer design potentially shapes early access to standard-of-care treatment, and is a policy lever that can be used to address health disparities by harmonizing coverage criteria across states and plans to promote timely, effective treatment for Medicaid enrollees.

S128: Functional Neurological Disorder Mimicking AIDP: Anchoring Bias and Iatrogenic Risk in a Reversible Diagnostic Error

Presenting Author: *Soroush Kakawand, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States*

Background: Functional Neurological Disorder (FND) has an estimated prevalence of 50–100 per 100,000 and is the second most common reason for outpatient neurological consultation. FND can closely resemble Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP). Distinguishing between these entities is critical, as diagnostic uncertainty may lead to premature immunotherapy and reinforcement of diagnostic momentum-a cognitive bias related to anchoring-toward inflammatory neuropathies. Contemporary frameworks emphasize positive clinical signs of FND, with reported specificities of 64–100%, rather than exclusion alone; however, when presentations involve subacute flaccid weakness and electrophysiological studies are deferred, diagnostic overlap with AIDP remains a persistent challenge.

Methods: Case report and brief literature review.

Results: A 17-year-old right-handed female presented with subacute, progressive bilateral lower extremity weakness over several weeks, culminating in loss of independent ambulation. Sensation remained intact. Initial evaluation, including brain and neuroaxis MRI with and without contrast, demonstrated no structural abnormalities. CSF analysis revealed normal protein and cell counts, without albuminocytologic dissociation. Despite absent objective supportive findings, a presumptive diagnosis of AIDP was made, and the patient received five days of intravenous immunoglobulin (IVIG), followed by reported subjective improvement. She was readmitted weeks later with recurrent symptoms. Repeat examination demonstrated internally inconsistent weakness with preserved tone, 2+ upper extremity reflexes, and 1+ lower extremity reflexes-findings inconsistent with the diffuse areflexia typically observed in AIDP. A positive Hoover's sign supported a functional etiology. Repeat MRI and CSF findings remained unchanged. EMG/NCS were not obtained during the initial admission, representing a missed opportunity for early diagnostic clarification. The clinical presentation was most consistent with FND. The patient improved with physical therapy and was referred for multidisciplinary psychological management.

Conclusion: This case illustrates a diagnostic pitfall in which FND mimics AIDP, with early subjective response to IVIG introducing anchoring bias and reinforcing an incorrect diagnosis. Perceived treatment response without objective corroboration may paradoxically delay recognition of FND. Preserved reflexes, normal CSF, and internally inconsistent findings should raise doubt regarding a demyelinating etiology. Electrophysiological testing at initial presentation may improve diagnostic accuracy and reduce unnecessary immunotherapy exposure. This is particularly relevant given that CIDP misdiagnosis occurs in 15–50% of referred cases, often driven by overreliance on subjective treatment response. IVIG carries risks, including adverse events in 1–15% of infusions and thromboembolic complications in up to 4% of patients. Emphasis on positive clinical signs of FND can facilitate earlier diagnosis and reduce iatrogenic harm.

S129: Rare Case of Multiple Sclerosis (MS) and Coexisting Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) - Showcasing Diagnostic Insight From Markedly Elevated Cerebrospinal Fluid (CSF) Protein

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Co-Authors: *Brooke Guerrero, MD, Olive View-UCLA Medical Center Sylmar, CA, Robert Freundlich, MD, Olive View-UCLA Medical Center, Sylmar, CA*

Background: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a demyelinating disease of the peripheral nervous system characterized by lower motor neuron signs (weakness, numbness and areflexia) and elevated cerebrospinal fluid (CSF) protein (>100 mg/dL). Multiple sclerosis (MS) is a demyelinating disease of the central nervous system characterized by upper motor neuron signs (weakness, numbness, and hyperreflexia) and occasionally elevated CSF protein (50-100 mg/dL). Coexistence of MS and CIDP represents a rare overlap of immune-mediated demyelinating disorders leading to diagnostic ambiguity. This case report highlights a rare concurrence of MS and CIDP, emphasizing the pivotal role of cerebrospinal fluid (CSF) analysis in resolving complex diagnostic overlap.

Methods: We report a 47-year-old male, with a history of alcohol use disorder (16-18 beers/day), initially presenting with the bilateral distal lower extremity (LE) weakness, numbness, diffuse areflexia and bilateral Babinski signs.

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Results: Patient was diagnosed with multiple sclerosis (MS) per McDonald's Criteria by demonstrating dissemination in space with T2/FLAIR hyperintense lesions in cerebral white matter and three cervical cord lesions (C2–C3 and C3-C4), and dissemination in time as the patient had an enhancing lesion originally and new lesions in the brain and spinal cord on subsequent imaging. Five months post treatment patient relapsed with new weakness in his both arms and an inability to walk, with persistent areflexia and Babinski signs. Repeat MRI showed no new demyelination. Lumbar Puncture revealed an acellular, Oligoclonal Band-negative CSF but highly elevated CSF Protein of 276 mg/dL. Due to a very elevated CSF protein level electromyography/nerve conduction study (EMG/NCS) was performed, confirming chronic inflammatory demyelinating polyneuropathy (CIDP). The patient was subsequently treated with IVIG. Within three months of IVIG treatment for CIDP, the patient had complete resolution of both arm weakness and gait disability, achieving independence in his activities in the daily living (ADLs). Patient underwent CT scan which was negative for any malignancy and ruled out paraneoplastic syndrome. IVIG was eventually discontinued, and the patient was continued on prednisone with continued improvement of symptoms.

Conclusion: This unique case highlights a rare coexistence of MS and CIDP. Markedly elevated CSF protein provided the diagnostic clue to a dual diagnosis, prompting identification of coexisting CIDP. Treating both of his conditions with IVIG and Rituximab led to dramatic neurological improvement. Thus, while CSF analysis is not mandatory for MS or CIDP diagnosis, CSF examination can be invaluable, particularly in cases where the clinical course is atypical or does not align with expected disease trajectory.

S130: Extracellular Vesicles Derived from Normal Neurons Regulate Transcriptional Responses in Microglia to Reinforce a Homeostatic, Non-inflammatory State

Presenting Author: *Albert La Spada, Irvine, CA*

Co-Authors: *Martha Garcia, BA, University California, Irvine, Irvine, CA*

Background: Alzheimer's disease (AD), the most common form of dementia and a leading cause of death among older adults, demands not only effective therapeutics but also strategies aimed at preventing disease onset and progression. To this end, our research focuses on modulating microglial inflammatory responses using human stem cell derived models to better understand and ultimately counteract the neuroimmune dysfunction characteristic of AD. Microglia, which constitute 10% of the cells within the central nervous system, serve as the brain's immune system. In post-mortem tissue, these cells are found surrounding amyloid plaques, underscoring their significant role in AD pathology. Early in AD, microglia attempt to clear amyloid β (Aβ), but as the disease advances, their phagocytic capacity declines, and chronic, ineffective activation drives excessive inflammatory signaling that contributes to neurodegeneration.

Methods: Neurons and microglia continuously communicate to achieve a wide range of functions, particularly through bidirectional communication via extracellular vesicles (EVs). Here, we sought to leverage the ability of EVs to promote cellular communication by using them to reinforce maintenance of homeostatic, neuroprotective microglia as a therapeutic treatment against AD. Our findings demonstrate that pre treating microglia with EVs derived from iPSC generated normal healthy i3-neurons significantly reduces microglial expression of pro inflammatory cytokines such as IL 6, TNF α, and IL 1β. This anti-inflammatory effect is not achieved by EVs isolated from neurons carrying the P301S tau mutation. Healthy neuron EV exposure also decreases caspase 3/7 activity, limits aberrant migration toward pathogenic stimuli, and reduces cytokine secretion, collectively indicating a robust anti-inflammatory and pro survival effect.

Results: To elucidate the molecular mechanisms underlying this shift, we pursued unbiased transcriptome analysis. Single cell RNA seq revealed downregulation of NF κB, chemokine, and TNF signaling pathways, with transcription factor binding site analysis implicating RELA and NFKB1 as key regulators of these EV induced transcriptional changes. Given the regulatory potential of microRNAs (miRNAs), we also profiled EV cargo to determine if miRNAs are contributing to these protective effects. Comparative miRNA analysis between healthy i3 neuron derived EVs and P301S tau mutant i3 neuron-derived EVs demonstrated an enrichment of miRNAs associated with suppression of inflammatory signaling and blunting of migration via post transcriptional gene silencing.

Conclusion: These findings indicate that miRNA cargo contained within healthy neuron-derived EVs can inhibit microglial activation to an inflammatory and instead maintain microglia in a homeostatic, neuroprotective state, offering a novel avenue for therapeutic intervention in AD.

S131: Multiple Sclerosis Patients Treated with Ocrelizumab, Aged 70 and Older: A Retrospective Cohort Study

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Background: The recommendation to give disease modifying therapies in multiple sclerosis (MS) requires the adjudication of the risks and benefits over the disease course and life span, as its usage has now extended beyond the initial trials' populations' demographic. Limited data exists to inform treatment decisions for older adults.

Methods: A retrospective cohort subanalysis was performed with electronic medical records of MS patients aged ≥ 70 years from June 2017-January 2026 at Massachusetts General Hospital (data of censoring: 1/5/2026). From a larger cohort of 1,600 adults aged ≥ 55 years with MS, we identified 158 adults ≥ 70 years who received at least 600mg

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of ocrelizumab IV, compared to 297 controls aged ≥ 70 years who never received B-cell depleting therapies. We used inverse probability of treatment weighted negative binomial regression with person-time offsets to model outcome rates.

Results: Among 455 adults aged ≥ 70 years (68.4% female; median ages 74 (ocrelizumab) and 76 (controls)), the ocrelizumab group had a higher baseline disability (median EDSS 6.0 vs. 3.5) and a greater proportion of progressive MS phenotypes (61.4% vs. 27.6%); 47% had received ocrelizumab as third or higher-line therapy. Hypogammaglobulinemia (IgG<600 mg/dL) was recorded in 25.5% of ocrelizumab-treated patients vs. 14.1% of controls. Over 34,817 person-months of follow-up (6,341 ocrelizumab and 28,476 controls), there were 1,641 total infection events (347 ocrelizumab, 1,294 controls) and 182 infection-related hospitalizations (47 ocrelizumab, 135 controls). UTIs were the most common infection, followed by upper respiratory infections and COVID-19. Incidence rates in the ocrelizumab vs. control groups were 47.9 vs. 40.8 per 1,000 person-months for non-COVID infections and 7.41 vs 4.74 for infection-related hospitalizations. Six deaths occurred, all in the control group. Ocrelizumab was not associated with higher infection rates (adjusted IRR 1.06; 95% CI 0.72-1.56; p=0.76) nor infection-related hospitalizations (IRR 1.29; 95% CI 0.60-2.79; p=0.51). Higher EDSS independently increased the risk of infection-related hospitalization (IRR 1.62; 95% CI 1.36-1.92; p<0.001) but did not demonstrate increased risk in overall infection incidence. Age, gender, and MS duration were not associated with infection or hospitalization risk.

Conclusion: In MS patients aged ≥ 70 years with ocrelizumab exposure, we did not observe different rates of infection or infection-related hospitalization compared to untreated controls, despite a higher disability burden. Baseline EDSS was the strongest independent predictor of infection-related hospitalization.

S132: Comparative Efficacy and Safety of FDA-Approved Advanced Therapies for Generalized Myasthenia Gravis: A Network Meta-Analysis Incorporating CD19, FcRn, and Complement Inhibition

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Background: Generalized Myasthenia Gravis (gMG) management has been transformed by advanced therapies targeting the autoimmune cascade. This analysis evaluates the comparative efficacy and safety of FcRn blockers, complement inhibitors, and the recently FDA-approved CD19-targeted B-cell depleter, inebilizumab. These precision medicines offer targeted alternatives to traditional immunosuppressants for achieving clinical stability.

Methods: A systematic search of PubMed, Scopus, Web of Science, and CENTRAL was conducted through April 2026 to identify RCTs of CD19, FcRn, and complement inhibitors in gMG. This analysis includes the recently FDA-approved CD19 inhibitor inebilizumab (December 2025). Network meta-analysis was performed using the netmeta package in R. Risk of bias was assessed using RoB 2.0.

Results: A total of 8 primary studies involving 1,002 patients were included, comprising 643 FcRn-targeted, 238 CD19-targeted, and 314 complement-inhibition participants. For the primary endpoint of MG-ADL response, inebilizumab demonstrated the highest efficacy (RR 2.15; 95% CI 1.68–2.76; SUCRA 0.89), followed by efgartigimod (RR 2.08; 1.55–2.80; SUCRA 0.82) and rozanolixizumab (RR 1.98; 1.42–2.75; SUCRA 0.74), while zilucoplan showed comparatively modest benefit (RR 1.65; 1.18–2.30; SUCRA 0.52). For QMG change, efgartigimod achieved the greatest improvement in muscle strength (MD −4.60; 95% CI −5.80 to −3.40; SUCRA 0.88), followed by inebilizumab (MD −2.50; −3.80 to −1.20; SUCRA 0.72) and eculizumab (SUCRA 0.65). Minimal symptom expression was most frequently attained with inebilizumab (RR 2.40; 1.45–3.98; SUCRA 0.86), followed by efgartigimod (SUCRA 0.79). Time-to-response favored efgartigimod, demonstrating the highest probability of rapid clinical improvement (SUCRA 0.94). Safety analyses showed zilucoplan had the most favorable profile for TEAEs (RR 0.94; 0.82–1.08; SUCRA 0.88), followed by ravulizumab (RR 0.98; 0.88–1.10; SUCRA 0.82) and inebilizumab (SUCRA 0.68). Rozanolixizumab was associated with increased adverse events, particularly headache (RR 1.18; 1.04–1.34; SUCRA 0.41). Overall, CD19 and FcRn-targeted therapies ranked highest for efficacy outcomes, whereas complement inhibitors demonstrated superior tolerability and safety within the network.

Conclusion: CD19 and FcRn therapies showed highest efficacy, with inebilizumab and efgartigimod ranking best. Complement inhibitors demonstrated superior safety. Overall, targeted therapies are effective and well tolerated in generalized myasthenia gravis.

S133: Prevalence and Diagnostic Significance of the Trident Sign in Spinal Neurosarcoidosis: A Systematic Review and Meta-Analysis

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Co-Authors: *Juan Fernando Ortiz, MD, Department of Neurology, Corewell Health, Grand Rapids, MI, Cesar Erazo, MD, Department of Internal Medicine, Cleveland Clinic, Cleveland, OH*

Background: Spinal neurosarcoidosis is an uncommon but clinically significant cause of longitudinally extensive transverse myelitis (LETM). The "trident sign," defined by the combination of central canal and dorsal subpial enhancement on post-gadolinium MRI, has emerged as a distinctive radiologic marker that may aid in the diagnosis of sarcoidosis-associated myelopathy. However, its prevalence and diagnostic relevance have not been systematically evaluated

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Methods: A systematic search of PubMed was conducted from inception through March 2026 to identify studies reporting MRI findings consistent with the trident sign in patients with spinal neurosarcoidosis. Case reports, case series, and observational cohort studies were included. Data on clinical presentation, imaging characteristics, diagnostic confirmation, and outcomes were extracted. Quantitative synthesis was restricted to cohort-level studies. A random-effects meta-analysis of proportions using the Freeman–Tukey double arcsine transformation was performed to estimate the pooled prevalence of trident-pattern enhancement.
Results: A total of 10 studies met inclusion criteria, comprising 7 case reports and 3 cohort studies. Across included studies, the trident sign was consistently associated with subacute LETM and frequently co-occurred with systemic sarcoidosis. MRI findings typically demonstrated longitudinally extensive T2 hyperintensity with dorsal subpial and central canal enhancement, reflecting a characteristic pattern of leptomeningeal and perivascular inflammation. Meta-analysis of 3 cohort-level studies demonstrated a pooled prevalence of trident-pattern enhancement of 0.67 (95% CI 0.56–0.77), with low heterogeneity ($I^2 = 14\%$, $p = 0.31$). Differential diagnoses included NMOSD, MOG-associated disease, and GFAP astrocytopathy, in which this pattern is less commonly observed.
Conclusion: The trident sign is a highly suggestive imaging feature of spinal neurosarcoidosis and may significantly narrow the differential diagnosis in patients presenting with LETM. Despite variability in reporting across studies, pooled analysis suggests it is present in approximately two-thirds of cases. Recognition of this pattern may facilitate earlier diagnosis, reduce diagnostic delay, and support timely initiation of immunosuppressive therapy.

S134-LB*: Neurosarcoidosis in a Tuberculosis-Endemic Region: Clinical Spectrum, Diagnostic Challenges, and Treatment Outcomes

Presenting Author: *Abhinav Maddipati, MBBS, Kochi, Kerala*
Co-Authors: *Chakravarthy Maddipati, MD, FACP, Amrita Institute of Medical Sciences Kochi, Kerala, Sirisha Mahankali, MD, Amrita Institute of Medical Sciences Kochi, Kerala*
Background: Neurosarcoidosis is a rare and heterogeneous manifestation of sarcoidosis, accounting for approximately 5–15% of sarcoidosis cases. This diagnostic challenge is substantially amplified in tuberculosis (TB)-endemic regions where both share overlapping clinical features and imaging findings. Large, region-specific neurosarcoidosis cohorts from India are limited. Hence we aim to elucidate region-specific disease patterns and emphasize on diagnostic and therapeutic dilemmas posed by TB endemicity.
Methods: Thirty-nine neurosarcoidosis patients were analysed (mean age 48.7 years; Male-20 Female-19). Using 2018 Consortium Consensus criteria, 58.9% were classified as probable, 33.3% possible, and 7.7% definite. Systemic sarcoidosis was identified in 92.3%. The most frequent neurological manifestation was cranial neuropathy (66.7%), predominantly facial nerve palsy, followed by meningeal involvement (41.1%) and peripheral neuropathy (23.1%). Serum ACE was elevated in 69%, and CSF protein in 65.2% of those tested. All patients received corticosteroids; 64% required second-line immunosuppression and 18% received biologics. At follow-up, 43.6% achieved remission, while 23.1% had refractory disease. Thirty-eight percent received empiric anti-tubercular therapy, with lower remission rates observed in this subgroup.
Results: This single-centre retrospective cohort provides one of the largest characterisations of neurosarcoidosis from a TB-endemic region. Cranial neuropathy was the predominant phenotype, with pachymeningeal involvement more frequent than leptomeningeal disease - a pattern which compounds diagnostic overlap with neurotuberculosis. Most strikingly, 38.5% of patients received empiric anti-tubercular therapy, a finding unreported in any prior neurosarcoidosis cohort, and was associated with lower remission rates and significant iatrogenic morbidity including ethambutol-induced optic neuropathy. Spinal cord involvement conferred the poorest prognosis, with no patient achieving remission. Overall remission was achieved in 43.6%, with 23.1% having refractory disease. These findings underscore that neurosarcoidosis in TB-endemic settings demands rigorous TB exclusion, early tissue diagnosis, and prompt immunosuppression. National granulomatous disease registries, region-specific diagnostic algorithms, and validated biomarkers are urgently needed to resolve the tuberculosis–sarcoidosis diagnostic interface and improve patient outcomes.
Conclusion: A retrospective observational cohort study was conducted using case records from January 2004 to December 2024. Inclusion Criteria: - Age>18years - fulfilment of the 2018 Neurosarcoidosis Consortium Consensus diagnostic criteria for definite, probable, or possible neurosarcoidosis. Exclusion Criteria - Alternative Diagnosis established - incomplete case records All relevant data (clinical/laboratory/imaging/treatment related/outcomes) were collected. Continuous variables were reported as means with standard deviations or medians with interquartile ranges, as appropriate. Categorical variables are presented as counts and percentages.

S135: Beyond the Brain: In Vivo Imaging of Spinal Cord Atrophy in Progressive Multifocal Leukoencephalopathy

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Background: Progressive multifocal leukoencephalopathy (PML) is a rapidly progressive opportunistic infection of the central nervous system (CNS). JC virus, the causative agent of PML, targets oligodendrocytes, producing multifocal demyelinating central nervous system lesions with

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unexplained, apparent sparing of the spinal cord. Spinal cord imaging in PML has not been systematically investigated, therefore occurrence of subclinical involvement is unknown. Furthermore, it is unknown whether there are late neurodegenerative changes in the spinal cord occurring as a result of widespread CNS injury. Thus, this project aims to characterize spinal cord morphology and volumetrics in long-term PML survivors relative to cerebral lesion burden and clinical measures; and to cross-sectionally and longitudinally evaluate spinal cord volumetrics in comparison to a healthy cohort.

Methods: Spinal cord MRIs were clinically reviewed by board certified neuroradiologists for focal demyelinating lesions. Spinal cord cross sectional area (SCCSA) was measured across 15 individuals with PML and 48 healthy volunteers using axial T1 weighted images reformatted at vertebral levels from C1 to T10. Area profiles were compared between groups evaluating for cord atrophy. Associations between mean SCCSA with clinical and radiologic factors - including disability (modified Rankin Scale [mRS]), cerebral burden (percent lesion volume [lesion volume divided by brain parenchymal volume], brain parenchymal fraction [brain parenchymal volume divided by intracranial volume]), lesion location, and time from PML diagnosis – were evaluated. Clinical and radiologic parameters were obtained from evaluations closest to the spine scan.

Longitudinal analysis was conducted on two patients with follow-up imaging taken 1 and 8 years later, respectively.

Results: On average, spine MRI was obtained 4 years after PML diagnosis. Among 15 patients, no focal spinal cord lesions were identified. Spinal cord morphometry varied widely, with cervical atrophy identified in 11 cases while thoracic cord appeared relatively spared. Cervical cord atrophy was not significantly associated with brainstem involvement, age, time from diagnosis, mRS, or PML lesion burden; nor with the distribution of supratentorial versus infratentorial lesions. Follow-up imaging in two patients demonstrated no progression of cervical atrophy at one-year follow up, in contrast with marked decrease in cervical cord thickness at eight-year follow up.

Conclusion: Cervical spinal cord atrophy appears unexpectedly prevalent in PML survivors. In this small cohort, no significant clinical or radiological predictors were identified. Initial results in two patients suggest atrophy may progress over time, however prevalence of this finding and relationship with long-term disability requires further investigation.

S136: A Rare Convergence of Cryptococcal Meningitis and Anti-NMDA Receptor Antibodies in an Elderly Adult: Case Report

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Co-Authors: *Rajesh Gupta, UTHealth Houston, Sugarland, TX*

Background: This case highlights a 79-year-old male with a past medical history of diabetes, hypertension, and A-fib who presented with new onset generalized status epilepticus. His family reported subacute onset functional and cognitive decline that started a few months before this presentation. He continued to decline, to the point where he was unable to do his ADLs (patient was completely independent before this onset), as well as having some fine tremors in upper extremities intermittently. Prior to the hospitalization, the patient had multiple witnessed generalized seizure activity. The patient underwent imaging at an outside facility which was reportedly unremarkable. He was intubated and sedated prior to arrival at our hospital. The patient was weaned off sedation but remained obtunded for several days while on mechanical ventilation. MRI brain didn't show any acute abnormality. cEEG during admission showed diffuse encephalopathy and highly epileptogenic focus in the right posterior head. Labs showed the presence of cryptococcus antigen in the CSF. Analysis of CSF showed pleocytosis (203 cells/uL), elevated protein and low glucose. He was given IV amphotericin 5mg/kg and IV flucytosine 1500 mg q6h for a total of 14 days during the admission for cryptococcus meningitis induction therapy. His mental status recovery was poor despite this treatment, and he was arousable but mostly somnolent on discharge. He was discharged with fluconazole 800 mg daily followed by maintenance therapy.

Paraneoplastic autoantibody evaluation was later positive for anti-NR1 antibodies, although immunotherapy was not initiated given lack of clearance from infectious disease. 5 months later, he was rehospitalized due to clinical deterioration with severe cognitive impairment and poor neurological recovery despite treatment for cryptococcus meningitis.

Conclusion: In summary, this case demonstrates a possible coexistence or overlap of cryptococcus meningitis and anti-NMDA encephalitis. Anti-NR1 antibodies could also be secondary to CNS infection, and it raises the question of whether cryptococcus infection can induce development of anti-NMDA receptor antibodies or trigger autoimmunity. Further investigation is needed to clarify this relationship, and recognition of this could lead to significant diagnostic and therapeutic improvements in this patient population.

S137: Natalizumab-Associated Acute Liver Injury with Autoimmune Features in Relapsing-Remitting Multiple Sclerosis: A Case Report

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Background: Multiple sclerosis is a chronic immune-mediated demyelinating disorder of the central nervous system. Natalizumab, a humanized monoclonal antibody targeting α4-integrin, inhibits leukocyte migration across the blood–brain barrier and is highly effective in relapsing disease. However, rare cases of acute liver injury have been reported, occasionally with autoimmune features, posing diagnostic challenges.

Methods: Case-report.

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Results: We report the case of a 20-year-old Black Woman with a history of relapsing-remitting multiple sclerosis (RRMS) who presented with a 15-day history of abdominal pain and distension, anorexia, choluria, and progressive jaundice. Her neurological history was notable for intermittent and asymmetric lower limb sensory-motor disturbances and Lhermitte-like phenomena at the age of 12, followed at age 15 by recurrent focal deficits (motor weakness on her right side, visual impairment, and dysarthria). A formal MS diagnosis was given at the age of 19, and Natalizumab was initiated. In total, she received two infusions administered within six weeks prior to presentation. On admission, she was hemodynamically stable, with scleral icterus and mild hepatomegaly. Laboratory evaluation revealed severe hepatocellular injury (AST 1575 U/L, ALT 845 U/L), marked hyperbilirubinemia (peak total bilirubin 15.75 mg/dL, and direct bilirubin 8.84), and coagulopathy (INR 2.1). Infectious workup was negative. Autoimmune testing demonstrated positive anti-smooth muscle antibodies (1:40) and a positive antinuclear antibody (ANA) with a speckled nuclear pattern at low titer (1:80), while anti-LKM-1 antibodies were negative and IgG levels were within normal range. The presence of autoantibodies raised the possibility of autoimmune hepatitis. However, the low titers, normal IgG, and strong temporal association with Natalizumab exposure favored drug-induced liver injury with autoimmune features. She responded well to supportive treatment and discontinuation of Natalizumab.To date, approximately 600 cases have been reported. The pathophysiology is not completely understood, but is thought to be related to drug-induced immune dysregulation, which can trigger autoimmune hepatitis.

Conclusion: Natalizumab-related hepatotoxicity is thought to involve idiosyncratic immune-mediated mechanisms and may mimic autoimmune hepatitis.This case highlights the diagnostic complexity of acute liver injury in patients receiving Natalizumab, particularly when autoimmune markers are present. In patients initiating Natalizumab, the early onset of jaundice accompanied by even low-titer autoantibodies should prompt immediate consideration of drug-induced liver injury with autoimmune features, as timely recognition and drug discontinuation may be decisive in preventing progression to liver failure.

S138: Clinical Efficacy and Safety of Tolebrutinib in Multiple Sclerosis: A Systematic Review, Meta-Analysis and Narrative Synthesis of Phase 3 Trials

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Background: Multiple Sclerosis affects approximately 2.8 million people worldwide and remains a leading cause of non-traumatic neurological disability in young adults. Despite advances in disease-modifying therapies, unmet need persists due to limited central nervous system penetration of treatments, allowing compartmentalized inflammation and disability progression. Tolebrutinib is a brain-penetrant Bruton's tyrosine kinase inhibitor targeting peripheral B-cell activity and central innate immune processes, including microglial activation. Early studies suggest reduced inflammatory activity, but evidence remains limited and heterogeneous, with emerging hepatotoxicity concerns. This systematic review and meta-analysis assessed the efficacy and safety of Tolebrutinib in Multiple Sclerosis.

Methods: This systematic review and meta-analysis was conducted according to PRISMA guidelines. Two independent reviewers searched PubMed, Embase, Cochrane CENTRAL, Scopus and ClinicalTrials.gov through 25 March, with reference lists also screened. Randomized controlled trials involving adults with multiple sclerosis reporting relevant efficacy or safety outcomes were included. Study selection, data extraction, and risk of bias assessment using the Cochrane Risk of Bias tool were performed independently. Meta-analysis used RevMan 5.4, calculating risk ratios or mean differences with 95% confidence intervals using a random-effects model. Heterogeneity was assessed using I^2, with sensitivity analyses performed when I^2 exceeded 50%.

Outcomes reported in fewer than three studies or with inconsistent definitions were assessed narratively.

Results: Three Phase 3 randomized controlled trials (GEMINI 1, GEMINI 2 and HERCULES) were included. Tolebrutinib did not demonstrate significant benefit over comparators in T2 lesion volume (MD −0.03, 95% CI−1.22 to 1.16; p=0.96), disability improvement (MD 0.07, 95% CI −2.12 to 2.26; p=0.95) or quality-of-life outcomes. In contrast, neurofilament light chain levels were significantly increased in the treatment group (MD 0.94, 95% CI 0.54 to 1.34; p<0.00001), indicating neuroaxonal injury. Heterogeneity in disability outcomes was driven by phenotype differences. Sensitivity analysis revealed a significant benefit confined to relapsing MS following exclusion of the HERCULES trial. Non-pooled outcomes reinforced this variability, demonstrating inconsistent immunological and radiological effects with some analyses suggesting increased short-term lesion activity in tolebrutinib-treated patients. Safety findings were mixed, with reduced neutropenia and hypertension but increased nasopharyngitis and headache.

Conclusion: Tolebrutinib did not demonstrate consistent clinical or radiological benefit in Multiple Sclerosis, with any potential effect restricted to relapsing subgroups, reflecting variable efficacy seen with other BTK inhibitors. Increased neurofilament light chain raises concern for ongoing neuroaxonal injury. Current evidence does not support a clear clinical advantage over comparator therapies and the safety-efficacy profile remains uncertain. Further long-term, adequately powered, phenotype-stratified trials are needed.

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S139: Progression of Optic Neuritis to Multiple Sclerosis, Neuromyelitis Optica Spectrum Disorder, and MOG Antibody Disease: A Real-World Retrospective Cohort Study Using TriNetX

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Background: Optic neuritis (ON) is an acute inflammatory optic neuropathy that often represents the first manifestation of central nervous system demyelinating diseases, including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD). Accurate early differentiation among these conditions is critical, as they differ in pathophysiology, prognosis, and treatment response. However, large-scale real-world data on long-term disease risk and demographic patterns following ON remain limited. This study used the TriNetX Research Network to evaluate the cumulative incidence and comparative risk of MS, NMOSD, and MOGAD following incident ON at 1-, 3-, and 20-year timepoints, and to characterize demographic differences among patients diagnosed within one year of ON.

Methods: The following study was a retrospective cohort study conducted using the TriNetX Research Network. Patients were eligible for inclusion if they received a new diagnosis of ON identified by ICD-20 code H46.0. To ensure that subsequent outcomes represented new-onset demyelinating disease rather than pre-existing conditions, patients with a recorded diagnosis of MS, NMOSD, or MOGAD prior to the index date were excluded. Following cohort assembly, patients were longitudinally assessed for the development of MS, NMOSD, or MOGAD after the index ON diagnosis.

Results: Among the 110,834 patients with optic neuritis, 19,618 (17.70%) were diagnosed with MS within one year, increasing to 21,263 (19.18%) at three years and 22,745 (20.52%) at twenty years. In comparison, NMOSD occurred in 2,905 patients (2.62%) at one year, rising slightly to 3,060 (2.76%) at three years and 3,194 (2.88%) at twenty years. MOGAD was identified in 1,117 of 107,247 patients (1.04%) at one year, increasing to 1,262 (1.18%) at three years and 1,326 (1.24%) at twenty years. Significant demographic differences were observed in sex distribution and racial/ethnic composition ($p < 0.001$ for all comparisons).

Conclusion: In this large real-world cohort, MS was the most common demyelinating diagnosis following optic neuritis, with significantly higher incidence and risk compared to NMOSD and MOGAD. The majority of diagnostic conversions occurred within the first year, with minimal progression thereafter, suggesting that disease trajectories are established early in the clinical course. Distinct demographic patterns across MS, NMOSD, and MOGAD were also observed, reinforcing known epidemiologic differences.

S140*: Proteomic Age Acceleration in Multiple Sclerosis Precedes Symptom Onset and Associates with Disease Severity

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Background: Biological aging is accelerated in people with multiple sclerosis (PwMS), but whether such acceleration occurs during the pre-symptomatic phase or varies by organ system is understudied.

Methods: We analyzed two independent proteomics datasets profiled using distinct platforms: the Johns Hopkins cohort profiled using the SomaScan platform (348 PwMS/49 age-matched controls) and the Department of Defense (DoD) cohort profiled using the Olink platform (134 PwMS/79 age-matched controls), including 117 pre-symptomatic samples from PwMS (median lead time: 4.0 years), to estimate systemic and organ-specific proteomic age gaps using established clocks in pre-symptomatic and symptomatic phases, and assess their associations with severity.

Results: In the Johns Hopkins cohort, PwMS demonstrated acceleration of systemic ($\beta=2.2$, 95% CI 1.2–3.2, $P<0.001$, $FDR<0.001$), brain ($\beta=1.7$, 95% CI 0.6–2.7, $P=0.003$, $FDR=0.01$), muscle ($\beta=2.5$, 95% CI 1.3–3.7, $P<0.001$, $FDR<0.001$), and immune age ($\beta=1.8$, 95% CI 0.6–2.9, $P=0.003$, $FDR=0.01$), with comparable findings in the DOD cohort for systemic ($\beta=0.7$, 95% CI 0.0–1.4, $P=0.04$, $FDR=0.34$) and brain age (3.2 years, 95% CI 2.1–4.3, $P<0.001$, $FDR<0.001$). Proteomic age acceleration was evident prior to symptom onset [systemic ($\beta=1.0$, 95% CI 0.4–1.7, $P=0.002$, $FDR=0.02$); brain ($\beta=2.4$, 95% CI 1.2–3.7, $P<0.001$, $FDR=0.002$)], whereas no immune age acceleration was detected before or after onset. Higher systemic age gap was associated with greater global Age-Related Multiple Sclerosis Severity (gARMSS) score ($\beta=0.14$, 95% CI 0.05–0.24, $P=0.005$, $FDR=0.03$) and slower walking speed ($\beta=0.02$, 95% CI 0.01–0.03, $P=0.006$, $FDR=0.04$), while higher muscle age gap was associated with greater gARMSS score ($\beta=0.17$, 95% CI 0.10–0.24, $P<0.001$, $FDR<0.001$), poorer manual dexterity ($\beta=0.28$, 95% CI 0.04–0.52, $P=0.03$, $FDR=0.30$), slower walking speed ($\beta=0.02$, 95% CI 0.01–0.03, $P=0.002$, $FDR=0.02$), lower peripapillary retinal nerve fiber layer (pRNFL) ($\beta=-0.26$, 95% CI -0.41 to -0.10, $P=0.001$, $FDR=0.02$) and ganglion cell-inner plexiform layer thicknesses ($\beta=-0.35$; 95% CI -0.65 to -0.05; $P=0.02$, $FDR=0.30$). Higher brain age gap was associated with several imaging measures, including lower whole-brain ($\beta=-0.002$, 95% CI -0.003 to -0.001,

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P=0.002, FDR=0.02), and lower pRNFL thickness (β= −0.21, 95% CI −0.39 to −0.03, P=0.02, FDR=0.10).

Conclusion: Proteomic age acceleration in multiple sclerosis is detectable years before symptom onset and distinct organ-specific aging signatures are associated with disease severity. Proteomic aging may provide a biologically informative marker of early disease processes and a clinically relevant readout of disease heterogeneity.

S141*: Thyroid Disorders as a Risk Factor for Neurodegenerative Proteinopathies: A Large-Scale Propensity Score-Matched Analysis

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Background: The relationship between thyroid disorders and neurodegenerative diseases remains poorly understood. This large-scale retrospective cohort study aimed to investigate the association between thyroid disorders and various neurodegenerative diseases, as well as the potential impact of thyroidectomy.

Methods: We analyzed data from 3,719,666 patients with thyroid disorders and 2,945,438 controls from 120 healthcare organizations (TriNetX database). After propensity score matching, each group included 2,033,096 patients. We compared the risk of neurodegenerative diseases between these groups and examined the effect of thyroidectomy in a subgroup analysis of 31,753 matched pairs.

Results: Patients with thyroid disorders showed significantly higher risks of Alzheimer's disease (RR = 1.15, 95% CI: 1.110–1.195), Parkinson's disease (RR = 1.25, 95% CI: 1.187–1.318), amyotrophic lateral sclerosis (RR = 1.35, 95% CI: 1.131–1.622), frontotemporal dementia (RR = 1.44, 95% CI: 1.219–1.702), Lewy body dementia (RR = 1.15, 95% CI: 1.107–1.186), progressive supranuclear palsy (RR = 1.41, 95% CI: 1.095–1.819), vascular dementia (RR = 1.32, 95% CI: 1.266–1.369), Niemann-Pick disease type C (RR = 1.34, 95% CI: 1.092–1.638), and Wilson's disease (RR = 1.26, 95% CI: 1.056–1.507). Interestingly, the risk of multiple sclerosis was lower (RR = 0.80, 95% CI: 0.738–0.862). Thyroidectomy was associated with a 44.2% lower risk of Lewy body dementia (RR = 0.558, 95% CI: 0.339–0.919, p = 0.020).

Conclusion: Thyroid disorders are significantly associated with an increased risk of several neurodegenerative diseases. Among patients with diagnosed thyroid disorders, thyroidectomy may have a protective effect against Lewy body dementia. These findings suggest a complex relationship between thyroid function and neurodegeneration, emphasizing the need for neurological monitoring in patients with thyroid disorders and further research into thyroid-brain interactions. Future research could elucidate the underlying mechanisms linking thyroid dysfunction and neurodegeneration via genetic factors and assessment of inflammatory markers.

S142: Inpatient Severity, Resource Utilization, and Discharge Outcomes in Neuromyelitis Optica Spectrum Disorder Versus Multiple Sclerosis: A National Inpatient Sample Analysis

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Background: Neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS) are inflammatory central nervous system disorders with overlapping clinical phenotypes but distinct pathobiology. NMOSD is characterized by severe relapse-driven attacks, suggesting that NMOSD hospitalizations demonstrate greater inpatient acuity and resource utilization compared with MS.Our objective is to compare inpatient severity, healthcare resource utilization, and discharge outcomes between NMOSD and MS hospitalizations while assessing demographic and socioeconomic disparities using national inpatient data in the ICD-10 era.

Methods: A retrospective, survey-weighted analysis of the National Inpatient Sample (2016–2019) was performed. Adult hospitalizations with a principal diagnosis of MS (G35) or NMOSD (G36.0) were identified. Outcomes included in-hospital mortality, home discharge, length of stay (LOS), total hospital charges, plasma exchange, mechanical ventilation, and vision loss. Multivariable logistic and linear regression models adjusted for ethnicity, insurance, median household income, and APR-DRG severity.

Results: A weighted 101,935 hospitalizations were identified, including 6,855 NMOSD admissions (6.7%). NMOSD patients were younger (44.9 vs 46.6 years, p<0.001), more often female (80.2% vs 71.8%, p<0.001), and more likely to be Black (41.6% vs 26.3%, p<0.001). Unadjusted analyses demonstrated greater resource utilization in NMOSD, including longer LOS (8.4 vs 5.1 days, p<0.001), higher charges ($86,369 vs $42,690, p<0.001), increased plasma exchange (25.9% vs 1.7%, p<0.001), higher mechanical ventilation (1.3% vs 0.4%, p<0.001), and increased vision loss (18.1% vs 2.9%, p<0.001). After adjustment, NMOSD remained independently associated with plasma exchange (OR 18.62, 95% CI 15.53–22.33), vision loss (OR 7.40, 95% CI 6.20–8.83), increased LOS (β 3.22, 95% CI 2.07–5.01) and higher total charges (+$12,344.5, p=1.80×10-9). In contrast, differences in mechanical ventilation (OR 1.56,

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95% CI 0.77–3.17), home discharge (OR 0.89, 95% CI 0.78–1.02), and in-hospital mortality (OR 0.82, 95% CI 0.30–2.26) were not statistically significant.

Conclusion: NMOSD hospitalizations are associated with greater inpatient resource utilization and prolonged hospitalization compared with MS, independent of sociodemographic factors and illness severity. The persistence of increased procedural intensity and costs, despite similar mortality and discharge outcomes, supports a distinct acute-care burden in NMOSD with implications for hospital resource allocation and neuroimmunology care delivery.

S143-LB: Comparative Effectiveness of Immunotherapies in Immune Checkpoint Inhibitor-Associated Autoimmune Encephalitis: A Case Report-Based Narrative Analysis

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Background: Immune checkpoint inhibitors(ICIs) are increasingly used as treatment for malignancies, and are reported to cause autoimmune encephalitis(ICI-AIE), a rare neurological immune-related adverse effect. Here, we summarize the published cases to compare treatment patterns and clinical outcomes.

Methods: PubMed was searched from 2016 through 2026. After screening 108 records, 20 case reports met inclusion criteria. Extracted data included underlying malignancy, ICI agent, autoantibody profile, treatment regimen, treatment sequence, and neurological outcome, classified as full recovery, partial recovery, or fatal.

Results: Malignancies included melanoma, NSCLC, SCLC, RCC, and others. Implicated agents were nivolumab, pembrolizumab, durvalumab, ipilimumab, atezolizumab, and combination nivolumab-plus-ipilimumab. Other immunological agents used were rituximab, infliximab, tocilizumab, mycophenolate mofetil and cyclophosphamide. Detected neural antibodies included paraneoplastic/onconeural antibodies such as KLHL11-IgG, anti-SOX1, anti-Hu, and anti-Ma2 IgG; neuronal surface/synaptic antibodies such as GABA-B receptor IgG/GABABR1, AMPA-R IgG, and NMDAR-IgG; and intracellular/enzyme-related antibodies such as anti-GAD65. Overall, 12-of-20(60%) cases achieved full recovery, 5 partial recovery, no recovery in 3 cases and none were fatal. Drugs used: Among 20 cases, IVIG plus corticosteroids was the most frequently reported regimen (n=6), followed by corticosteroids alone (n=5). Other approaches included IVIG, corticosteroids, and plasmapheresis (n=2); corticosteroids followed by plasmapheresis (n=2); IVIG, corticosteroids, and rituximab (n=2); corticosteroids plus cyclophosphamide (n=1); corticosteroids plus infliximab (n=1); and sequential corticosteroids, IVIG plus corticosteroids, and infliximab (n=1). Corticosteroids alone were used in 5 seronegative cases. No specific immunotherapy combination demonstrated a consistent recovery advantage. Full recovery and poor outcomes were both observed across overlapping regimens, suggesting that outcomes were likely influenced by clinical severity, antibody status, malignancy factors, and timing of treatment rather than treatment combination alone.

Conclusion: ICI-associated autoimmune encephalitis is a rare but serious neurological complication with a generally favorable prognosis, with 60% of cases achieving full recovery and no fatalities observed. A diverse range of ICIs and autoantibody profiles were identified, reflecting the heterogeneity of this condition.

Corticosteroids with or without IVIG were the most commonly used first-line approaches; however, no single regimen demonstrated a consistent outcome advantage. Recovery appeared more likely influenced by antibody status, clinical severity, underlying malignancy, and timing of intervention than by treatment combination alone. These findings underscore the need for early recognition, individualized management, and larger prospective studies to establish evidence-based treatment guidelines.

S144: The Association Between Thalamic Atrophy and Fatigue Severity in Multiple Sclerosis: A Systematic Review and Meta-analysis

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Background: Fatigue is one of the most common and disabling symptoms in multiple sclerosis (MS), often presenting early in the disease course. Emerging neuro-imaging evidence suggests that thalamic structural and functional abnormalities may play a key role in its pathophysiology.

Methods: A systematic search was conducted in PubMed, Scopus, Cochrane Library, and Google Scholar to identify studies assessing the relationship between thalamic structural changes and fatigue in MS. Eligible studies were screened based on predefined criteria. Risk of bias was assessed using the NIH quality assessment tool for observational cohort studies. A random-effects meta-analysis was performed, and heterogeneity was evaluated using the I^2 statistic.

Results: Meta-analysis demonstrated a significant moderate association between increased fatigue severity and reduced thalamic volume in MS patients ($r = 0.416$). Ten studies were included in the analysis. Across studies, thalamic atrophy, including nuclei-specific volume loss, and disrupted thalamocortical connectivity were consistently associated with fatigue. Moderate heterogeneity was observed, likely reflecting variability in imaging modalities, fatigue assessment tools, and study populations.

Conclusion: Thalamic atrophy and disrupted thalamocortical connectivity are significantly associated with fatigue severity in MS, supporting a neurobiological basis for this symptom.

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Standardized longitudinal studies are needed to further clarify causal mechanisms and clinical implications.

S145: OCT Based Criteria for MS Diagnosis; Percentile Analysis of Retinal Layer Thickness Improves Accuracy When Combined With Inter-eye Differences

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Background: The 2024 revised McDonald criteria incorporate optic nerve involvement as a diagnostic topography for multiple sclerosis (MS). Optical coherence tomography (OCT)-derived ganglion cell-inner plexiform layer (GCIPL) and peripapillary retinal nerve fiber layer (pRNFL) thinning are established markers of optic neuritis (ON). Current criteria rely on inter-eye difference (IED) thresholds (≥4 μm for GCIPL or ≥6 μm for pRNFL), which are optimized for unilateral ON but may miss bilateral involvement due to reliance on inter-eye asymmet ry. This study evaluated whether age- and sex-adjusted first percentile GCIPL and pRNFL thresholds improve overall discrimination of MS and bilateral ON when combined with IED-based criteria.

Methods: In this single-center study, people with MS (pwMS) and non-MS controls underwent OCT imaging. OCT IED were defined based on the revised 2024 McDonald criteria. Percentile-based models of optic nerve involvement in MS were defined as GCIPL or pRNFL thickness below the 1st percentile in either eye.

Discrimination was assessed using area under the curve (AUC) from receiver operating characteristic (ROC) analysis, with comparisons performed using the DeLong's test. Analyses were conducted for overall MS vs control discrimination and across ON subgroups.

Results: The cohort included 182 pwMS and 24 non-MS controls. In the MS cohort, 119 had no ON history, 52 had unilateral ON, and 11 had bilateral ON. Compared to IED-based criteria alone, incorporating 1st percentile thresholds improved discrimination of pwMS from controls (AUC 0.67 [95% CI 0.57–0.77; sensitivity 63%, specificity 71%] vs 0.62 [95% CI 0.52–0.72; sensitivity 53%, specificity 71%], $p<0.001$). Among pwMS with ON history, further improvement in diagnostic accuracy was observed versus controls (AUC 0.82 [95% CI 0.72–0.92; sensitivity 93%, specificity 71%] vs 0.76 [95% CI 0.66–0.87; sensitivity 82%, specificity 71%], $p=0.005$). For unilateral ON, the improvement was modest and not statistically significant (AUC 0.81 [95% CI 0.71–0.92] vs 0.79 [95% CI 0.68–0.89], $p=0.077$). The most pronounced improvement was observed in bilateral ON cases, where the combination of percentile-based and IED thresholds significantly outperformed IED-based criteria alone (AUC 0.85 [95% CI 0.76–0.95; sensitivity 100%, specificity 71%] vs 0.65 [95% CI 0.47–0.84; sensitivity 60%, specificity 71%], $p=0.014$).

Conclusion: Percentile-based OCT thresholds, when combined with IED improve MS diagnostic accuracy, particularly in pwMS with bilateral optic nerve involvement. These findings support percentile-based approaches as a complementary framework for identifying optic nerve pathology in MS.

S146: Real-World Impact of CSF Metagenomic Sequencing in Suspected CNS Infections: Early Diagnostic and Management Insights from a Tertiary Care Center

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Background: Central nervous system (CNS) infections and inflammatory neurologic syndromes remain diagnostically challenging, particularly in immunocompromised patients, where conventional cerebrospinal fluid (CS/F) testing often fails to identify an etiology. Metagenomic next-generation sequencing (mNGS) offers an unbiased, hypothesis-free approach to pathogen detection and may improve diagnostic yield and guide management. We assessed the diagnostic yield and downstream clinical impact of CSF mNGS in a real-world cohort.

Methods: We conducted a retrospective case series of patients who underwent CSF mNGS from 2024-2025 at CUIMC. Clinical indications, underlying risk factors, diagnostic results, downstream diagnostic testing burden, management changes, and hospital outcomes were abstracted from the medical record. Descriptive statistics were used to summarize patient characteristics, diagnostic yield, and clinical impact.

Results: Sixteen patients underwent CSF mNGS testing. Mean age was 60.6 ± 16.0 years, and 9/16 (56%) were male. Presenting syndromes included encephalitis/cerebritis (6/16, 38%), meningitis (5/16, 31%), autoimmune encephalitis (2/16, 13%), other CNS infections (2/16, 13%), and non-infectious neurologic syndromes (1/16, 6%). Most patients were immunocompromised (10/16, 63%), including malignancy (3/16, 19%), immunosuppressive therapy (5/16, 31%), HIV (1/16, 6%), and transplant recipients (3/16, 19%); 4/16 (25%) had no clear risk factors. mNGS identified a pathogen or relevant signal in 5/16 (31%), including bacteria (2/16, 13%), DNA viruses (3/16, 19%), RNA viruses (1/16, 6%), parasites (1/16, 6%), and fungi (1/16, 6%).

Autoimmune or non-infectious findings were seen in 2/16 (13%), while 6/16 (38%) were negative. Across the cohort, 28 lumbar punctures and 109 CSF studies were performed. Management changed in 4/16 (25%), primarily through antimicrobial discontinuation and antiviral initiation. Mean length of stay was 31.6 ± 29.9 days. Most patients were discharged (14/16, 88%), and 2/16 (12%) died.

Conclusion: CSF mNGS showed moderate diagnostic yield in a heterogeneous cohort of suspected CNS infections and

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neuroinflammatory syndromes, with greatest utility in immunocompromised patients. Results influenced management mainly through antimicrobial de-escalation and targeted antiviral therapy. These findings suggest a potential complementary role for mNGS alongside conventional CSF testing. Prospective studies are needed to define its optimal placement in diagnostic pathways, incremental yield, and cost-effectiveness.

S147: Establishing Age Specific Reference Intervals for Serum Neurofilament Light Chain in a Healthy Indian Cohort

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Background: Neurofilament light chain(NfL) is a highly sensitive biomarker of neuroaxonal injury with levels known to increase with age (Hviid CVB, Scandinavian Journal of Clinical and Laboratory Investigation, 2020). Age specific reference intervals are essential for accurate clinical interpretation. However, population specific data in the Indian setting remains limited.

Methods: In this cross-sectional study, 173 healthy individuals aged 0–96 years were included after excluding neurological and systemic illnesses. Serum NfL levels demonstrated non-normal distribution (Kolmogorov–Smirnov and Shapiro–Wilk, $p < 0.001$), and were analyzed using log transformation and non-parametric methods. A log-linear regression model was constructed with age as the independent variable. Age-stratified reference intervals (5th–95th percentiles) were derived from model-predicted values.

Results: The mean serum NfL level was 23.1 ± 14.4 pg/mL, with a median of 18.6 pg/mL (IQR 14.75). NfL levels showed a significant positive correlation with age ($r = 0.582$, $p < 0.001$). The fitted model ($R^2 = 0.486$) demonstrated an age-dependent increase described by $\ln(\text{NfL}) = 2.324 + 0.015 \times \text{Age}$, corresponding to an approximate annual rise consistent with prior literature (Harp C, Annals of Clinical and Translational Neurology, 2022). Age-stratified analysis revealed a progressive increase in NfL levels, with mean values rising from 12.6 pg/mL in individuals aged 0–15 years to 35.0 pg/mL in those aged 66–96 years. The upper reference limits (95th percentile) increased from 21.2 pg/mL in younger individuals to 63.3 pg/mL in older age groups. No significant sex-based differences were observed.

Conclusion: Serum NfL levels demonstrate a robust age-dependent increase in healthy individuals. This study establishes age-adjusted reference ranges for serum NfL in an Indian population, aligning with global trends while addressing a critical gap in population-specific data. These findings enhance the clinical interpretability of NfL and support its integration into diagnostic and monitoring frameworks for neurological disorders.

S148: Clinical Spectrum and Treatment Outcomes in LGI1 Antibody Encephalitis: A Retrospective Cohort from South India

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Background: Leucine-rich glioma-inactivated 1 (LGI1) antibody associated encephalitis is a subtype of autoimmune limbic encephalitis characterized by seizures, cognitive dysfunction, and hyponatremia, with generally favorable outcomes following early immunotherapy. However, variability in clinical phenotype, including underrecognized movement disorders, and functional outcomes remains underreported, particularly in the Indian population (Rodriguez et al., Journal of Neurology, Neurosurgery & Psychiatry, 2022).

Methods: We conducted a retrospective observational study of patients with LGI1 antibody positivity evaluated and treated at Amrita Institute of Medical Sciences, Kochi, India, between May 2013 and April 2026. Patient data was taken from the hospital's electronic medical records and neuroimmunology laboratory register. Clinical features, laboratory findings, treatment modalities, and outcomes were analyzed. Functional status was assessed using the modified Rankin Scale (mRS) at admission, discharge, and follow-up.

Results: A total of 34 patients were included, mean age at presentation was 60.4 ± 17.0 years. The most common clinical manifestations were seizures (61.7%), cognitive impairment (55.9%), and hyponatremia (47.1%). Extrapyramidal symptoms (EPS) were observed in 20.6% of patients, expanding the recognized clinical spectrum. A favorable functional outcome (mRS ≤2 at follow-up) was achieved in 82–85% of patients, consistent with good response to immunotherapy. Relapse was infrequent (5.8%), and mortality was 11.7%, primarily among those with severe initial presentations which is lower than previously reported relapse rates of approximately 20–40% (van Sonderen et al., Neurology, 2016). 16 patients (47%) who received early and escalated immunotherapy such as rituximab and cyclophosphamide demonstrated better functional recovery compared to patients receiving steroid sparing agents like mycophenolate or azathioprine. Notably, patients with extrapyramidal features did not demonstrate worse functional outcomes compared to those without EPS, suggesting these manifestations may represent a phenotypic variant rather than a marker of disease severity.

Conclusion: LGI1 antibody encephalitis demonstrates a broad clinical spectrum, including extrapyramidal manifestations. Early diagnosis and aggressive immunotherapy are associated with significant functional improvement and high rates

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of favorable outcomes. Recognition of atypical features is essential to optimize management and prognosis.

S149: Upstream Versus Downstream Complement Blockade: Potential Mechanistic Advantages of aC1s Targeting in Myasthenia Gravis

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Background: In generalized myasthenia gravis (gMG), pathogenic antibodies activate the classical complement pathway, culminating in membrane attack complex (MAC)-mediated injury at the neuromuscular junction (NMJ). Levels of complement components (C3) have been associated with disease severity in animal models. C5 inhibitors block MAC formation and improve clinical outcomes, without reducing the upstream inflammatory fragments (C3a, C3b), which potentially drive NMJ injury and amplify immune responses in addition to MAC formation. Here, we determined whether active C1s (aC1s) inhibition by claseprubart (DNTH103) suppresses generation of C3a, C3b and MAC in comparison with C5 inhibitor ravulizumab.

Methods: MAC formation was quantified using the Wieslab® Complement Classical Pathway assay in 1% normal human serum (NHS). C3a in supernatants was measured by ELISA and C3b deposition on sensitized human red blood cells in 5% NHS was assessed by flow cytometry. For each assay, we tested dilution series of claseprubart, ravulizumab, and an isotype control.

Results: In head-to-head assays, claseprubart and ravulizumab produced comparable inhibition of MAC formation, confirming similar downstream blockade. Only upstream aC1s inhibition with claseprubart resulted in near-complete reduction of C3a and C3b levels, while ravulizumab did not. Findings were reproduced across three independent experiments, supporting a mechanistic upstream (aC1s)-downstream (C5) inhibition distinction.

Conclusion: Upstream aC1s inhibition with claseprubart prevented MAC formation and reduced C3a and C3b levels, demonstrating broader inflammatory control beyond C5 blockade. Thus upstream inhibition may provide both pathological and immunological advantages.

S150: Sustained Safety and Efficacy of Active C1s Inhibitor Claseprubart in Patients with Generalized Myasthenia Gravis: Results from the MaGic Study Open-Label Extension

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Background: Claseprubart is the first monoclonal antibody in development for the treatment of generalized myasthenia gravis (gMG) that inhibits the upstream classical complement pathway by blocking active C1s. The phase 2 MaGic study demonstrated that claseprubart was well-tolerated with clinically meaningful efficacy improvements after 13 weeks of treatment in adults with acetylcholine receptor antibody positive (AChR+) gMG. Here, we assessed the sustained efficacy and safety of approximately 1 year of claseprubart treatment in the MaGic open-label extension (OLE).

Methods: MaGic (NCT06282159) is a randomized, double-blind, placebo-controlled Phase 2 trial. Patients with AChR+ gMG received subcutaneous claseprubart 300mg (Q2W), claseprubart 600 mg (Q2W), or placebo for 13 weeks. Patients eligible for the 52-week OLE were switched to, or continued, Q2W 300 mg claseprubart.

Results: Sixty-three patients completed the 13-week randomized controlled trial (RCT); 60 enrolled in the OLE.

To date, 52 patients are currently enrolled or completed the OLE. At OLE Week 36 (49 total weeks of treatment), claseprubart 300mg patients continuing treatment (n=15) showed sustained improvement in MG-activities of daily living (MG-ADL; -4.9 [standard deviation, SD 2.19]) and Quantitative MG score (QMG; -5.1 [SD 3.47]) versus RCT study baseline. Safety and tolerability of claseprubart in the OLE was consistent with the RCT. No patients in the continuous 300mg claseprubart arm developed a treatment-related serious adverse event. Additionally, patients switching from placebo to claseprubart showed rapid improvements in MG-ADL an QMG.

Conclusion: Forty-nine weeks of Q2W subcutaneous 300mg claseprubart treatment demonstrated sustained efficacy with a well-tolerated safety profile in patients with AChR+ gMG.

S151: Assessing the Relationship between Focal Neurodegeneration and Chronic Inflammation in Early Multiple Sclerosis

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Background: In multiple sclerosis (MS), paramagnetic rim lesions (PRLs) detected on susceptibility-sensitive magnetic resonance imaging (MRI) serve as biomarkers of chronic active lesions (CALs), whereas T1-hypointensities, referred to as chronic black holes (cBHs), represent focal neurodegeneration. Longitudinal studies indicate that both cBHs and PRLs typically arise from active lesions, rather than from the late evolution of pre-existing chronic lesions. However, the extent of overlap between PRLs and cBHs remains unclear.

Addressing this gap is essential for advancing our understanding of the relationship between chronic inflammation and neurodegeneration.

Methods: We examined the overlap between PRLs and cBHs and differences in microstructural injury among lesions with these phenotypes in 43 newly diagnosed, treatment-naïve patients with MS and clinically or radiologically isolated syndrome. All participants underwent 3.0 Tesla MRI and neurocognitive assessments on the same day. The MRI protocol included a gradient-echo sequence for phase-map computation and a quantitative magnetization transfer method to deliver the macromolecular-to-free pool size ratio (PSR) and the relaxation rate of the free-water pool (R1f). We applied a Mixed Model for Repeated Measures analysis, incorporating a random effect for participants and an unstructured correlation matrix, to evaluate differences across lesion phenotypes. Test statistics were derived from unadjusted t-tests based on least-squares means and their standard errors. Group differences in clinical metrics were assessed using a Mann-Whitney test.

Results: We identified 994 T2-hyperintense non-enhancing lesions. Among these, 66.6% were double-negative (DN), meaning they were neither PRLs nor cBHs; 0.1% were PRLs, 28.3% were cBHs, and 4.2% were double-positive (DP), exhibiting both PRLs and cBHs. DN lesions were smaller ($p \leq 0.04$) and had larger PSR ($p \leq 0.04$) than any other lesion phenotype. DN lesions also had a larger R1f ($p \leq 0.0001$) relative to DP and cBHs. No differences were seen in any of the examined variables between any other pair. PRLs were identified in 20 (46.5%) patients, all of whom also exhibited cBHs. In contrast, cBHs were present in 36 patients (83.7%), of whom 20 (55.6%) also had PRLs. Patients with DP lesions demonstrated poorer performance on the 25-foot walk ($p=0.04$) and 9-hole peg tests of the non-dominant hand ($p=0.01$) compared to those with DN lesions only.

Conclusion: Our findings suggest that chronic inflammation persists in most lesions in which neurodegeneration occurs early, but focal neurodegeneration can occur even in the absence of chronic inflammation. These results imply that chronic inflammation and neurodegeneration may be independent processes, each requiring targeted therapeutic strategies to prevent irreversible tissue injury.

CEREBROVASCULAR DISEASE

S153: Chronic Kidney Disease Predicts Intracerebral Hemorrhage Mortality Independent of ICH Score

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Background: Spontaneous intracerebral hemorrhage (ICH) is the deadliest form of acute stroke, accounting for 20-30% of all strokes and carrying a 30-day mortality rate of 40-50%. First reported in 2001, the ICH score is a widely utilized prognostic tool used to estimate 30-day mortality following spontaneous ICH, and is calculated based on hematoma location and volume, presence of intraventricular hemorrhage (IVH), Glasgow Coma Scale (GCS) on admission, and patient age. The score often guides clinical management and goals of care discussions with families. However, since its original publication, multiple studies have called into question the predictive value of the ICH score. In this project, we aimed to investigate whether common comorbidities affect the prognostic value of the ICH score.

Methods: We performed a retrospective analysis of 580 patients diagnosed with spontaneous ICH at the University of Kentucky from 2021-2023. Multivariable regression was used to assess the association between hypertension, HLD, T2DM, COPD, CKD, heart failure, malignancy, IV drug use, dementia and ICH score with mortality (defined as hospice or death on discharge).

Results: Patients diagnosed with CKD at any stage had threefold higher odds of mortality compared to those without CKD (OR 3.01, $p=0.004$), independent of ICH score or any other comorbidities. None of the other conditions were significantly associated with mortality. ICH score remained a strong predictor of mortality, with each 1-point increase associated with 3.5 times increase in odds of death (OR 3.52, $p < 0.001$).

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Conclusion: CKD appears to be an independent predictor of mortality in ICH and may contribute to disease severity beyond what is captured by the ICH score. These findings support the potential value of incorporating renal function into prognostic models. The ICH score continues to be a useful tool in the setting of other comorbidities.

S154: Persistent Vestibular Dysfunction After Neurologic Decompression Sickness in an Experienced Diver With Patent Foramen Ovale and Atrial Septal Defect and Chronic Topiramate Use

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Background: Neurologic decompression sickness (DCS) is classically associated with deep or repetitive dives and persistent vestibular or neurologic dysfunction. Shallow dives are traditionally considered low risk. This case highlights an atypical presentation following a prolonged shallow-water dive and emphasizes the role of intracardiac right-to-left shunts and medication-related physiologic factors in prolonged neurologic sequelae. A 56-year-old woman with over 30 years of recreational diving experience developed acute neurologic symptoms after a prolonged shallow dive to a maximum depth of 21 feet. She presented with diffuse cutaneous hypersensitivity, severe bilateral lower- extremity neuropathic pain, and gait instability. Her medical history was notable for chronic topiramate use. Neurologic examination demonstrated preserved strength and intact cranial nerve function with functional gait impairment and balance instability.

Methods: Clinical data were obtained through medical record review, including symptom onset, neurologic findings, treatment response, rehabilitation course, and diagnostic imaging. The patient underwent six sessions of hyperbaric oxygen therapy with partial improvement. Persistent balance impairment, particularly in low-visual-input conditions, prompted referral for vestibular rehabilitation. Transesophageal echocardiography (TEE) was performed to evaluate for intracardiac shunting. A focused literature review examined neurologic DCS in relation to patent foramen ovale (PFO), highly prevalent and present in an estimated 25% of individuals, atrial septal defect (ASD), and topiramate-associated physiologic effects.

Results: Hyperbaric oxygen therapy resulted in transient incomplete symptom resolution. The patient continued to experience balance impairment without vertigo. Vestibular rehabilitation led to gradual improvement. TEE revealed both a PFO and ASD. This case demonstrates that neurologic DCS can occur after shallow dives and may result in prolonged vestibular dysfunction despite standard therapy. Finding PFO and ASD supports the role of paradoxical embolization in atypical or persistent neurologic presentations. Additionally, chronic topiramate use, which induces metabolic acidosis, may alter physiologic responses relevant to decompression and warrants consideration in risk assessment.

Conclusion: Neurologic decompression sickness may occur after shallow dives and lead to persistent vestibular deficits. Evaluation for intracardiac shunts should be considered in atypical or prolonged neurologic presentations. Medication-related physiologic effects, including topiramate-associated metabolic acidosis, may influence susceptibility and should be considered in clinical assessment.

S155: Racial and Ethnic Disparities in Stroke Among Hypertensive Adults by Antihypertensive Medication Use

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Background: Despite improvements in hypertension management, racial and ethnic disparities in stroke persist. Whether intervention intensity modifies stroke disparities remains unclear.

Methods: We analyzed 10,005 adults aged ≥20 years with hypertension in the National Health and Nutrition Examination Survey (NHANES) from March 2013 to March 2020. Stroke history was self-reported. Antihypertensive therapy was categorized as untreated, monotherapy, or combination therapy. Multivariable logistic regression models adjusted for demographic, socioeconomic, and clinical variables and included a race/ethnicity × medication group interaction term. Analyses accounted for complex NHANES sampling design. Outcomes were reported as odds ratios (OR) and accompanying 95% confidence intervals (CI).

Results: Overall, 5.0% of adults with hypertension reported a history of stroke. After full adjustment, current smoking (OR=1.80, 95% CI 1.27-2.56), history of cardiovascular disease (OR=2.38, 95% CI 1.70-3.35), and Medicaid insurance coverage (OR=3.06, 95% CI 1.40-6.68) were independently associated with stroke.

Racial/ethnic disparities in stroke prevalence appeared attenuated among those receiving combination antihypertensive therapy. The relative Black-White participant difference in stroke prevalence was larger among those on combination therapy (25% relative difference when untreated vs 2% absolute difference on combination therapy). Compared with White participants, Asian participants demonstrated lower odds of stroke on combination therapy (adjusted OR 0.23, 95% CI 0.06-0.96) compared with untreated individuals (adjusted OR 0.49, 95% CI 0.22-1.09). A similar attenuation was observed among Hispanic participants when compared to White participants (adjusted OR 0.57, 95% CI 0.37-0.90 combination therapy vs. 0.66, 95% CI 0.48-0.92 untreated). The interaction between race/ethnicity and medication group was not statistically significant (P=0.346).

Conclusion: Treatment intensity may attenuate racial/ethnic disparities in stroke among adults with hypertension, particularly Black-White differences. Although interaction testing was not statistically significant, findings suggest that treatment intensification could narrow disparity gradients. Larger longitudinal studies are needed to determine whether intensive antihypertensive therapy meaningfully mitigates racial disparities in stroke risk.

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S156-LB: Clinical and Procedural Outcomes of IVUS-Guided versus Angiography-Guided Carotid Artery Stenting (CAS): A Systematic Review and Meta-Analysis

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Background: Intravascular ultrasound (IVUS) guidance allows real-time visualization throughout carotid artery stenting (CAS), possibly leading to safer stent deployment and improved outcomes when compared with angiography guidance alone. Whether IVUS guidance improves safety and outcomes compared to angiography guidance during CAS procedures remains unclear. Our objective was to systematically review safety, efficacy, and procedural outcomes of IVUS-guided carotid artery stenting compared to angiography guidance.

Methods: Fourteen studies (total n = 1,778 patients) were included; 1 randomized trial, 12 cohort studies, and 1 cross-sectional study. IVUS guidance was associated with significantly lower rates of periprocedural stroke compared with angiography guidance alone: 1.07% (95% CI 0.00%, 2.02%) vs. 3.73% (95% CI 2.32%, 5.97%), respectively ($P < 0.01$). This corresponds to a relative risk reduction of 71% (absolute risk reduction 2.66%, number needed to treat = 38) with no heterogeneity between studies (I^2=0%). Rates of 30-day mortality were low (0.93%, 95% CI 0.00%, 3.09%). Secondary outcomes included rates of 30-day stroke (2.02%, 95% CI 1.00%, 4.04%, I^2=57.96%), 30-day TIA (2.02%, 95% CI 1.00%, 3.09%, I^2=61.85%), and 30-day MI (0.93%, 95% CI 0.00%, 2.01%, I^2=0%). IVUS guidance detected plaque protrusion into the lumen in 5% (95% CI 3%, 8%), stent malposition in 10% (95% CI 7%, 14%) and embolization during the procedure in 44% (95% CI 4%, 87%) of cases. Proportion of patients with long-term outcomes of in-stent restenosis and stent thrombosis were 8% (95% CI 5%, 11%) and 1% (95% CI 0.00%, 0.02%), respectively. Risk of bias was low for half of studies. The quality of evidence was rated moderate for the primary outcome.

Results: IVUS-guided carotid artery stenting results in lower periprocedural stroke rates than angiography guidance and better identifies procedural complications. The findings encourage exploring IVUS guidance for CAS, but randomized trials remain necessary.

Conclusion: We searched 10 databases from inception to January 2026 for studies reporting IVUS-guided or angiography-guided CAS outcomes. Primary outcomes, secondary, mechanistic, and long-term outcomes were assessed. Pooled proportions with 95% confidence intervals (CIs) were estimated using random-effects models incorporating Freeman-Tukey double arcsine transformation. Heterogeneity was quantified with I^2 statistics. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool for randomized controlled trials and Joanna Briggs Institute risk of bias tools for observational studies. Quality of evidence was graded with GRADE.

S157: Bilateral Cerebellar Infarcts Associated with Combined Testosterone Replacement, Finasteride, and Anastrozole Use

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Co-Authors: *Shormista Kar, DO, MORGANTOWN, WV, Curtis Amankwah, MD, West Virginia University Morgantown, WV*

Background: Exogenous testosterone therapy promotes thrombotic risk through erythrocytosis, platelet activation, and impaired fibrinolysis. Finasteride inhibits 5α-reductase, raising circulating androgen levels, while anastrozole suppresses aromatase-mediated estrogen synthesis. This combination creates a state of relative androgen excess and estrogen deficiency that may synergistically amplify cerebrovascular risk. The combined effect of these agents on stroke risk has not been previously described.

Methods: This is a case report.

Results: A 53-year-old man with no prior disability (mRS 0) presented with acute vertigo, severe headache, and gait instability. Last known well was greater than 21 hours prior, precluding thrombolysis consideration. Blood pressure on arrival was 220 mmHg. Medications included intramuscular testosterone twice weekly for seven years, finasteride 5 mg daily, and anastrozole 1 mg daily. Neurologic examination revealed an NIHSS of 0. CT angiography demonstrated bilateral cerebellar hypodensities without large vessel occlusion. MRI brain confirmed scattered bilateral cerebellar infarcts in an embolic distribution. Hemoglobin was elevated at 18.2 g/dL with hematocrit 54%, consistent with testosterone-induced erythrocytosis. Hypercoagulability panel was unremarkable. Cardiac evaluation revealed preserved ejection fraction (72%) without intracardiac thrombus.

Transthoracic echocardiography was negative for intracardiac shunt; transesophageal echocardiography demonstrated a late-positive bubble study consistent with intrapulmonary arteriovenous shunting. No atrial fibrillation was detected on continuous telemetry. The patient was treated with dual antiplatelet therapy for 21 days followed by aspirin monotherapy, with symptomatic improvement. Persistent fatigue and cognitive slowing were reported at follow-up.

Conclusion: This case describes bilateral embolic cerebellar infarcts in a patient on combined testosterone, finasteride, and anastrozole - a hormonal combination with convergent prothrombotic effects. Erythrocytosis-driven hyperviscosity, androgen-mediated platelet activation, and estrogen-depleted loss of vascular protection likely acted in concert. The discovery of intrapulmonary shunting introduces an additional mechanistic question: whether the embolic burden was amplified by paradoxical passage through pulmonary

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arteriovenous channels rather than exclusively via cardiac or in situ mechanisms. As use of performance and hormonal optimization agents grows, prospective pharmacovigilance studies examining cerebrovascular outcomes in men on combined androgen-modulating regimens are needed.

S159: VZV CNS-Vasculitis Causing Sequential Bilateral Pontine Strokes, A Case Report

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Background: A 69 year old man with past medical history of hypertension, hyperlipidemia, type 2 diabetes, prostate cancer and psoriasis presents to ED with right sided hemiparesis after falling 3 days prior. The patient was seen two weeks prior experiencing right ear pain, tinnitus, and jaw pain characterized as "electrical shocks" radiating to the temporal region which was diagnosed as otitis media. MRI revealed an acute ischemic infarct of the left ventral pons. Given symptom onset within 72 hours, the patient was treated with DAPT. Three days later a stroke alert was activated for left hemibody hemiplegia. On physical exam the patient had declined to a minimally conscious state with severe encephalopathy, unable to follow commands and with LHB strength 0/5, RHB strength 3/5. MRI revealed a new right ventral and paremedian pontine acute ischemic stroke. Confronted with Early Neurological Deterioration (END) in a non-thrombectomy candidate, the team pivoted to aggressive medical management based on the RESCUE-BT2 trial and tirofiban infusion was initiated.

Methods: Data and imaging were obtained from the electronic medical record. All patient-identifying information has been removed.

Results: Given severe encephalopathy and the unusual presentation of recurrent strokes despite DAPT, a decision was made to obtain extensive work-up for infectious, inflammatory, and paraneoplastic etiology. Vessel-wall MRI demonstrated the bilateral infarctions and evidence of subtle non-stenotic linear enhancement of the basilar artery symmetrically. Lumbar puncture was obtained with CSF Varicella Zoster Virus (VZV) IgG >8 and PCR positive for VZV. The overall clinical picture was highly suspicious for VZV vasculitis and medical therapy with acyclovir and methylprednisolone was initiated. Two days later the patient's neurological exam was unchanged and the patient was transitioned to comfort care.

Conclusion: The diagnosis of VZV vasculitis in this patient highlights a critical blind spot in standard stroke algorithms: the existence of "angiographically occult" inflammation. VZV can induce a non-stenotic vasculitis where inflammation remains confined to the vessel wall without narrowing of the lumen. This explains why the patient's CTA and standard MRA were unremarkable. This case underscores the utility of high-resolution vessel wall MRI (Black-Blood imaging) in "ESUS" (Embolic Stroke of Undetermined Source) or progressive posterior circulation ischemia. While often reserved for younger patients, its application here revealed concentric enhancement characteristic of vasculitis in a patient who otherwise would have gone undiagnosed. This case reviews pathophysiology, epidemiology, radiological and laboratory findings of VZV vasculitis for which specific testing and early initiation of medication should be considered.

S160: Trends in Mortality from Thromboembolism and Cerebrovascular Diseases Among U.S. Adults Aged ≥65 Years, 1999–2034

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Background: Thromboembolism (TE) and Cerebrovascular diseases (CVD) are major cause of mortality in United States and often co-occurring due to shared risk factors. However, stratified mortality trends across demographic and geographic groups remain insufficiently defined.

Methods: Our study conducted an in-depth analysis using the CDC WONDER database using ICD-10 codes I26.0–I26.9 (pulmonary embolism), I74.0–I74.9 (arterial embolism and thrombosis), I80.0–I80.9 (phlebitis and thrombophlebitis), I81 (portal VT), I82.0–I82.9 (VTE), and I60–I69 (CVD). Age-adjusted (AAMR) and crude mortality rates (CMR) per 100,000 were calculated across demographic and regional groups. Joinpoint regression was used to estimate APC and AAPC with 95% CIs, with $p \leq 0.05$ considered statistically significant. An autoregressive integrated moving average (ARIMA) model was used to forecast AAMR 's through 2034

Results: Between 1999-2024, a total of 103,011 elderly individuals died from VT and CVD. The overall AAMR increased from 1999 to 2024 [AAPC: 1.2622* (95% CI, 0.5228 to 2.007], with an early decline from 1999-2013 [APC: -1.80; 95% CI -2.11 to -1.49, $p < 0.000001$], followed by an increase till 2018 [APC: 2.42; 95% CI 0.46

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to 4.42, p = 0.0186], preceded by a sharp significant acceleration from 2018 to 2021 [APC 14.75; 95% CI 8.98 to 20.82, p = 0.000043] and a subsequent surge from 2021 to 2024 [APC: 1.19; 95% CI -1.04 to 3.48, p = 0.276]. Men had a higher AAMR than women (8.18 vs 7.38). Age-group of 85 years and above had higher CMRs (21.61). Non-Hispanic (NH) Black had the highest AAMR (13.7), followed by NH Whites (7.71), Hispanics (5.81), and Asian (3.93). Regionally, The Northwest region (8.43) and Midwest (8.41) showed higher AAMRs than the South (8.26) and the Northeast (6.77), while the non-metropolitan areas demonstrated highest AAMRs than metropolitan (8.14 vs 7.26). State-wise mortality ranged from District of Columbia (13.57) to Hawaii (4.18). Forecasting projects a continued rise in AAMR expecting to reach 17.73 by 2034

Conclusion: Mortality rates showed an overall rising trend throughout the study period with a higher AAMRs reported in males, age-group 85 and above individuals, NH-Blacks, Northwest region, and rural residents. ARIMA based forecasting further reinforces this uprising trajectory demanding targeted interventionism.

S161: Beyond the Cranium: Lumbar Spinal Subdural Hematoma as a Rare Cause of Intractable Headache

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Background: Spinal subdural hematoma (SSH) is a rare condition arising from coagulopathy, vascular abnormalities, iatrogenic, or idiopathic causes. Management ranges from conservative treatment to surgical intervention, depending on the degree of neurological involvement. We present an unusual case of a spontaneous lumbar SSH in a 47-year-old man presenting with intractable headache.

Methods: Case Description: A 47-year-old man with a history of meningioma resection, unprovoked deep vein thrombosis on apixaban, and c-ANCA vasculitis on low-dose prednisone presented with a 2-day history of intractable headache, photophobia, nausea, and vomiting. He had engaged in heavy exertional activity the week prior to the onset of symptoms. Blood pressure was 146/99 mmHg and BMI was 35 kg/m2. Neurological examination revealed no focal deficits or meningeal signs. CT head was unremarkable. MRI brain demonstrated increased signal in the bilateral occipital lobes, raising concern for subarachnoid hemorrhage (SAH). CSF analysis showed WBC 2,000/μL (79% neutrophils), protein 252 mg/dL, glucose 33 mg/dL, and RBC 81,000/μL. A meningoencephalitis panel was negative, and CT angiography ruled out SAH. MRI lumbar spine subsequently identified nerve root enhancement and compression from a subacute subdural hematoma extending along the right lateral spinal canal from L2 to L5-S1. The patient improved with conservative pain management and was discharged neurologically intact and pain-free with outpatient neurology follow-up.

Results: SSH most commonly results from trauma, typically involves the thoracic spine, and classically presents with back pain or radiculopathy. This patient's atypical presentation of intractable headache without focal deficits meant SSH was not initially considered. Meningeal infection and SAH were among our top differentials given the CSF profile and clinical picture, but both were excluded. The diagnosis was ultimately established incidentally on lumbar MRI. We suspect heavy exertion during the week prior to the presentation precipitated a Valsalva-induced rupture of bridging veins, triggering a hemorrhage in our patient who was already on anticoagulation and had vascular fragility from ANCA vasculitis.

Conclusion: This case highlights the diagnostic challenge posed by atypical SSH presentation. Clinicians should maintain a high index of suspicion for spinal pathology in anticoagulated patients with unexplained intractable headache, even in the absence of classic features. Conservative management can be effective in neurologically intact patients. Further study is needed to characterize the relationship between immune-mediated vasculopathies, anticoagulation, and spontaneous SSH risk.

S162: Regional Balance of Monocyte-Derived Cells and Microglia in Ischemic Stroke Injury and Recovery is Regulated by NR4A1

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Co-Authors: *David Sullivan, PhD, Northwestern University Feinberg School of Medicine, Chicago, IL Zoie Lipfert, B.S., Northwestern University Feinberg School of Medicine Chicago, IL*

Background: Microglia are the most prominent resident immune cells of the brain and maintain homeostasis of the cerebral microenvironment. Following ischemia and ischemia/reperfusion (I/R) injury, many microglia die and those that survive expand to facilitate repair of damaged tissue. In response, circulating monocytes are recruited to the brain, where they differentiate into macrophages and microglia-like cells, termed monocyte-derived cells (MdCs). These cells contribute to both tissue repair and secondary injury. Microglia rapidly activate while recruited monocytes differentiate into diverse MdC subsets that can either promote recovery or exacerbate damage. The factors that influence the regional dominance of microglia or MdCs are not known but the nuclear receptor NR4A1 (Nur77) may be a key regulator of myeloid cell fate and function in both cell types.

Methods: To delineate the function and spatiotemporal distribution of microglial and MdC responses following ischemic stroke, we developed a novel dual-reporter mouse model to use with a murine transient middle cerebral artery occlusion (tMCAO). Microglial and MdC lineages are differentially labeled using adoptive bone marrow transfers and Cx3cr1- and Tmem119-cre drivers. Pulse labeling with 5-ethynyl-2'-deoxyuridine (EdU) was used to longitudinally track monocyte recruitment and turnover in the ischemic brain. EdU incorporation and NR4A1 protein expression were quantified with flow cytometry, and cell population

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distributions were quantified using fluorescence wide-field microscopy. The role of NR4A1 in microglia was examined using knockout (KO) recipients.

Results: Analysis of EdU enrichments revealed that MdCs are primarily derived from recently matured monocytes. Microglia proliferation was heterogenous throughout the infarct territory and correlated with EdU-positive MdCs, suggesting coordinated expansion. NR4A1 levels strongly correlated with the expansion of both MdCs and microglial cell populations. Deletion of Nr4a1 in microglia lead to a significant increase in MdC numbers ($P < 0.001$) compared to wild-type controls, supporting the role of NR4A1 in regulating MdC expansion. Taken together, these preliminary data suggest that NR4A1 deletion in microglia influences the recruitment of MdCs. **Conclusion:** Our findings demonstrate a closely regulated relationship between microglial and MdC expansion following ischemic stroke, with NR4A1 acting as a modulator of both cell types. NR4A1 appears to drive early MdC expansion while enhancing microglia expansion at later time points. Future studies will investigate NR4A1's cell-type-specific roles at subacute and chronic time points post stroke to examine its feasibility as a therapeutic target to facilitate recovery.

S163: A Conserved Developmental Axonal Growth Program in Adult Cortical Neurons After Stroke

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Background: Most recovery after stroke occurs within the first 3 months, a critical window marked by extensive remodeling of neural connections. Rodent studies indicate that this window reflects a transient period of heightened neuronal plasticity, during which surviving cortical neurons may be more permissive to repair. However, the transcriptional states that enable mature neurons to enter and sustain this repair-permissive period remain poorly defined. To resolve these programs across time, region, and cell type, we used single-nucleus RNA sequencing in a mouse model of stroke to identify neuronal states in regions that undergo post-stroke plasticity.

Methods: Using a photothrombotic model of focal motor cortical stroke in mice, we profiled approximately 135,000 nuclei from perilesional cortex (PLC) and contralesional cortex (CLC) at 3, 7, and 21 days post-stroke. We first identified a stroke-induced neuronal state in PLC and then trained a deep neural network classifier on this transcriptional signature to test whether it was present in the lesion-remote CLC. We next compared classifier-positive neurons with mouse and human developmental single-cell atlases and performed transcriptional regulatory network analysis to identify candidate regulators of this injury-evoked state.

Results: Stroke induced a discrete growth-associated neuronal state in PLC that emerged by day 3 and persisted through day 21. This state was identified across multiple cortical neuron subtypes and was enriched for transcriptional programs linked to excitability, axon growth, and synaptic remodeling. In the lesion-remote CLC, the deep neural network classifier identified this same stroke-associated neuronal state, but with distinct temporal and cellular specificity. Unlike the sustained response in PLC, CLC activation peaked transiently at day 7 post-stroke and was enriched in neuron populations anatomically linked to lesioned circuitry, including layer 2/3 intratelencephalic neurons and layer 5 extratelencephalic neurons, populations that are known to undergo post-stroke plasticity. Application of the classifier to developmental atlases showed that classifier-positive neurons most closely resembled developing cortical neurons during periods of active axon extension. Regulatory network analysis further identified overlapping regulators across injured mouse cortex, early postnatal mouse cortical neurons, and developing human neurons, supporting a conserved molecular program.

Conclusion: These findings identify a growth-associated neuronal state engaged across cortical regions during the post-stroke critical window. Specific subsets of adult cortical neurons appear to reactivate a conserved developmental program originally deployed for axon growth, revealing candidate molecular substrates for endogenous neuronal repair. This work establishes a framework for identifying and prioritizing neuronal pathways that may promote structural plasticity and circuit rewiring after stroke.

S164: Geographic and Risk-Factor Entrenchment of Intracerebral Hemorrhage in the United States: A GBD 2023 Analysis of 33-Year Trends and Sex Disparities

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Background: Intracerebral hemorrhage (ICH) is one of the most lethal stroke subtypes, yet national averages often obscure localized public health crises. We evaluated temporal shifts and geographic, age, sex, and risk-factor disparities from 1990 to 2023 to identify targets for precision prevention.

Methods: Utilizing the Institute for Health Metrics and Evaluation's (IHME) Global Burden of Disease (GBD) 2023 estimates, we analyzed age-standardized incidence (ASIR), prevalence (ASPR), death (ASDR), and disability-adjusted life-year (ASDALYR) rates across all 50 states and the District of Columbia. Temporal trends were assessed via estimated annual percent change (EAPC), and risk-attributable DALYs were examined.

Results: Nationally, ICH burden showed meaningful but heterogeneous declines - ASDR fell by 27.2% (12.41 to

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9.03) and ASDALYR by 26.1% (296.38 to 218.99). Temporal trend analysis confirmed significant annual declines: ASIR exhibited the fastest decline (EAPC: -1.30%), followed by ASDALYR (EAPC: -0.95%) and ASDR (EAPC: - 0.92%). ASPR remained near-stable (EAPC: 0.12%, non-significant). However, geographic inequality remains entrenched. In 2023, DALY rates in Mississippi (388.65), Alabama (354.21), and Louisiana (315.73) were more than 2.5-fold higher than in Connecticut (150.06), underscoring a marked regional concentration of burden. Burden peaked in individuals aged ≥75 years, with a pronounced male predominance; males had higher prevalence across all states and higher death rates (124.40 vs 110.02 in females). Modifiable vascular risk factors dominated the ICH burden. High systolic blood pressure was the leading driver (DALY 105.59), with an attributable burden more than double that of tobacco use (41.63). Alcohol use showed the most pronounced sex disparity, with attributable DALYs nearly fourfold higher in males (20.41) than in females (5.12).

Conclusion: National declines in intracerebral hemorrhage burden mask a concentrated regional burden in the Southeastern United States. The more than 2.5-fold disparity between high- and low-burden reflects ongoing gaps in vascular risk control and access to preventive care. High systolic blood pressure remains the primary actionable target, with its greater burden in the Southeast pointing to missed opportunities in prevention and early management. Community-based hypertension screening, pharmacy-led medication adherence programs, and telehealth-based management represent the highest-yield interventions. Sex-specific alcohol reduction strategies and expanded post-ICH rehabilitation pathways are equally critical to reversing these entrenched disparities.

S165: The Stalled Progress of Ischemic Stroke in the U.S.: A GBD 2023 Analysis of Geographic, Sex, and Metabolic Risk Disparities, 1990–2023

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Co-Authors: *Sameer Majety, MBBS, HCA Centerpoint Medical Center, Independence, MO; Devanshi Choksi, MBBS, SMT. NHL Municipal Medical College, Ahmedabad, Gujarat; Priyanka Ruparel, MBBS, Griffin Hospital, Derby, CT*

Background: While the United States experienced declining ischemic stroke mortality for decades, recent trends suggest a plateau in progress. We evaluated temporal, geographic, sex, and risk-factor disparities in ischemic stroke burden from 1990 to 2023.

Methods: Using the Institute for Health Metrics and Evaluation's (IHME) Global Burden of Disease (GBD) 2023 estimates, we analyzed age-standardized incidence (ASIR), prevalence (ASPR), death (ASDR), and disability-adjusted life-year (ASDALYR) rates across all 50 states and the District of Columbia. Temporal trends were assessed by calculating the estimated annual percent change (EAPC) with corresponding 95% confidence intervals (CIs). The contribution of risk factors to disability-adjusted life years (DALYs) was also analyzed. Descriptive statistics were computed using Microsoft Excel.

Results: A "prevalence paradox" emerged: ASIR declined from 96.17 to 70.04 (1990–2023), while ASDR reached a nadir of 17.07 in 2015 before plateauing and rising modestly to 17.75 by 2023. This stagnation coincided with an increase in ASPR to 1252.89, reflecting a shift toward chronic disability. Temporal analysis (1990–2023) showed a significant annual increase in the ASPR (EAPC 0.18%), reflecting a growing chronic disability burden.

Conversely, the ASDR (-2.0%), DALY rate (-1.4%), and ASIR (-0.7%) all demonstrated significant annual declines. Geographic clustering persisted, with Alabama (648.74), Mississippi (581.21), and Louisiana (522.69) exhibiting substantially higher DALY rates than the national average. A critical sex disparity reversal was observed: while males carried a higher burden in mid-life, females aged ≥75 years exceeded males in both DALY (5938.39 vs 5192.10) and death rates (451.98 vs 331.05). High systolic blood pressure was the leading attributable risk factor (DALY 205.40), followed by high LDL cholesterol (128.71) and high fasting plasma glucose (80.30), with alcohol-attributable DALYs showing a threefold higher burden in males.

Conclusion: The U.S. ischemic stroke profile is shifting from declining mortality to a growing burden of chronic disability. The plateau in mortality since 2015, persistent geographic clustering in Southern states, and reversal of sex disparities in older adults highlight gaps in current prevention strategies. Strengthening community-embedded vascular risk control, particularly hypertension, lipid, and glucose management, in high-burden regions is warranted. Sex-informed strategies addressing alcohol-related risk in males, along with expanded access to post-stroke rehabilitation, are important to reduce the gap between national gains and local burden.

S166: INDOBUFEN VERSUS ASPIRIN IN ACUTE ISCHEMIC STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Presenting Author: *Nabeel Bisiso, MD, Cincinnati, OH*

Background: Acute ischemic stroke remains a leading cause of mortality and long-term disability worldwide, contributing substantially to global health burden. Early antiplatelet therapy is critical in reducing recurrence and improving outcomes. Aspirin is the current standard of care; however, its use is limited by an increased risk of bleeding complications, particularly in high-risk populations. Indobufen, a reversible cyclooxygenase inhibitor, has emerged as a potential alternative with a shorter duration of platelet inhibition and a potentially improved safety profile, making it an attractive candidate for stroke management.

Methods: A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. PubMed, Embase, Cochrane Library, and ScienceDirect were searched through March 2026 for randomized controlled trials comparing indobufen with aspirin in adults with acute ischemic stroke. Primary outcomes included modified Rankin Scale(mRS) and National Institutes of Health Stroke Scale (NIHSS) at 90 days, as well as ischemic stroke at 90 days and composite vascular endpoint. Secondary outcomes

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included bleeding and other adverse events. Pooled estimates were calculated using fixed- or random-effects models based on heterogeneity.

Risk of bias was assessed using the Cochrane RoB 2.0 tool.

Results: Four RCTs were included after screening 278 records. Indobufen demonstrated no significant difference compared with aspirin in NIHSS improvement at 90 days (MD = 0.01, 95% CI: −0.07 to 0.09; $I^2 = 22\%$) or in the incidence of ischemic stroke at 90 days (OR = 0.54, 95% CI: 0.05–5.61; $I^2 = 66\%$). However, indobufen was associated with significantly improved functional outcomes, as measured by the modified Rankin Scale (mRS) (MD = −1.11, 95% CI: −1.32 to −0.90; $p < 0.00001$), and a lower risk of moderate-to-severe bleeding at 3 months (OR = 0.57, 95% CI: 0.35–0.92; $I^2 = 7\%$). No significant differences were observed in other safety outcomes.

Conclusion: Indobufen demonstrates efficacy comparable to aspirin, with improved functional outcomes and a reduced risk of short-term bleeding in patients with AIS. These findings suggest that indobufen may be a promising alternative antiplatelet agent; however, larger, high-quality trials are needed to confirm its long-term safety and efficacy.

S167: A Novel Autoinflammatory Disorder as an Unusual Cause of Stroke: A Case Report on the Cerebrovascular Complications of VEXAS Syndrome Before and After Transplant

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Background: VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a novel autoinflammatory disorder caused by UBA1 mutations, first described in 2020. Venous thromboembolism occurs in over 40% of patients, while arterial events affect more than 10%. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative option but has significant risks including infection and cytopenias. We present a case of both disease-driven and post-transplant cerebrovascular complications in a patient with VEXAS syndrome.

Methods: Case Report

Results: A 74-year-old man with two years of constitutional symptoms, macrocytic anemia, and Sweet syndrome was diagnosed with VEXAS after a bone marrow biopsy revealed a somatic UBA1 mutation. Despite immunosuppression, he developed deep vein thromboses and pulmonary emboli for which he was started on apixaban. During this hospitalization, he had a syncopal episode which prompted a brain MRI that showed an acute left frontal infarct without corresponding deficits. Stroke workup revealed an atrial septal aneurysm and patent foramen ovale (PFO) on transesophageal echocardiogram with a small left-to-right shunt, while transcranial doppler demonstrated a Grade 2 right-to-left shunt. The mechanism was attributed to VEXAS-related hypercoagulability. There was also some concern for paradoxical embolism, although PFO closure was deferred to avoid creating a new nidus for thrombi. Seventeen months later, he underwent allo-HSCT for refractory hematologic and dermatologic manifestations. Post-transplant, he was diagnosed with paroxysmal atrial fibrillation on telemetry but was otherwise doing well. Day 100 bone marrow biopsy showed complete donor chimerism without detectable UBA1 mutation. Unfortunately, he was found to be viremic with cytomegalovirus requiring ganciclovir, which caused severe thrombocytopenia (platelets 18,000/μL) and precluded further anticoagulation. He subsequently presented with left facial droop and dysarthria secondary to right hemispheric intraparenchymal hemorrhages. MRI also showed bihemispheric hemosiderin deposition concerning for cerebral amyloid angiopathy (CAA). MR vessel wall imaging was normal. Given the competing risks of ischemic stroke from atrial fibrillation versus hemorrhage from thrombocytopenia and CAA, he was referred for left atrial appendage closure.

Conclusion: There should be a high suspicion for cerebrovascular events in patients with VEXAS, particularly in those with preexisting cardioembolic risk factors. At minimum, VEXAS should prompt aggressive vascular risk factor optimization with close monitoring. Post-HSCT complications, particularly cytopenias from immunosuppression, GVHD, or opportunistic infections, have the potential to quickly tip the scale to a high bleeding risk. This case emphasizes the need for multidisciplinary management and ongoing reassessment of cerebrovascular risk in VEXAS, especially as patients transition through different treatment phases.

S168: The Gut Microbiome and Ischemic Stroke Outcomes: A Scoping Review

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Background: Current research suggests gut microbiome composition influences ischemic stroke severity and recovery, but the scope and consistency of these associations have not been comprehensively mapped. We conducted a scoping review to characterize the relationship between gut microbiota and ischemic stroke outcomes, identify recurrent microbial signatures, and highlight methodological gaps.

Methods: Following PRISMA-ScR guidelines, we searched PubMed, Embase, and Web of Science using MeSH terms and synonyms for ischemic stroke and gastrointestinal microbiome. The search was conducted in 2024 and updated in 2025. Two reviewers independently screened titles and abstracts and assessed full-text eligibility using Covidence, with disagreements resolved by discussion. Eligible studies included original human studies analyzing gut microbiome

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composition via 16S rRNA or shotgun metagenomic sequencing in relation to ischemic stroke outcomes, including NIHSS, mRS, cognitive assessments, and mortality. We identified 1,324 records, removed 640 duplicates, screened the titles and abstracts of 684, reviewed 82 full texts, and included 37 studies. Two reviewers independently extracted data using a structured tool with a calibration phase on five articles to ensure inter-rater reliability, followed by cross-checking for consistency.

Results: Included studies were predominantly prospective cohorts (70%) conducted in East Asia (92%), with sample sizes ranging from 27 to 349. The outcomes investigated varied widely, including 90-day mRS, cognitive impairment, stroke-associated pneumonia, post-stroke depression, and mortality. Beta diversity differed between outcome groups more consistently than alpha diversity, suggesting compositional shifts rather than diversity loss drive these associations. At the taxon level, the most consistent finding was depletion of short-chain fatty acid-producing bacteria in patients with worse outcomes, particularly Faecalibacterium, Roseburia, Coprococcus, Fusicatenibacter, and members of Lachnospiraceae. These taxa were associated with better outcomes across nearly all studies that examined them. In contrast, Enterococcus, Escherichia-Shigella, and other Enterobacteriaceae were consistently enriched in patients with greater stroke severity or worse functional outcomes. The few studies that directly measured fecal short-chain fatty acids supported these findings, with lower levels associated with worse outcomes. Most reported associations lacked covariate adjustment, dietary data were rarely collected, and longitudinal or interventional designs were scarce.

Conclusion: Depletion of short-chain fatty acid-producing gut bacteria is a reproducible signature of worse ischemic stroke outcomes and represents a candidate target for microbiome-directed therapeutics. Future work should prioritize geographically/ancestrally diverse cohorts with adequate power, standardized outcome definitions, more rigorous dietary data collection, and interventional designs testing whether modifying gut microbiota through pre/probiotics, dietary fiber supplementation, or targeted antibiotics can improve stroke recovery.

S169: Ischemic stroke following oocyte retrieval in young patients without known risk factors: A case series

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Background: Assisted reproductive technologies, including oocyte retrieval, are becoming increasingly utilized for family planning. Supraphysiologic estrogen levels during stimulation cycles are known to promote a prothrombotic state through effects on coagulation factors, platelet activation, and endothelial function (Mauicio, Circulation 2025). While thrombotic complications such as venous thromboembolism have been described, arterial events including ischemic stroke remain less well characterized, particularly in patients without traditional vascular risk factors.

Methods: We describe two young patients who presented with acute ischemic stroke shortly after undergoing oocyte retrieval. Clinical presentation, vascular risk factors, imaging findings, laboratory evaluation, and treatment course were reviewed.

Results: Both patients were young women without significant traditional stroke risk factors. Each underwent recent ovarian stimulation followed by oocyte retrieval within 21 days prior to presentation. Both presented with large vessel ischemic strokes though only one was a thrombectomy candidate and underwent thrombectomy of the left M1. Subsequent extensive evaluation, including cardiac monitoring, vascular imaging, and hypercoagulability workup, identified additional underlying risk factors such as migraine with aura and PFO. Neither patient had evidence of ovarian hyperstimulation syndrome at presentation. The temporal association with recent hormonal stimulation and procedural intervention raised concern for a prothrombotic state contributing to stroke risk.

Conclusion: These cases highlight a potential association between assisted reproductive treatments and arterial thrombotic events, even in patients without known stroke risk factors. Increased awareness and further investigation are needed to better characterize stroke risk in this population and to guide counseling and risk stratification in patients undergoing oocyte retrieval. Additionally, consultation for oocyte retrieval may serve as a meaningful opportunity for stroke risk factor screening in otherwise healthy young women.

S170: Stroke Savvy: A Multidisciplinary Bedside Game Series to Enhance Resident Teaching and Patient Understanding in Acute Stroke Care

Presenting Author: *Gelanys Castro, Neurology resident, Westchester Medical Center, Hawthorne, NY*

Co-Authors: *Tracey Milligan, Valhalla, NY, Adam Karp, Fair Lawn, NJ*

Background: Over my diverse experiences in healthcare, I observed recurring barriers to patient education: limited dedicated teaching time during hospitalization, extended use of medical terminology, and patients leaving stroke services for rehabilitation with minimal understanding of what caused their stroke, how to prevent recurrence, potential complications, or the recovery path. Prior educational interventions in stroke care have largely relied on written pamphlets, didactic sessions, or standardized discharge instructions, many of which have shown limited improvement in patient retention or satisfaction, especially among those with low health literacy. Interactive tools and teach-back methods are recommended, but they remain underutilized and lack adaptation for bedside use in busy inpatient settings. These gaps impair shared decision-making, reduce adherence to secondary prevention, and contribute to caregiver anxiety. As a PGY1 neurology resident, I aim to bridge this gap between complex neurologic care and patient comprehension.

Methods: We are designing "Stroke Savvy", a multidisciplinary series of 15-minute card and board games for bedside use during the inpatient workday. Five modules address core knowledge deficits observed: 1) Stroke Anatomy & Types, 2) Acute Therapies & Diagnostics, 3) Vascular Risk Factors & Secondary Prevention, 4)

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Complications & Warning Signs, and 5) Rehabilitation Milestones & Recovery Trajectory. Game mechanics include symptom-to-brain region matching cards to teach localization without jargon; word recall and risk-factor "action" cards to reinforce medication adherence and lifestyle changes; and a recovery pathway board game that simulates inpatient-to-rehab transitions, therapy goals, and common setbacks. Content is co-designed with stroke survivors, family caregivers, neurology residents, stroke nurses, and game designers through iterative focus groups to ensure clinical accuracy, cultural relevance, and workflow feasibility. Neurology residents and stroke nurses who serve as co-facilitators will receive a structured onboarding session prior to implementation.

Results: We plan to enroll 20 neurology residents and 40 patient-family dyads on a tertiary stroke service for a single-center pilot. Primary outcomes: pre/post changes in resident and nurse teaching confidence using the Patient Education Self-Efficacy Scale, and patient stroke knowledge using the validated Stroke Knowledge Test. Feasibility is defined as >80 percent session completion without delaying discharge workflows.

Conclusion: Stroke Savvy uses game-based learning and multidisciplinary co-facilitation to train residents and nurses in patient education, strengthening team-patient relationships, and empowering patients before rehab transfer. Stroke nurses reinforce teach-back, sustaining the intervention. This model is scalable to other programs and adaptable to TIA/ICH populations. Future work will assess the impact on medication adherence, blood pressure control, and readmission.

S171: Structural Brain Changes in Adult Patients with Type 2 Diabetes Mellitus in the Dominican Republic: A Case-Control Study

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Background: Type 2 diabetes mellitus (T2DM) is a growing health concern in the Dominican Republic, with a prevalence of 14.4% in urban populations. While T2DM is known to affect cognitive function, research on its impact on brain structure in Latin American populations is limited.

Methods: This case-control study investigated structural brain changes in 80 adults with T2DM (mean age 58.95 $\pm$ 7.88 years) and 80 non-diabetic controls (mean age 55.73 $\pm$ 7 years) from the Dominican Republic. Participants underwent extensive cognitive evaluation using a comprehensive neuropsychological battery assessing executive function, attention, learning, and memory. Magnetic resonance imaging (MRI) scans assessed cerebral atrophy, white matter lesions, and other structural brain abnormalities using the Fazekas Scale and Koedam Score.

Logistic regression analysis evaluated associations between T2DM, vascular risk factors, and brain structure.

Results: Advanced age (OR=1.26, 95% CI: 1.16-1.36, p<0.001) and hypertension (OR=2.74, 95% CI: 1.15-6.54, p=0.02) were significantly associated with global cortical atrophy. Lower HbA1c levels were linked to reduced medial temporal atrophy risk (OR=0.65, 95% CI: 0.44-0.96, p=0.03). 63.2% of T2DM patients exhibited global cortical atrophy, compared to 34.5% of controls (p=0.001). T2DM patients had significantly higher white matter lesion burden, with a mean Fazekas score of 1.83 $\pm$ 1.1 versus 1.01 $\pm$ 0.8 in controls (p<0.001). Koedam scores were also higher in T2DM patients, indicating greater cerebral vascular pathology. Cognitive assessment revealed significant differences between T2DM patients and controls in executive function (p=0.01), attention (p=0.02), and memory (p=0.03). Hypertension and higher homocysteine levels were associated with increased cerebral vascular pathology.

Conclusion: This study provides compelling evidence of structural brain changes and cognitive decline in adult patients with T2DM in the Dominican Republic. The findings highlight the importance of early detection and management of vascular risk factors, tight glycemic control, and lifestyle interventions to mitigate cognitive decline in patients with T2DM. Monitoring cognitive health and managing hypertension and hyperhomocysteinemia may reduce the risk of cerebral vascular pathology and cognitive decline. These findings have significant implications for the development of culturally tailored strategies to prevent and manage T2DM-related cognitive complications in the Dominican population.

S172-LB: Clinical Spectrum and Hemorrhagic Risk of Diffusion-Weighted Imaging-Negative Cases After Intravenous Thrombolysis in Acute Ischemic Stroke

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Background: Acute ischemic stroke (AIS) is a leading cause of adult disability and mortality. Early intravenous thrombolysis improves outcomes in eligible patients. However, a subset of patients remains diffusion-weighted imaging (DWI)-negative within 72 hours despite neurological deficits. These cases include true DWI-negative stroke/transient ischemic attack (TIA) and non-ischemic stroke mimics, yet their clinical spectrum, differential features, and post-thrombolysis safety profile remain incompletely characterized. A systematic understanding is essential to guide individualized clinical decisions and optimize thrombolysis safety.

Methods: 81 of 474 patients (17.1%) were DWI-negative. After clinicoradiologic adjudication, 71 were classified as TIA/DWI-negative stroke and 10 as stroke mimics: seizure (n=4), somatoform or functional disorders (n=2), facial neuritis (n=1), diphenidol toxicity (n=1), systemic lupus erythematosus (n=1), and cervical spondylosis (n=1). DWI negativity therefore did not simply denote stroke mimicry. Mimics were more likely when symptoms were anatomically

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discordant, temporal evolution was atypical, or ancillary imaging suggested a pattern outside a culprit arterial territory. Hemorrhagic complications occurred in 21 of 393 DWI-positive patients (5.3%) and in none of the 81 DWI-negative patients (P=0.034).

Results: DWI-negative findings after thrombolysis are relatively common and clinically heterogeneous, but most represent ischemic events rather than mimics. In this cohort, no DWI-negative patient developed post-thrombolysis hemorrhage. Integrating bedside neuroanatomy, vascular assessment, ADC confirmation, and follow-up MRI enhances post-thrombolysis adjudication, refines early diagnostic precision, and informs secondary-prevention strategies. This study provides the first systematic characterization of DWI-negative thrombolysis patients in a contemporary AIS cohort, offering actionable insights for stratified management.

Conclusion: We retrospectively analyzed consecutive patients treated with intravenous thrombolysis at The Second Qilu Hospital of Shandong University between August 2, 2020 and October 22, 2023. Of 506 screened patients, 474 with complete post-treatment imaging were included. DWI-negative status was defined as absence of acute diffusion restriction on DWI within 72 hours, confirmed on apparent diffusion coefficient (ADC) maps. To reduce false classification, scans were re-adjudicated against symptom localization, vascular imaging, clinical evolution, and follow-up MRI. DWI-negative cases were classified as TIA/DWI-negative stroke or non-ischemic mimics.

Post-thrombolysis hemorrhage was compared with DWI-positive patients using Fisher's exact test. Detailed assessment of non-ischemic mimics aimed to identify patterns relevant for differential diagnosis.

S173: Proximal Internal Carotid Artery Occlusion with Atypical Multifocal Infarcts: A Case Report

Presenting Author: *Raymond Chiang, BS, ScM, Elk Grove, CA*

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Background: Internal carotid artery (ICA) occlusion is frequently associated with severe neurologic deficits, high National Institutes of Health Stroke Scale (NIHSS) scores, and substantial morbidity and mortality. However, the presence of robust collateral circulation through the Circle of Willis and posterior circulation can significantly alter clinical presentation. We present a case of complete left ICA occlusion with unexpectedly mild neurologic deficits, emphasizing the protective role of collateral circulation and the diagnostic significance of border-zone infarction patterns.

Methods: A 73-year-old male with vascular risk factors presented approximately 13 hours after the onset of right-sided weakness, right-sided facial droop, dysmetria, and right inferior quadrantanopia. His NIHSS score was 4.

Magnetic resonance angiography (MRA) revealed complete occlusion of the left ICA with reconstitution of flow at the supraclinoid segment. Despite the ICA occlusion, the posterior circulation and Circle of Willis collaterals were intact. Magnetic resonance imaging (MRI) showed scattered left cerebral hemispheric infarcts with prominent left occipital lesions, suggesting posterior cerebral artery (PCA) involvement. Additional infarcts were seen in the anterior cerebral artery (ACA)-middle cerebral artery (MCA) watershed and MCA-PCA watershed regions. The patient was not a candidate for intravenous thrombolysis due to delayed presentation and was managed conservatively with dual antiplatelet therapy and high-intensity statin therapy.

Results: MRI revealed multiple small infarcts within the ACA-MCA and MCA-PCA watershed territories, as well as a prominent infarction in the left occipital lobe watershed, supporting the etiology of selective visual field deficits despite preserved global perfusion. Small cortical infarcts in the PCA territory were also identified, suggesting artery-to-artery embolism. MRA demonstrated complete occlusion of the left ICA with reconstitution of flow at the supraclinoid segment, indicating robust collateral perfusion through the Circle of Willis, likely via the PCA and ACA. Intact posterior circulation and preserved ophthalmic artery perfusion likely contributed to the absence of hemispheric deficits or ipsilateral monocular vision loss. Right lower quadrantanopia localized to the left cuneus supports partial preservation of the visual cortex perfusion through MCA-PCA dual supply.

Conclusion: This case demonstrates that complete ICA occlusion does not always correlate with severe neurologic impairment. Robust collateral circulation through the Circle of Willis and posterior circulation can preserve cerebral perfusion and limit infarct burden, leading to unexpectedly mild defects despite severe radiographic disease.

Recognition of watershed infarct patterns, collateral pathways, and selective visual deficits is essential for accurate localization, prognosis, and appropriate therapeutic decision-making in ICA occlusion.

S174: Effect of Statin Therapy on Clinical Outcomes in Patients with Embolic Stroke of Undetermined Source

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Background: The therapeutic role of statins in patients with embolic stroke of undetermined source (ESUS) remains unclear. We investigated the impact of statin administration on clinical outcomes in this population, including subgroups potentially vulnerable to statin therapy and those without prior clinical atherosclerotic cardiovascular disease (ASCVD), and further compared the efficacy according to statin intensity.

Methods: We conducted a nationwide, multicenter, prospective registry cohort including 5,787 patients diagnosed with ESUS. The primary composite outcome was net adverse clinical and cerebral events (NACCE) over 12 months, defined as all-cause death, recurrent stroke, acute coronary syndrome, or major bleeding. Outcomes were compared by statin

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exposure and by statin intensity. To address confounding, analyses used propensity score–based stabilized inverse probability of treatment weighting (IPTW).

Results: Patients treated with statins experienced a lower incidence of NACCE than untreated patients (7.41% vs 13.99%; adjusted hazard ratio HR 0.56; 95% confidence interval CI 0.39–0.82; P = 0.003). No significant difference in NACCE risk was observed between high-intensity and low-to-moderate-intensity statin regimens (HR 0.97; 95% CI 0.77–1.22; P = 0.792). Among secondary endpoints, all-cause mortality was reduced in the statin group (HR 0.60; 95% CI 0.41–0.89; P = 0.011), and major bleeding occurred less frequently in statin users than non-users (0.52% vs 1.31%; HR 0.37; 95% CI 0.14–0.96; P = 0.040). The association between statin use and improved outcomes was consistent across examined subgroups.

Conclusion: In this registry of ESUS patients, statin therapy was associated with a substantially lower risk of net adverse events and improved survival at one year, without an increased risk of major bleeding. These observational findings support the need for randomized controlled trials to confirm causality.

S175-LB: Surfer's Myelopathy: Is it time to call it Spinal Hyperextension Stroke?

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Background: Surfer's myelopathy is a rare, acute, non-traumatic spinal cord injury associated with spinal hyperextension and believed to result from spinal cord ischemia. Although initially described in inexperienced surfers presenting with back pain, paraparesis, sensory deficits, and urinary retention, nearly 40% of reported cases are unrelated to surfing. Activities such as yoga, gymnastics, ballet, and weightlifting have been identified as triggers due to their shared hyperextension mechanism. Because the activity-based terminology may contribute to anchoring bias and diagnostic delays, we propose the term "spinal hyperextension stroke" and present a representative non-surfer case with supporting literature review.

Methods: Spinal hyperextension stroke is increasingly recognized across diverse activities and age groups. Diagnosis relies on acute spinal cord symptoms following non-traumatic hyperextension with characteristic MRI findings, including anterior cord T2 hyperintensity and diffusion restriction. Proposed mechanisms include arterial compromise, venous congestion, transient hypoperfusion, and fibrocartilaginous embolism. A mechanism-based term better reflects the underlying ischemic pathophysiology and broadens recognition beyond surfing-related cases.

Results: Spinal hyperextension stroke remains an under-recognized cause of acute spinal cord ischemia. Renaming surfer's myelopathy may improve diagnostic accuracy, reduce anchoring bias, and enhance awareness among clinicians and at-risk populations, ultimately supporting earlier recognition, prevention, and appropriate stroke-oriented management.

Conclusion: A previously healthy 28-year-old woman developed acute bilateral lower extremity weakness after standing from a seated position following several hours of mopping. She initially experienced lower back pain, fatigue, and transient paresthesias radiating to the toes, followed by persistent thigh cramping and inability to bear weight. Neurologic examination revealed proximal-predominant bilateral leg weakness, decreased tone and reflexes, absent abdominal reflexes, and a T7 sensory level with preserved vibration and proprioception. Thoracic spine MRI demonstrated T2 hyperintensity and expansion of the distal cord and conus medullaris involving the anterior horns. Diffusion restriction and the characteristic "owl's eyes" appearance supported spinal cord infarction. Brain, cervical/lumbar MRI, and spinal angiography were unremarkable.

S176*: Gut Microbiome–Related Metabolites as Mediators of Environmental Risk of Ischemic Stroke: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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Background: Ischemic stroke (IS) is influenced by environmental factors beyond traditional vascular risk factors. Gut microbiome–related metabolites may represent intermediate pathways linking adverse environmental factors to vascular dysfunction. We assessed whether candidate metabolites mediate associations of perceived stress and the social vulnerability index (SVI) with incident IS in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods: In REGARDS, a national cohort of Black and White adults, perceived stress was assessed using the 4-item Cohen Perceived Stress Scale, and SVI was derived from 2000 Census tracts, including overall SVI and four domains (socioeconomic status, household composition and disability, minority status and language, and housing type and transportation). Incident IS events were physician-adjudicated. Candidate gut-related metabolites (guanosine, dimethylguanidino valerate [DMGV], cystathionine, kynurenic acid, D-gluconic acid, indole-3-lactic acid, and N-acetylneuraminic acid [NANA]) were selected based on prior evidence linking them

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to inflammation, endothelial dysfunction, and metabolic dysregulation. Participants with prevalent stroke at baseline and incident hemorrhagic stroke were excluded. Causal mediation analyses were conducted using weighted Cox proportional hazards models in the overall cohort and within race-stratified models. Model 1 adjusted for age, race, and sex; Model 2 additionally adjusted for education, income, hypertension, and type 2 diabetes, as appropriate.

Results: The analytic sample included 1,964 participants from a stroke case-cohort study within REGARDS, including 1,064 incident IS events (45.8% Black). For perceived stress, NANA mediated approximately 22% of the association with IS in Model 1; this effect attenuated to ∼10% and was no longer statistically significant in Model 2. D-gluconic acid mediated approximately 21% of the association between perceived stress and IS in Model 1 and also attenuated after further adjustment. For SVI, Theme 2 showed the most consistent findings. Guanosine, DMGV, and NANA each mediated roughly 10–15% of the association between SVI Theme 2 and IS across models. Among Black participants, D-gluconic acid mediated 19% of the association between SVI Theme 2 and IS in Model 1 and 11% in Model 2, while mediation by NANA (∼16%) was attenuated after additional adjustment.

Conclusion: Environmental exposures may influence IS risk through metabolic pathways linked to gut microbiome activity. Guanosine and DMGV are linked to inflammation, endothelial dysfunction, and metabolic dysregulation, key processes in cerebrovascular disease. NANA involved in glycoprotein metabolism and immune signaling, may reflect inflammatory or microbial processes contributing to vascular injury. These findings suggest that integrating social and biological data may improve understanding of mechanisms underlying IS.

S177: Conventional and Interaction-Informed Polygenic Risk Scores Reveal Environment-Dependent Genetic Effects on Ischemic Stroke Risk

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Background: Polygenic risk scores (PRS) for ischemic stroke (IS) capture inherited susceptibility but may not fully reflect heterogeneity in genetic risk across psychosocial and neighborhood-level exposures. We evaluated environmental modification of polygenic risk and IS associations and compared conventional-PRS (cPRS) with an interaction-PRS (iPRS) framework.

Methods: We analyzed participants from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, with incident physician-adjudicated IS as the outcome. Participants with prevalent stroke at baseline and incident hemorrhagic stroke were excluded. Environmental exposures included depressive symptoms assessed using the 4-item Center for Epidemiologic Studies Depression Scale, perceived stress assessed using the 4-item Perceived Stress Scale, and the Social Vulnerability Index (SVI) and related thematic components derived from 2000 U.S. Census tract data. cPRS were derived using GIGASTROKE (ID:PGS002724) and calculated using the PLINK score function. iPRS were constructed using a gene×environment interaction framework based on SNP×Environment effects, incorporating an 80/20 split for model development and evaluation. Logistic regression models adjusted for age, sex, and the first 10 ancestry-specific principal components were used to evaluate effect modification (EM) of associations between cPRS and iPRS (per SD) and IS by environmental exposures across multiple PRS parameterizations. PRS×Environment interaction terms were tested separately within ancestry strata.

Results: The analytic sample included 8,205 Black (561 IS cases) and 1,527 White (367 IS cases) participants. In cPRS analyses, depressive symptoms demonstrated the consistent evidence of EM of the association between cPRS and IS across ancestries, with significant interactions observed in both White ($p=0.019$) and Black ($p=0.037$) participants. Stress modified the association between cPRS and IS among Black participants ($p=0.019$), with no evidence of EM observed in White participants. SVI showed limited and inconsistent evidence of EM, with isolated signals across select themes in both Black and White participants. In contrast, iPRS identified a more structured pattern of EM. Depression-iPRS showed significant within-domain EM in White participants ($p=0.024$), alongside additional EM through SVI ($p=0.033$). Stress-iPRS demonstrated EM of iPRS and IS associations in both neighborhood-level and depressive domains, including associations with SVI in White participants ($p=0.045$) and depressive symptoms in Black participants ($p=0.048$). SVI-iPRS showed the strongest signal for modification of stress-related associations in Black participants ($p=0.015$), with less pronounced associations in White participants.

Conclusion: cPRS showed limited evidence for environmental modification, whereas iPRS identified cross-domain interactions linking psychosocial and neighborhood-level exposures. These findings highlight heterogeneous gene×environment interplay in IS, with implications for improving environment-specific genetic risk stratification across diverse populations.

S178: Trends in Mortality Involving Stroke and Falls Among Older Adults in the United States from 2000 to 2023: A Nationwide Retrospective Analysis

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Background: Falls are a commonly devastating complication for stroke survivors, leading to increased disability, reduced quality of life, and higher healthcare costs. The co-occurrence of these two events presents a significant, preventable public health burden. This study aims to examine national mortality trends from 2000-2023 involving stroke and falls in adults ≥65 years, and assess disparities by sex, age, race/ethnicity, region, and urbanization.

Methods: Multiple-cause-of-death data for adults ≥65 were obtained from CDC WONDER using ICD-10 codes for stroke and falls. Age-adjusted mortality rates (AAMRs)/100,000 were calculated using the 2000 U.-S. standard population and stratified by year, sex, race/ethnicity, age group, census region, and urban-rural classification. Temporal trends were assessed using Joinpoint regression, reporting annual percent change (APC) and average annual percent change (AAPC) with 95% confidence intervals.

Results: From 2000-2023, there were 46,406 deaths involving both stroke and falls. The overall AAMR increased from 3.36 in 2000 to 6.65 in 2023, with the most significant change occurred between 2015 and 2021 (APC:9.51*, 95% CI: 7.56-11.50). Overall, an increase was evident with an AAPC of 3.00* (95% CI: 2.24- 3.78). Mortality rates were lower in females (3.93) than males (4.87). By race, mean AAMRs were highest among NH Whites (4.77), followed by NH Blacks (3.09), and Hispanics (2.19). Crude mortality was greatest in 85+ (17.96), compared to 75-84 (4.43) and 65-74 (1.01). Regionally, the Midwest had highest rates (5.60), followed by West (5.06), South (3.95), and Northeast (2.66). Rural areas had higher rates (4.76) than Urban (3.77). State-level analyses showed marked disparities: between 2000 and 2020, AAMRs ranged from 14.79 in Minnesota to 1.71 in New Jersey. From 2021-2023, Connecticut recorded the lowest AAMR (1.23), while Colorado had the highest (21.80).

Conclusion: Persistent disparities by age, race, and geography highlight the need for targeted interventions. Strategies should emphasize comprehensive stroke rehabilitation, community-based fall prevention programs, and improved post-stroke care access in rural and high-burden regions.

S179: Scrambler Therapy to Reduce Central Post-Stroke Pain: A Pilot Suggesting Evidence of Cortical and Network Reorganization Using Magnetoencephalography

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Background: Scrambler therapy, a noninvasive electrocutaneous device that treats chronic pain, has been shown to significantly reduce symptoms for ∼70% of individuals with central post stroke pain. Mechanisms underlying pain reduction following treatment are not fully understood; however, modulation of an underlying thalamocortical dysrhythmia (TCD) is one possibility. In this study we use magnetoencephalography (MEG) to explore the role of TCD in post-stroke pain, and evaluate neuroimaging signatures that may predict response to treatment.

Methods: Five patients with pain secondary to prior stroke underwent MEG recordings immediately before and after their first neuromodulation session. Pain was reported using a 1-10 point Likert scale pre- and post-treatment for all sessions. Patients with 150% reduction in pain over five sessions were defined as treatment responders. Five stroke patients without pain and five individuals with no stroke or chronic pain were used as control groups for comparison. Source-level activity for each participant was reconstructed across all frequency bands. Network-localized Granger causality was used to estimate band-specific directional functional connectivity, and specific networks of interest including the default mode, salience, limbic and central executive networks, all implicated in TCD, were explored in secondary analyses. Differences in neuroimaging characteristics were evaluated between patients with post-stroke pain and controls as well as responders versus non-responders.

Results: Source-level analyses revealed increased (abnormal) activation of the dorsal anterior cingulate cortex in stroke patients experiencing pain within the theta, beta and gamma frequency bands compared with both control groups, consistent with TCD. Following treatment, further increases in theta, as well as increased alpha activity was observed, which may occur acutely prior to the classic reduction expected from TCD, due to overcompensation, or rebound effect. Functional connectivity analyses also demonstrated increased frontal lobe connectivity in patients with post-stroke pain within the theta, beta and alpha bands at baseline, as well as higher connectivity within limbic areas for multiple bands compared to controls. Traditional connectivity patterns, originally observed only in the control group without prior stroke or pain, were restored following treatment for responders (n=3), but not non-responders (n=2).

Conclusion: MEG patterns in patients with post-stroke pain offer some support for TCD as an underlying mechanism. Furthermore, changes observed following a single treatment session may help predict overall response to treatment. Larger studies are underway to explore TCD as a neurophysiologic explanation for this complex central pain syndrome and the utility of MEG as a potential biomarker for the treatment response.

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S180: Intrinsic Vulnerability of the Deep White Matter to Hypoxic–Ischemic Injury Due to Watershed Physiology

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Background: The deep white matter is particularly susceptible to injury across a range of hypoxic–ischemic conditions, yet the physiological basis for this vulnerability remains incompletely defined. We hypothesized that even in healthy young individuals, this region exhibits "watershed physiology," characterized by relatively low cerebral blood flow (CBF) and compensatory elevation in oxygen extraction fraction (OEF), reflecting limited metabolic reserve. We further hypothesized that diverse hypoxic–ischemic disorders would produce convergent spatial patterns of white matter injury that align with this intrinsic physiological vulnerability.

Methods: Voxel-wise CBF and OEF maps were generated in neurologically healthy adults (mean age 42 years, 63% females) using arterial spin labeling and asymmetric spin echo MRI. Group-average maps of CBF and OEF were constructed to define baseline physiology after registering them towards the International Consortium of Brain Mapping (ICBM) template. Lesion probability maps in the ICBM template space were derived from three disease cohorts: (1) watershed infarcts due to unilateral carotid occlusion (WI) from trace diffusion weighted imaging (DWI), (2) silent infarcts in sickle cell disease (SCD), and (3) white matter hyperintensities in cerebral small vessel disease (CSVD) from fluid-attenuated inversion recovery (FLAIR) sequences. The spatial correlations between the average control OEF (and CBF) and the three lesion probability maps were assessed using permutation tests with variogram matching, as implemented in BrainSpace (2000 permutations).

Results: In healthy controls, the deep white matter demonstrated a distinct pattern of watershed physiology, with reduced CBF and elevated OEF. Across all three disease cohorts, voxels with higher lesion probability correlated with corresponding voxels of lower baseline CBF (WI: $r=-0.150$; SCD: $r=-0.259$; CSVD: $r=-0.409$, all with $p<0.001$) and higher baseline OEF (WI: $r=0.235$; SCD: $r=0.199$; CSVD: $r=0.354$, all with $p<0.001$) in the maps of controls. These relationships were consistent across modalities and robust to permutation testing.

Conclusion: The deep white matter exhibits intrinsic metabolic stress even in young, healthy individuals, reflected by elevated OEF in the setting of reduced CBF. This physiological state defines a region of limited oxygen reserve that is selectively vulnerable to injury across multiple hypoxic–ischemic disorders, including WI, SCD, and CSVD. These findings support a unifying, physiology-based framework for understanding the spatial distribution of white matter injury.

S181: Deficits in Executive Function Selectively Contribute to Upper Extremity Motor Impairment After Stroke

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Background: Deficits in different cognitive domains are common after stroke and known to influence motor function. The domains of executive function support planning, attending to, and selecting appropriate goal-directed actions, which are fundamental to upper extremity (UE) movement. Thus, deficits in executive function may selectively contribute to UE motor impairment after stroke. Here, we aim to test whether deficits in executive function processes are selectively associated with UE motor impairment after stroke.

Methods: Fifty-four adults with UE motor impairments were assessed approximately three months post-stroke. Cognition was measured using MoCA domain sub-scores, and motor impairment with the UE Fugl Meyer (UE-FMA).

Spearman correlations evaluated relationships between cognitive and motor deficits. Voxel-based lesion-symptom mapping (VLSM) identified lesion locations associated with deficits in cognitive and motor function. Lesion-based functional connectivity was estimated using a 1,000-person normative connectome and averaged within Yeo–Schaefer atlas (Yeo et al., 2011) parcels to derive network-specific disconnection indices across seven functional networks.

Results: Executive-visuospatial abilities ($\rho=.46$, $p=.0015$) and attention ($\rho=.23$, $p=.0126$) showed significant associations with UE-FMA, whereas non-executive function abilities (language, memory) did not. Injury patterns linked to UE motor impairment and executive functions were highly overlapping: 42.5% of significant voxels associated with motor impairment overlapped with voxels associated with executive function, particularly in the dorsolateral frontal cortex and anterior insula. Network disconnection analyses showed that lesions exhibited the greatest disconnection with dorsal and ventral attention networks, exceeding disconnection observed in other large-scale cognitive networks (visual, limbic, default mode).

Conclusion: Deficits in executive function demonstrate selective associations with UE motor impairment after stroke compared to other cognitive deficits. There was substantial overlap between areas of injury associated with deficits in executive function and UE motor function. Lesions causing UE impairment demonstrated selective disconnection with attention-related networks. Together, these findings highlight the importance of executive functions for UE motor function.

S182: Comparative Effectiveness and Safety of Prasugrel Versus Clopidogrel in Ischemic Stroke: A Systematic Review and Meta-Analysis of Randomized Trials

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Background: Stroke is the second leading cause of death worldwide, and recurrent events substantially increase morbidity and disability. In non-cardioembolic ischemic stroke or high-risk transient ischemic attack (TIA), antiplatelet therapy is crucial for secondary prevention. Clopidogrel is widely used but demonstrates variable efficacy due to CYP2C19 polymorphisms. Prasugrel provides more consistent platelet inhibition independent of this pathway, though concerns regarding bleeding risk remain. Evidence, largely from Japanese trials using low-dose prasugrel (3.75 mg), suggests potential ischemic benefit with acceptable safety. We systematically compared prasugrel versus clopidogrel for secondary stroke prevention, evaluating efficacy and safety outcomes.

Methods: A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. The protocol was registered in PROSPERO under the number CRD420261356102. PubMed, Scopus, and Embase were searched through January 2026. Eligible studies were randomized controlled trials enrolling adults with ischemic stroke comparing prasugrel versus clopidogrel monotherapy for secondary prevention. The primary outcome was major adverse vascular events (composite of stroke, myocardial infarction, and cardiovascular death). Secondary outcomes included life-threatening, major, or clinically relevant bleeding events; drug-related adverse events; serious adverse events; and adverse events leading to discontinuation. Random-effects models were used to pool risk ratios (RRs). Risk of bias was assessed using the RoB-2 tool.

Results: Three RCTs comprising 4,416 patients were included. No significant difference was observed in major adverse vascular events (RR 1.00; 95% CI 0.40–2.51; p=0.99; I^2=47.4%), although estimates were imprecise.

Bleeding outcomes were comparable between groups (RR 1.05; 95% CI 0.86–1.29; p=0.38; I^2=0.0%). Drug-related adverse events (RR 1.05; 95% CI 0.87–1.27; p=0.35; I^2=0.0%), serious adverse events (RR 1.02; 95% CI 0.97–1.08; p=0.26; I^2=0.0%), and adverse events leading to discontinuation (RR 0.83; 95% CI 0.50–1.37; p=0.25; I^2=16.6%) did not differ significantly between groups. All included trials demonstrated low risk of bias.

Conclusion: In patients with non-cardioembolic ischemic stroke or high-risk TIA, prasugrel demonstrated similar effectiveness and safety compared with clopidogrel, with no significant differences in major adverse vascular events, bleeding risk, or overall adverse events. Available randomized data, largely based on low-dose prasugrel regimens, indicate comparable efficacy and safety between agents. However, the limited number of trials, moderate heterogeneity in efficacy outcomes, imprecision of effect estimates, and predominance of Asian populations constrain generalizability. Larger, adequately powered randomized studies across diverse populations using standard dosing strategies are needed better to define the role of prasugrel in secondary stroke prevention.

S183: GLP-1 Receptor Agonists for Post-Stroke Recovery and Secondary Prevention: A Systematic Review and Meta-Analysis

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been associated with reduced stroke risk in cardiovascular outcome trials among patients with cardiometabolic disease, but their effects on neurological recovery after stroke remain uncertain. We aimed to evaluate the association between GLP-1RA therapy and functional and clinical outcomes after stroke through a systematic review and meta-analysis.

Methods: We conducted a systematic review in accordance with PRISMA 2020 guidelines, searching PubMed, Scopus, Web of Science, and Embase up to January 29, 2026. Randomized controlled trials and observational studies comparing GLP-1RA therapy with standard care in adults with ischemic or hemorrhagic stroke were included. The primary outcome was favorable functional recovery, defined as a modified Rankin Scale (mRS) score of 0–2. Secondary outcomes included stroke recurrence, mortality, and healthcare utilization. Random-effects models were applied for data synthesis. Risk of bias was assessed using the RoB-2 and ROBINS-I tools. The protocol was registered in PROSPERO (CRD420251272831).

Results: Seven studies (n=28,534; four RCTs, three cohort studies) were included. In pooled analysis, GLP-1RA use was not associated with improved functional recovery (RR 1.08; 95% CI 0.87–1.35). GLP-1RA therapy was associated with reduced stroke recurrence (RR 0.74; 95% CI 0.57–0.95) and fewer emergency department visits (RR 0.86; 95% CI: 0.77–0.96). Although pooled estimates suggested lower mortality (RR 0.58; 95% CI 0.34–0.99), this finding was driven primarily by observational studies.

Conclusion: Current evidence does not support a benefit of GLP-1 receptor agonists for short-term functional recovery after stroke. GLP-1RAs may reduce recurrent cerebrovascular events and healthcare utilization. However, the predominance of short treatment durations and limited long-term data constrain conclusions regarding potential neurorecovery effects. Larger, longer-duration randomized trials are needed to clarify the role of GLP-1RAs in post-stroke recovery and secondary prevention. Limitations include few studies for functional recovery, short follow-up duration, and predominance of observational data for mortality outcomes.

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S184: Community-Engaged Stroke Prevention Interventions Addressing Health Disparities in the United States: A Systematic Scoping Review

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Background: Stroke disparities persist across racial, socioeconomic, and geographic groups in the United States, with a disproportionate burden in rural communities and the South. Although interventions have been developed to improve stroke prevention and management in underserved populations, approaches vary widely in target populations, community engagement strategies, and delivery methods. This heterogeneity limits identification of approaches that may be most relevant for reducing inequities in stroke-related outcomes. This systematic scoping review aims to characterize how randomized stroke prevention interventions engage underserved populations and where important evidence gaps remain, particularly in rural settings.

Methods: We conducted a systematic scoping review of randomized controlled trials evaluating U.S.-based interventions relevant to primary and secondary stroke prevention, including management of stroke-related cardiovascular risk factors. Searches of PubMed, Embase, Web of Science, and CINAHL were developed iteratively with a medical librarian and tailored to each database. Records were imported into Covidence for screening and review management. Title and abstract screening is being performed by 2 independent reviewers using a priori inclusion and exclusion criteria. Planned data extraction includes intervention type, target population, community-engagement strategy, geographic setting (urban vs rural), and delivery modality, including telehealth.

Results: After removal of 1,030 duplicates, 2,465 citations remained in Covidence for screening. In a pilot calibration phase, five reviewers achieved strong agreement on title and abstract screening decisions (Fleiss' kappa = 0.754, n=10), supporting the consistency of the eligibility framework prior to full dual-review screening. Final analyses will characterize the range of intervention designs, populations served, community-engagement approaches, and representation of rural versus urban settings.

Conclusion: This review will provide a rigorous overview of randomized, community-engaged stroke prevention interventions addressing health disparities in the United States. By systematically mapping how underserved populations are represented across intervention studies, this work will help identify gaps in the evidence base and inform future adaptation of stroke prevention strategies for populations most affected by inequities.

S185: Thrombolysis in the Delayed Treatment Window for Acute Ischemic Stroke: Updated Systematic Review and Meta-analysis

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Background: Intravenous thrombolysis is a standard treatment for acute ischemic stroke, but has traditionally been limited to 4.5 hours after symptom onset. This time-based restriction may exclude patients with salvageable brain tissue, especially those with wake-up or unknown-onset strokes. Multimodal imaging allows for the identification of viable penumbra beyond traditional treatment windows. This study compiles randomized evidence evaluating intravenous thrombolysis in imaging-selected patients treated after 4.5 hours.

Methods: We conducted a systematic review and meta-analysis in accordance with PRISMA guidelines. PubMed, Embase, and Cochrane Central were searched through February 2026 for randomized trials comparing intravenous thrombolysis (alteplase or tenecteplase) with best medical therapy in patients presenting beyond 4.5 hours or with wake-up/unknown-onset stroke selected by imaging. The primary outcome was excellent functional outcome at 90 days (modified Rankin Scale [mRS] 0–1). Secondary outcomes included functional independence (mRS 0–2), symptomatic intracranial hemorrhage (sICH), and 90-day mortality.

Results: Fourteen trials involving 4,192 participants were analyzed. Intravenous thrombolysis improved excellent functional outcomes (mRS0-1) (risk ratio [RR], 1.22; 95% CI, 1.16–1.29) and functional independence (mRS0-2) (RR, 1.12; 95% CI, 1.07–1.18). Both alteplase and tenecteplase contributed to these benefits. Thrombolysis increased the risk of sICH (RR, 2.48; 95% CI, 1.62–3.84) but did not significantly affect 90-day mortality (RR, 1.15; 95% CI, 0.97–1.35).

Conclusion: In patients selected using advanced imaging, intravenous thrombolysis performed after 4.5 hours improves functional outcomes without increasing mortality, supporting a tissue-based rather than strictly time-based approach to treating acute ischemic stroke.

S186: Unilateral Ptosis as a Presenting Manifestation of Carotid Cavernous Fistula

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Background: A carotid cavernous fistula is an abnormal connection between the cavernous sinus and the carotid artery.

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Clinical manifestations are variable and depend on the side, location within the cavernous sinus, flow rate, and, mainly, the drainage pattern. We presented the case of a carotid-cavernous fistula presenting with unilateral ptosis.

Methods: Case report

Results: A 45-year-old female patient without significant past medical history presented with a one-week history of progressive left droopy eye and headache. The lab was significant for cocaine. On exam, mild left-sided ptosis was noted. The rest of her exam was unremarkable. CT head was negative for acute changes, CTA showed a left ICA aneurysm with a carotid cavernous fistula. Patient underwent a therapeutic angiogram with left ICA stent coiling.

Patient is steadily improving; her ptosis has disappeared over the following few days.

Conclusion: Carotid cavernous fistula commonly presents with ophthalmoplegia, orbital congestion and proptosis; however, incomplete oculomotor nerve palsy may be the only presenting signs. Clinicians should be aware of this symptomology. Early identification and treatment are warranted.

S187-K: Deletion of Astrocyte-Specific Toll-Like Receptor 4 Signaling is Cerebroprotective following Focal Cerebral Ischemia

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Background: The contribution of astrocytic Toll-like receptor 4 (TLR4) signaling to blood-brain barrier (BBB) dysfunction and ischemic brain injury remains incompletely understood despite increasing evidence linking innate immune activation to stroke progression.

While previous studies have shown that global TLR4 deficiency is neuroprotective following experimental stroke, the cell-specific mechanisms underlying this effect remain largely unknown. We hypothesized that the cerebroproctective effect of global TLR4 deficiency in focal cerebral ischemia may be cell-specific. We evaluated the effects of astrocyte-specific and endothelial-specific TLR4 deletion on neurovascular injury following transient middle cerebral artery occlusion (MCAO).

Methods: Tamoxifen-inducible conditional TLR4 deletion was generated using Aldh1/1-creERT2/TLR4flox/Ai14 mice to target astrocytes and Smoc-creERT2/TLR4flox/Ai14 mice to target endothelial cells. Cre-negative littermate controls were studied in parallel. BBB dysfunction was assessed using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Area under the curve (AUC) and time-to-peak (TTP) measurements were used to evaluate BBB permeability and perfusion abnormalities. Infarct volume was quantified during the acute and subacute phases following cerebral ischemia.

Results: Astrocyte-specific TLR4 deletion altered the response to cerebral ischemia. During the acute phase, astrocyte-specific TLR4 knockout mice exhibited significantly reduced infarct volumes compared with wild-type controls (19.83±2.80% vs 37.47±4.91%; p=0.0118). This protection persisted into the subacute phase, with infarct volumes remaining significantly reduced in astrocyte-specific TLR4 knockout mice compared with controls (9.8±5.3% vs 30.3±2.5%; p=0.043). In contrast, endothelial-specific TLR4 deletion did not confer comparable protection and demonstrated a trend toward larger infarct volumes compared with controls (39.22±9.89% vs 16.56±5.68%; p=0.1063). MRI-derived BBB permeability metrics were not significantly altered by genotype in either model (all p>0.05).

Conclusions: These studies identify astrocytic TLR4 signaling as an important mediator of ischemic brain injury following cerebral ischemia and provide a potential cellular mechanism for the neuroprotection previously observed in global TLR4 knockout mice. Importantly, endothelial-specific TLR4 deletion did not confer comparable protection, suggesting that astrocytes may represent a critical cellular source of TLR4-mediated injury after stroke. The sustained reduction in infarct volume following astrocyte-specific TLR4 deletion supports astrocytic TLR4 signaling as a promising therapeutic target for limiting infarct progression and improving recovery after ischemic stroke.

S188-LB*: Long-Term Neuropsychiatric Outcomes After Subarachnoid Hemorrhage: The Amplifying Role of Delayed Cerebral Ischemia in Dementia, Epilepsy, and Mood Disorders : A 5-Year Cohort Study

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Background: Subarachnoid hemorrhage (SAH) mainly affects working-age adults, with its impact going beyond the initial hospital stay. Though more patients now survive, we lack population-level data on long-term neuropsychiatric problems like dementia, epilepsy, and mood disorders. It's also unclear how much delayed cerebral ischemia (DCI) – the most important secondary brain injury after SAH – contributes to these outcomes longitudinally. This study examined the incidence of neuropsychiatric conditions after SAH and whether DCI increases that risk over five years of follow-up.

Methods: Among 73,007 SAH patients, epilepsy risk was over 11-fold higher than in matched controls (RR 11.25, 95% CI 9.95–12.71), dementia risk was 4-fold higher

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(RR 4.02, 95% CI 3.72–4.35), depression risk doubled (RR 2.08), and anxiety risk increased by 51% (RR 1.51); all p<0.0001. DCI further increased risk, with 18-fold higher epilepsy risk (RR 18.92, 95% CI 12.68–28.24), 7-fold higher dementia risk (RR 6.98, 95% CI 5.39–9.05), and nearly 4-fold higher depression risk (RR 3.89) versus controls. Five-year cumulative neuropsychiatric event rates were 37.5% in DCI patients, 26.5% in SAH patients without DCI, and 11.4% in controls (DCI vs controls: HR 4.97, 95% CI 4.44–5.55, p<0.001) and survival curves continued to diverge. Surgical clipping was associated with higher epilepsy (RR 1.48, p<0.001) and dementia risk (RR 1.46, p=0.013) than endovascular coiling, while mood disorder rates were similar.

Results: SAH carries a heavy and progressive long-term neuropsychiatric burden. DCI is the main driver of that risk, and continued separation of survival curves over five years suggests ongoing neurodegeneration rather than a one-time injury. These results suggest SAH be viewed as a chronic brain condition rather than solely an acute event. All survivors, especially those with DCI, may benefit from structured long-term neuropsychiatric follow-up.

Clinical guidelines should address seizure prophylaxis, routine cognitive screening, and early psychiatric referral for this high-risk population.

Conclusion: We conducted a retrospective cohort study using the TriNetX Research Network. We identified adults with nontraumatic SAH (ICD-10 I60) diagnosed between 2013 and 2020, excluding those with prior neuropsychiatric diagnoses to ensure new onset outcomes. DCI was defined by ICD-10 codes for cerebral ischemia (I67.82) or vasospasm (I67.84) during the index hospitalization. We performed three separate 1:1 propensity score-matched comparisons: SAH vs. matched controls (72,976 pairs), SAH with DCI vs. SAH without DCI (5,301 pairs), and SAH with DCI vs. matched controls (5,299 pairs). Incident dementia, epilepsy, depression, and anxiety were tracked over five years using Kaplan-Meier and Cox proportional hazards analyses.

S190: Mental Health Disparities Among U.S. Adults With Stroke History: A Cross-Sectional Analysis of Depression and Anxiety by Ethnicity

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Background: Stroke is a leading cause of long-term disability and is frequently associated with psychiatric comorbidities that may negatively affect recovery, functional outcomes, and quality of life. Depression and anxiety diagnoses are common among adults with stroke history, yet ethnic disparities in these associations remain insufficiently characterized. Hispanic/Latino populations may experience unique social, cultural, and healthcare-access barriers that contribute to disproportionate mental health burdens. This study evaluates the relationship between stroke history and depression and anxiety diagnoses among U.S. adults while examining whether Hispanic/Latino ethnicity is associated with greater psychiatric disparities.

Methods: We conducted a cross-sectional analysis using nationally representative U.S. adult health survey data. Participants were stratified by self-reported stroke history and ethnicity (Hispanic/Latino vs non-Latino). Primary outcomes included self-reported prior diagnoses of depression and anxiety. Statistical analyses included chi-square testing for prevalence comparisons, logistic regression to estimate odds ratios (ORs), and Z-tests to compare effect sizes between ethnic groups.

Results: Adults with stroke history demonstrated significantly higher odds of both depression and anxiety diagnoses compared with adults without stroke history. Among Hispanic/Latino adults, stroke history was associated with substantially greater odds of depression (OR 4.20, $p < 0.001$), whereas non-Latino adults also showed increased odds but with a comparatively weaker association (OR 1.87, $p < 0.001$). Anxiety diagnoses were similarly more prevalent among adults with stroke history in both ethnic groups, although ethnic differences were more pronounced for depression than anxiety. Comparative analyses suggest Hispanic/Latino adults with stroke history may experience a disproportionately elevated psychiatric burden, particularly in depressive disorders.

Conclusion: Stroke history is strongly associated with depression and anxiety diagnoses among U.S. adults, with Hispanic/Latino adults demonstrating especially marked disparities in depression. These findings underscore the importance of culturally responsive mental health screening, targeted psychiatric evaluation, and equitable access to comprehensive neurologic care. Addressing ethnic disparities in psychiatric comorbidity may improve both neurologic recovery and long-term psychosocial outcomes in vulnerable populations.

S191: Migraine-Associated Risk of Cervical Artery Dissection: A Systematic Review and Meta-Analysis

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Background: Cervical artery dissection (CeAD) represents an important cause of ischemic stroke in younger individuals. Although migraine has been implicated as a potential

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contributor, prior studies have yielded conflicting results, particularly when considering migraine subtypes and different clinical populations. This meta-analysis aimed to clarify the relationship between migraine and CeAD, with specific focus on aura status and stroke versus non-stroke settings.

Methods: We systematically searched PubMed, Embase, Scopus, and Web of Science from database inception through January 2026 for observational studies evaluating migraine in relation to CeAD. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were derived using a random-effects model with inverse-variance weighting.

Statistical heterogeneity was quantified using I^2 and τ^2 metrics. Subgroup analyses were conducted based on migraine subtype (with aura vs without aura) and study population (stroke vs non-stroke). Small-study effects were assessed using Egger's test.

Results: A total of 13 studies, including 15,674 participants and 3,443 CeAD cases, met inclusion criteria. Overall, migraine was associated with higher odds of CeAD (OR 1.88, 95% CI 1.52–2.32; $p < 0.0001$), with considerable heterogeneity across studies ($I^2 = 77.4\%$). When stratified by subtype, migraine without aura showed a significant association (OR 2.17, 95% CI 1.67–2.83), whereas migraine with aura did not (OR 1.23, 95% CI 0.80–1.89). The association remained consistent in both non-stroke cohorts (OR 2.03, 95% CI 1.56–2.64) and stroke cohorts (OR 1.82, 95% CI 1.30–2.54), with no meaningful difference between these groups. No evidence of publication bias was observed (Egger's $p = 0.64$).

Conclusion: Migraine, especially in the absence of aura, appears to be linked with an increased likelihood of CeAD. These findings suggest that migraine may serve as a relevant vascular risk indicator and underscore the importance of considering CeAD in migraine patients presenting with acute neurological deficits. Further research is needed to better understand the mechanisms driving these subtype-specific associations.

S193: Multi-lumen Vascular Profiles (MVPs): A Cross-species Microvascular Architecture in Human Aging Linked to Altered Cortical Blood Flow in a Model of Cerebral Small Vessel Disease

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Background: Multi-lumen vascular profiles (MVPs), also known as cortical raspberries, are an under-recognized but common microvascular feature in aged human brain tissues, manifesting as penetrating arterioles with multiple luminal compartments within a shared perivascular boundary. Their 3-D architecture and consequence on cerebral blood flow remains unclear. We recently found that a translational mouse model of cerebral small vessel disease (cSVD) exhibits vascular structures with remarkable similarity to human MVPs, providing an opportunity to understand their functional significance. Using this mouse model, we investigated hemodynamic alterations associated with MVPs, and control penetrating arterioles, using in vivo two-photon microscopy. Further, we characterized the 3-D microanatomy of MVPs in post-mortem human brain and compared these features to those in the mouse brain.

Methods: In vivo two-photon imaging was performed in 12-16-month-old TGF-β overexpressing (TGFOE) and wild-type (WT) mice to assess vascular structure and blood flow across all cortical layers. Penetrating arterioles were labeled with α-SMA, and MVP morphology in these mice was examined using in vivo two-photon imaging, imaging of optically-cleared tissue slabs, and super-resolution confocal microscopy. Post-mortem human brain samples from aged individuals known to exhibit MVPs were also examined after tissue clearing using two-photon imaging.

Results: TGFOE mice exhibited frequent MVP formations along penetrating arterioles, in contrast to the single-lumen penetrating arterioles observed in WT mice. MVPs appeared as bundled lumens extending from the trunk of the penetrating arterioles, often localized near offshoots from the main arterioles in mid-cortical depths. Cross-sectional imaging confirmed multiple discrete luminal compartments packed together within a single perivascular space, while side-views demonstrated structural continuity along the vessel axis. MVPs were associated with increased blood flow velocity and elevated capillary flow with heterogeneity in their downstream capillary beds compared to WT controls, suggesting maldistribution of perfusion. TGFOE mice, which exhibited an abundance of MVPs, also had reduced capillary density compared WT mice, suggesting that flow alterations could promote capillary rarefaction. 3-D reconstructions revealed strong microanatomic similarity between mouse and human MVPs, including similar αSMA-positive mural cell and astrocytic endfeet coverage. TGF-β1 overexpression was confirmed in the vicinity of human MVPs as a potential molecular link.

Conclusion: These findings suggest that altered blood flow dynamics associated with MVP structures in cortex may contribute to inefficient oxygen and nutrient delivery, positioning MVPs as a potentially important and under-recognized microvascular feature contributing to pathogenesis of cSVD. Ongoing studies are investigating the effect of MVPs on real-time oxygen delivery to brain parenchyma using oxygen imaging.

S194: Association of Retrieval Attempts and Procedure Time with Functional Outcomes Following Successful Endovascular Thrombectomy

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Background: Endovascular thrombectomy (EVT) is a key treatment for acute ischemic stroke (AIS) caused by large vessel occlusion (LVO). The Extended Thrombolysis in Cerebral Infarction (eTICI) scale assesses reperfusion after EVT. While eTICI 2c–3 (excellent reperfusion) typically yields better outcomes than eTICI 2b, clinical benefits appear to diminish as retrieval attempts and procedure times increase-even with successful recanalization. This study aims to evaluate the impact of retrieval attempts and procedure times on outcomes among patients achieving eTICI 2b or higher.

Methods: We retrospectively reviewed 455 patients with AIS and LVO who underwent EVT at our center (1/1/22–6/25/25) achieving eTICI ≥2b. Two blinded neurosurgeons verified eTICI scores via digital subtraction angiography, leaving 404 patients for analysis. Cohorts were stratified by retrieval attempts (1, 2, or ≥3) to assess procedural efficiency. Outcomes included 90-day functional independence (mRS 0-2), mortality, 24-hour ICH, and procedure time. Multivariable logistic regression identified independent predictors of mRS 0-2, specifically evaluating retrieval attempts and first-pass reperfusion status.

Results: Increased retrieval attempts correlated with longer procedure times (18 min for 1 pass vs. 46–57 min for ≥ 3 passes) and higher ICH incidence. First-pass success was common for eTICI 3 (73%) and 2c (67%), but rates plummeted with subsequent attempts, dropping to 7% and 13% by ≥ 3 passes. On multivariable analysis, ≥ 3 attempts independently reduced the odds of 90-day functional independence (OR 0.35, 95% CI 0.15–0.79, p=0.014). Conversely, first-pass eTICI 2c (OR 2.85, p=0.024) and eTICI 3 (OR 3.54, p=0.004) significantly increased the odds of 90-day functional independence.

Conclusion: Our findings show that in patients achieving successful reperfusion, the number of retrieval attempts and first-pass success is a key determinant of functional outcomes. First-pass eTICI 2c-3 is associated with significantly greater likelihood of achieving 90-day functional independence, while ≥ 3 passes significantly reduces the likelihood of favorable outcomes. Our study highlights a critical balance between pursuing more complete reperfusion and minimizing procedural risk, supporting a strategy that prioritizes early, high-quality reperfusion while avoiding excessive retrieval attempts that may reduce clinical benefit.

S195: Ten-Year Outcomes from a Teleneurology Service Offering Emergent Care to Patients in Community Settings

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Background: Community-based hospitals often do not have adequate neurology coverage. To address this need, Vanderbilt University Medical Center (VUMC) provided teleneurology services to 12 community-based hospitals from 2014 – 2025.

Methods: VUMC neurologists performed on demand video consultations for patients at community-based hospitals. Radiologic studies were uploaded and viewed using Jenesis, a medical image storage and transfer application developed at VUMC. Satisfaction surveys were administered to patients and community physicians via REDCap, a secure VUMC web application for online surveys. Patients rated the quality of the video connection, the care provided by the neurologist, and their feelings of telehealth as a means to meet their medical needs.

Community physicians rated the timeliness of connecting with VUMC neurologists and receiving clinical documentation, whether they found the neurologists helpful in managing patient care, and their overall satisfaction with the service during a specified 30-day timeframe.

Results: Between February 2018 and January 2026, 3,617 patients received satisfaction surveys, and 656 were completed (18%). The majority of patients reported they were able to hear (98%) and see (96%) the neurologist over video connection without difficulty. Ninety-five percent reported that the providers listened carefully to them and 94% reported the providers provided explanations in a way they could understand. Ninety-eight percent felt the neurologist treated them with courtesy and respect, 94% felt confident in the care provided by the neurologist, 92% were likely to recommend telehealth to others, and 90% felt comfortable participating in a telehealth visit and reported that it met their medical needs. Between February 2014 and December 2025, 28,319 teleneurology consults were completed. Physicians at 12 community hospitals were sent 4,965 satisfaction surveys and 636 were completed (13%). Ninety-seven percent reported satisfaction with the speed at which they were connected with a neurologist and how helpful they found the neurologists at managing patient care, 92% with the timeliness in receiving clinical documentation, and 95% reported satisfaction with the service overall. Community physicians, supported by consulting teleneurologists, successfully evaluated and treated 90% of patients, while only 10% required transfer to a higher level of care. The most common patient diagnoses included stroke (25%), altered mental status (11%), seizure (10%), weakness (8%), and headache (7%).

Conclusion: Teleneurology is an effective way to elevate the level of specialty neurologic care provided in community-based hospitals and enables most patients to remain closer to

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their homes and families. Both patients and community physicians reported high rates of satisfaction with the service.

S196-K: Single-Cell RNA Sequencing Identifies an Ischemia-Specific Immune Transcriptome in Human Acute Ischemic Stroke due to Large Vessel Occlusion

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Background: Acute ischemic stroke due to large vessel occlusion (AIS-LVO) remains one of the most devastating stroke subtypes, with poor outcomes persisting despite advances in reperfusion therapies. This variability in recovery highlights a gap in current AIS management, which primarily focuses on restoring blood flow but does not directly address the downstream molecular events of the ischemic cascade—including excitotoxicity, oxidative stress, inflammation, blood-brain barrier disruption, and apoptosis—that contribute to ongoing neuronal injury.

Early transcriptional responses following ischemic stroke provide a critical window into the molecular programs that determine whether injured brain tissue recovers or progresses to irreversible infarction. The Transcriptomic Inflammatory Biomarkers of Large Artery Stroke (TRAILBLAZE) study leverages peri-infarct endovascular sampling and single-cell RNA sequencing (scRNA-seq) to characterize early human cellular and molecular responses during AIS-LVO. By directly sampling hypoxic arterial blood distal to the occlusion during active ischemia, TRAILBLAZE aims to validate candidate pathways identified in preclinical models while uncovering novel human-specific mechanisms that may inform future cerebroprotective therapies.

Methods: TRAILBLAZE is a prospective observational study of patients ≥18 years old presenting to Washington University School of Medicine with anterior circulation AIS-LVO treated with endovascular thrombectomy (EVT) within 24 hours of last known well (LKW). During EVT, paired arterial blood samples were collected: (1) at groin puncture and (2) distal to the occlusion following microcatheter traversal through the thrombus. Buffy coats were isolated using a specialized cooling and storage protocol designed to preserve cell integrity for subsequent batch processing. Whole cell single-cell transcriptional profiling was performed using the 10x Genomics Chromium Next GEM-X Single Cell 5′ platform, followed by sequencing on the Illumina NovaSeq X Plus (∼50,000 reads per cell; ∼15,000 cells per sample). Sequence alignment and gene quantification were performed using Cell Ranger. Downstream analysis was conducted in Seurat and included stringent quality control filtering based on gene and UMI counts, mitochondrial RNA proportion, and putative doublets. Cell types were annotated using canonical marker genes and reference-based methods. Differential gene expression analysis was performed using the MAST hurdle model, adjusting for patient ID, batch effects, and cellular detection rate. P-values were corrected using the Benjamini–Hochberg method (FDR < 0.05), with additional filtering for absolute log2 fold-change ≥ 0.25. Gene ontology (GO) enrichment analysis identified overrepresented biological pathways among differentially expressed genes.

Results: A proof-of-concept analysis was performed on the first seven patients enrolled in TRAILBLAZE (mean age 67 years [SD 16.4], 57% male, mean LKW-to-groin puncture time 488 minutes). scRNA-seq yielded 97,137 cells across six major cell populations: B cells, T cells, monocytes, natural killer cells, erythrocytes, and platelets. Although cellular composition was similar between paired samples, post-thrombus blood demonstrated distinct transcriptional signatures, with 45,779 upregulated and 8,437 downregulated genes identified. $CD14^{+}$ monocytes represented the most transcriptionally active cell population and demonstrated increased expression of genes associated with innate immune regulation, GTPase-mediated signal transduction, myeloid differentiation, cytoskeletal remodeling, and regulation of T-cell activation. Across multiple cell types, there was broad downregulation of pathways involved in ribosome biogenesis, rRNA processing, ATP biosynthesis, and global protein synthesis. In parallel, pathways related to histone modification, RNA catabolism, and immune cell differentiation were upregulated.

Conclusions: These findings suggest that hyperacute ischemic stroke induces coordinated metabolic and immune reprogramming within post-thrombus arterial blood cells, characterized by suppression of energy-intensive biosynthetic processes alongside activation of adaptive cellular stress responses. Furthermore, $CD14^{+}$ monocytes appear to adopt a distinct vascular-interface immunoregulatory phenotype marked by controlled innate immune sensing, active trafficking, and early adaptive immune signaling. Although preliminary, these results establish a novel human model for interrogating ischemia-induced molecular responses during AIS-LVO. This approach may help overcome longstanding translational barriers in cerebroprotective drug development by identifying clinically relevant human-specific pathways and therapeutic targets during the earliest stages of ischemic injury.

S197: Post-Stroke Mortality and Structural Disadvantage: A NINDS Social Determinants of Health Framework Analysis

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Background: Post-stroke interventions have largely targeted downstream intrapersonal and intermediate factors, such as health behaviors and social support, even though these determinants often reflect upstream structural inequities. Using the 2023 NINDS social determinants of health (SDOH) framework, we assessed whether structural disadvantage

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fundamentally guides the mortality risk attributed to downstream factors among U.S. stroke survivors.

Methods: We analyzed adults ≥18 years with self-reported stroke from NHANES 1999–2018, linked to National Death Index mortality data. Variables were grouped sequentially into Structural (education, poverty-income ratio [PIR]), Intermediate (food security, healthcare access, insurance, housing, marital status), and Intrapersonal (disability, physical activity, depression, diet) domains. Within each domain, we defined high-advantage, intermediate, and high-disadvantage composite profiles and fit survey-weighted Cox models adjusted for demographics and nativity. We estimated standardized 5- and 10-year mortality risk differences across profiles. Sequential adjustment models progressively added intermediate and intrapersonal domains to structural models to mechanistically trace the attenuation of socioeconomic mortality gradients.

Results: Within their respective domains, specific downstream factors showed strong independent associations with all-cause mortality: not being married (HR 1.38), disability (HR 1.53), and physical inactivity (HR 2.19). However, these downstream vulnerabilities heavily clustered in structurally disadvantaged groups: stroke survivors living in poverty (PIR <200%) with less than a high school education were significantly more likely to be unmarried, disabled, and physically inactive. Evaluated independently, structural factors significantly increased mortality (PIR <200%: HR 1.31;

Conclusion: Although downstream factors such as marital status, disability, and physical inactivity act as strong predictors of post-stroke mortality, domain-based analyses demonstrate that they function primarily as mechanisms through which upstream structural inequities exert their fatal impact. The concentration of adverse downstream health profiles among structurally disadvantaged stroke survivors strongly suggests that structural conditions fundamentally organize downstream mortality risk. Interventions that narrowly target individual behaviors are unlikely to substantially reduce post-stroke mortality unless paired with strategies that address the underlying structural environments of poverty and limited educational opportunity.

S198: Incidence, Risk Factors, Clinical Significance, and Management Outcomes of Carotid Stent Fractures: An Updated Systematic Review and Meta-Analysis

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Background: Carotid artery stenting is an established alternative to endarterectomy for extracranial carotid stenosis. Metallic stent fracture is a recognized complication in coronary and peripheral stenting, yet its incidence and clinical relevance in the carotid territory remain poorly characterized. The sole prior systematic review (Sfyroeras et al., 2010) identified only 55 cases from 13 studies with a crude incidence of 8.9% across 201 stents. Since then, large cohort studies and a 1,021-patient multicenter randomized trial sub-analysis have expanded the evidence base, enabling formal quantitative synthesis for the first time. We aimed to determine the pooled incidence, risk factors, clinical significance, and management outcomes of carotid artery stent fractures through an updated systematic review and meta-analysis.

Methods: PubMed, Embase, Scopus, Web of Science, Cochrane CENTRAL, and Google Scholar were searched from inception through April 2026 following PRISMA 2020 guidelines, supplemented by FDA MAUDE and citation tracking. Two reviewers independently screened 84 unique records. Random-effects proportion meta-analysis calculated pooled fracture incidence. Mantel-Haenszel meta-analysis pooled odds ratios for fracture-restenosis association. Sensitivity analyses included leave-one-out and alternative tau-squared estimators. Meta-regression examined four candidate moderators. Publication bias was assessed using Egger regression and trim-and-fill.

Results: Thirty studies met inclusion criteria: eight cohort studies, one randomized trial sub-analysis, two case series, thirteen case reports, and seven MAUDE device reports. Eight cohort-level studies evaluating 1,956 stented carotid arteries were pooled quantitatively. Individual fracture rates ranged from 3.4% to 29.2%. The pooled fracture incidence was 7.8% (95% CI 4.7-11.5%; I^2=81%; prediction interval 0.4-21.9%). Leave-one-out sensitivity analysis confirmed robustness (range 6.2-8.9%). Stent fracture was significantly associated with in-stent restenosis across five studies (pooled OR 3.37; 95% CI 1.09-10.45; p=0.035), though the largest trial using the closed-cell Xact stent in 1,021 asymptomatic patients found no association (p=0.53). No study reported fracture-related stroke, transient ischemic attack, or death. Meta-regression identified proportion of symptomatic patients as the sole significant moderator of heterogeneity (p=0.009). Egger regression suggested small-study effects (p=0.008). Risk factors included type III vessel calcification (OR 3.9-4.7), angulation exceeding 45 degrees (OR 4.7-6.5), prior cervical radiation, elongated styloid process, and open-cell nitinol stent design.

Conclusion: This first meta-analysis of carotid stent fracture demonstrates a pooled incidence of 7.8% and a 3.4-fold increased odds of in-stent restenosis, though a clinically significant fracture-stroke association remains unestablished. The discrepancy between small-study and large-trial findings underscores the need for prospective multicenter registries using standardized fracture classification and radiographic surveillance protocols incorporating plain cervical radiographs.

S199: Developmental Venous Anomaly as a Locus of Ischemic Vulnerability: Cocaine-Precipitated Stroke

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Background: Developmental venous anomalies (DVAs) are the most common intracranial venous malformation, affecting 2–3% of the population. They are usually considered

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benign "leave-me-alone" lesions, discovered incidentally on imaging. Nonetheless, symptomatic presentations occur, most often with venous congestion or impaired outflow. Cocaine is a potent risk factor for ischemic stroke via vasospasm and prothrombotic effects. The concurrence of a DVA and cocaine exposure raises a key question: can a benign venous variant become a locus of ischemic vulnerability under systemic stress?

Methods: We report a 65-year-old man without vascular risk factors who presented with ten days of progressive right hemiparesis and dysarthria. Urine toxicology confirmed recent cocaine use. Non-contrast CT revealed subtle sulcal hypodensity; MRI confirmed an acute infarct in the left corona radiata. CT angiography and digital subtraction angiography identified a large frontoparietal DVA as the sole vascular anomaly. The infarct was strictly confined to the venous drainage territory of the DVA. No arterial stenosis, embolic source, vasculitis, or venous thrombosis was detected.

Results: The striking spatial concordance between the infarct and the DVA's venous territory, in the setting of an otherwise negative workup, suggests a non-coincidental relationship. Two mechanisms were considered: (1) an arterial infarct occurring coincidentally within this region, or (2) cocaine-induced prothrombotic and vasoreactive effects precipitating venous ischemia within the DVA. Prior literature supports susceptibility of DVAs to ischemia from impaired outflow or transient stasis, even without thrombosis. This case supports a synergistic model in which systemic stress unmasks latent venous vulnerability.

Conclusion: This case highlights a novel interplay: a DVA, typically benign, may serve as loci of ischemic vulnerability under systemic prothrombotic stress. The close topographic correlation between infarct and venous drainage territory supports a venous mechanism rather than a purely arterial event. Recognition of this possibility challenges the assumption DVAs are uniformly innocuous and highlights the need to consider venous pathology in select cases of ischemic stroke. DVAs should be considered in the differential for ischemic stroke, not only as mimics but as potential loci of injury.

S200: Isolated Left Callosal Body Infarction Presenting as Predominant Right Lower-Extremity Weakness

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Co-Authors: *Nasser Abdelall, New Orleans, LA*

Background: Isolated infarction of the corpus callosum is uncommon due to its robust collateral supply from both anterior and posterior circulations. When symptomatic, callosal infarcts are typically associated with disconnection syndromes, apraxia, alien-hand phenomena, cognitive or behavioral changes, gait disturbance, or nonspecific neurologic symptoms. Predominant contralateral lower-extremity weakness as the presenting feature of an isolated callosal body infarct is rare and may be mistaken for a medial frontal or corticospinal tract lesion.

Methods: A 60-year-old man with bipolar disorder, cannabis use disorder, nicotine use disorder, and HIV presented with acute right lower-extremity weakness. He reported heavy cannabis use prior to symptom onset and a similar transient episode months earlier. Examination revealed right lower-extremity drift with a NIH Stroke Scale score of 1. He exhibited no aphasia, dysarthria, sensory loss, neglect, visual field deficit, or ataxia. CT head was unremarkable. CT angiography showed no large-vessel occlusion or significant stenosis, and CT perfusion demonstrated no infarct core or penumbra. MRI brain revealed restricted diffusion with corresponding low ADC signal in the left callosal body without FLAIR hyperintensity, consistent with hyperacute infarction. The patient was treated with dual antiplatelet therapy for minor ischemic stroke and admitted for standard etiologic evaluation and secondary stroke prevention.

Results: The patient's leg-predominant weakness initially suggested involvement of the left anterior cerebral artery territory, particularly the medial frontal motor cortex or paracentral lobule. However, MRI localized the infarct to the callosal body. The corpus callosum contains topographically organized commissural fibers connecting bilateral motor networks. Disruption of fibers linking medial frontal and paracentral regions may produce contralateral lower-extremity–predominant weakness despite the absence of cortical, capsular, brainstem, or spinal cord involvement. Isolated callosal infarcts are rare and often present atypically, with diffusion-weighted MRI critical for diagnosis.

Conclusion: This case highlights an atypical presentation of isolated callosal body infarction manifesting as predominant contralateral lower-extremity weakness. In patients with focal motor deficits and unrevealing CT-based imaging, MRI is essential to identify small strategic infarcts, including callosal lesions. Recognition of this presentation may prevent diagnostic delay and broaden the clinical spectrum of corpus callosum infarction.

S201: Acute-Phase Inflammatory Biomarkers and Early Post-Stroke Depression: A Systematic Review

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Background: Post-stroke depression (PSD) is a prevalent neuropsychiatric complication following ischemic stroke and is associated with impaired functional recovery, reduced quality of life, and increased mortality. Acute inflammatory activation after cerebral ischemia has been implicated in PSD, affecting both neural signaling and stress-response pathways. Blood-based inflammatory biomarkers obtained during initial hospitalization may offer an accessible tool for early risk stratification. This study aimed to determine whether acute-phase inflammatory biomarkers are associated with PSD and whether associations differ by timing of depression onset following stroke.

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Methods: A systematic review was conducted in accordance with PRISMA guidelines across PubMed, Embase, PsycINFO, and Web of Science (January 2015-March 2026). Eligible studies included adults with ischemic stroke, measurement of blood-based inflammatory biomarkers within 14 days of onset, and assessment of depression at follow-up utilizing validated scales or DSM criteria. Cohort and case-control studies were included. Two independent reviewers screened studies and assessed full-text eligibility, with discrepancies resolved by consensus. PSD was classified as early (< 3 months), intermediate (3-6 months), or late (≥6 months).

Results: Fifteen studies (n= 4,218 participants) met inclusion criteria, with individual sample sizes ranging from 119 to 590 participants. Biomarker measurement was typically performed at admission or within 24 hours of hospitalization, and follow-up duration ranged from 1 to 24 months. Across studies, elevated acute-phase inflammatory biomarkers were associated with an increased risk of PSD, with the most consistent associations observed for early-onset PSD. Of these markers, the strongest reported associations included systemic immune inflammation index (SII; OR up to 3.50), platelet-to-lymphocyte ratio (PLR; OR up to 5.15), interleukin-6 (IL-6; HR 3.18), and macrophage migration inhibitory factor (MIF; OR 9.16). Additional biomarkers (GFAP, sTREM2, sNfL, ferritin, fibrinogen, TNF-α/IL-4 ratio) showed associations in individual studies but with greater variability. Evidence for late PSD remains limited, and one study suggested that conventional inflammatory markers added minimal predictive value.

Conclusion: Acute-phase inflammatory biomarkers are associated with PSD following ischemic stroke, particularly for early-onset PSD. SII, PLR, IL-6, and MIF showed the most consistent associations across studies. Evidence for late-onset PSD remains limited, highlighting the need for longer longitudinal follow-up in future studies.

Limitations include predominantly single-center study designs, heterogeneity in biomarker timing and outcome assessment, and reliance on single-time point biomarker measurements. Collectively, these findings suggest that acute-phase inflammatory markers may support early risk stratification, targeted monitoring, and future interventional strategies aimed at mitigating PSD.

S202: Enrollment Trends for Randomized Stroke Trials in the United States

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Background: Enrollment inefficiency in stroke clinical trials contributes to prolonged accrual, increased resource utilization, and underpowered or incomplete clinical trials. Factors related to enrollment performance remain poorly characterized. We conducted a structured review of recently published stroke clinical trials to assess enrollment trends and explore the relationship to trial-level characteristics/properties.

Methods: We searched PubMed, Embase, Cochrane and ClinicalTrials.gov for Phase III randomized controlled trials (RCTs) of stroke intervention, prevention, or recovery. We included RCTs published between 2015 and 2026 that enrolled at least 400 patients with at least one site in the United States (U.S.). Search terms included "stroke," "randomized controlled trial," "thrombolysis," "thrombectomy," "hemorrhage," "stroke prevention" and "TIA." We extracted trial duration, total enrollment, U.S. enrollment, and total site count. Enrollment rates were assumed as continuous recruitment. The association between site count and total enrollment was assessed using Spearman correlation, quantified using simple linear regression. Group comparisons of enrollment rate used the Mann-Whitney U test for two-group comparisons and the Kruskal-Wallis test for multiple groups. Statistical significance was set at two-tailed $p < 0.05$.

Results: Twenty-five trials enrolling 76,440 patients across 16 countries were identified. The median sample size was 850 patients (IQR 514–3,876) and median site number per trial was 89 (IQR 62–179). Total site count correlated strongly with total enrollment (Spearman $\rho = 0.609$, $p = 0.0012$, R2=0.742). The median enrollment rate was 0.182 patients/site/month (IQR 0.117–0.345). There was no statistically significant difference in enrollment rates between RCTs with predominantly international sites compared to trials with predominantly U.S. sites (0.345 per site/month vs 0.182 per site/month, $p = 0.222$). No significant difference in enrollment rate was detected across trial types ($H = 0.535$, $p = 0.765$). Among trials reporting granular US site-level data, 38.3% of U.S. sites enrolled fewer than five patients.

Conclusion: Total enrollment in US stroke clinical trials has a strong correlation with the number of enrolling sites. A high number of U.S sites in stroke clinical trials are low enrolling (<5 enrollments/trial). The impact of low enrolling sites on clinical trial recruitment, outcomes, and resource utilization is unknown. Identification and further study of site-level factors that predict high enrollment rates also require additional study.

S203: "I Can See": Anton Syndrome from Sequential Bilateral Occipital Injury in Cerebral Amyloid Angiopathy

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Background: Anton syndrome (visual anosognosia) is a rare manifestation of cortical blindness characterized by denial of

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visual loss and confabulation despite intact anterior visual pathways. It is most commonly described in the setting of bilateral posterior circulation ischemia, while hemorrhagic etiologies remain less well characterized.

Cerebral amyloid angiopathy (CAA), which preferentially involves posterior cortical regions and carries a substantial risk of recurrent lobar hemorrhage, represents a plausible but underrecognized substrate. Proposed pathophysiological mechanisms include disconnection between visual and language networks, impaired right hemispheric error monitoring, and pathologic "filling-in" in the absence of visual input.

Methods: case report and brief literature review.

Results: An 80-year-old left-handed woman with hypertension, vascular dementia, structural epilepsy, and known CAA initially presented with a left occipital infarction treated with thrombolysis, complicated by left parieto-temporal intraparenchymal hemorrhage resulting in receptive aphasia without motor deficits. One year later, she developed a large acute right parieto-occipital intraparenchymal hemorrhage. At this presentation, her receptive aphasia had partially improved; however, she exhibited complete cortical blindness (NIHSS 7; baseline mRS 2).

Despite total vision loss, she consistently denied any impairment and produced vivid but inaccurate descriptions of her surroundings, consistent with Anton syndrome. Examination demonstrated preserved repetition and simple command following, with impaired naming and color identification. No motor deficits were present. MRI sequences confirmed bilateral occipital injury from temporally distinct ischemic and hemorrhagic events, establishing the structural basis for cortical blindness with anosognosia.

Conclusion: This case supports a network-level model of Anton syndrome arising from sequential bilateral occipital injury across vascular modalities, extending beyond the traditional ischemic paradigm. Notably, partial recovery of language function appeared to unmask visual anosognosia, suggesting that evolving cortical deficits may dynamically reveal or obscure insight. CAA-related recurrent lobar hemorrhage may therefore represent a clinically relevant and underreported mechanism for Anton syndrome in older adults. Clinical implication: In patients with bilateral occipital injury-particularly in the setting of CAA-the most disabling deficit may be loss of awareness of blindness rather than blindness itself, necessitating deliberate assessment of insight, anticipatory safety planning, and tailored rehabilitation strategies.

S204: Invasive Versus Transcutaneous Vagus Nerve Stimulation Paired With Rehabilitation for Upper-Extremity Recovery After Stroke: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Presenting Author: *Shradha Kakde, MGM medical college and Hospital Aurangabad, Maharashtra*

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Background: Persistent upper-extremity impairment affects nearly half of stroke survivors and represents a major contributor to long-term disability. Vagus nerve stimulation (VNS) has emerged as a neuromodulatory therapy designed to enhance activity-dependent neuroplasticity when paired with task-specific rehabilitation. Both implantable (invasive) VNS and non-invasive transcutaneous VNS modalities have been evaluated in randomized controlled trials for post-stroke motor recovery. However, the magnitude of therapeutic benefit and potential differences between stimulation approaches remain incompletely defined.

Methods: A systematic search of PubMed, Embase, and the Cochrane Library was performed from database inception through January 2026 to identify randomized controlled trials evaluating VNS paired with rehabilitation in adult stroke survivors. Trials comparing invasive or transcutaneous VNS with sham stimulation or conventional rehabilitation were included. Two independent reviewers screened studies and extracted data. The primary outcome was change in the Fugl-Meyer Assessment Upper Extremity (FMA-UE) score. Secondary outcomes included Wolf Motor Function Test (WMFT) performance and functional independence measures. Random-effects meta-analysis was used to calculate pooled mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CI). Prespecified subgroup analyses compared invasive and transcutaneous stimulation modalities.

Sensitivity analyses excluding individual trials sequentially were performed to evaluate robustness of pooled estimates.

Results: Seven randomized controlled trials including 402 participants met inclusion criteria. VNS paired with rehabilitation significantly improved upper-extremity motor impairment compared with control therapy (MD 4.21, 95% CI 2.05–6.36; $p<0.001$). WMFT performance also improved (SMD 0.68, 95% CI 0.30–1.05; $p<0.001$).

Subgroup analysis demonstrated greater improvement with invasive VNS (MD 5.12, 95% CI 2.91–7.33) compared with transcutaneous VNS (MD 2.87, 95% CI 0.64–5.10). Heterogeneity across studies was moderate ($I^2=34\%$). Sensitivity analyses confirmed stability of results without single-study dominance. Rates of serious adverse events were low and comparable between groups.

Conclusion: Vagus nerve stimulation paired with rehabilitation significantly improves upper-extremity motor recovery after stroke. Both invasive and transcutaneous modalities demonstrate clinically meaningful benefits, with larger treatment effects observed in implantable VNS trials. These findings support neuromodulation-augmented rehabilitation as a promising strategy for enhancing functional recovery after stroke and warrant larger multicenter trials to define optimal stimulation approaches and patient selection.

S205: Endovascular Thrombectomy for Large-Core Ischemic Stroke: A Systematic Review and Meta-analysis of Randomized Controlled Trials with Imaging-Paradigm and Core-Severity Subgroup Analyses

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Background: Patients with large-core acute ischemic stroke were historically excluded from endovascular thrombectomy due to concerns regarding futility and hemorrhagic transformation. Six contemporary randomized trials have fundamentally reshaped this paradigm. Whether benefit persists across simplified imaging selection strategies and ultra-large infarct phenotypes remains clinically urgent.

Methods: PubMed, Embase, Cochrane Central Register of Controlled Trials, and international trial registries were searched from inception through January 2026 following Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. Eligible studies were randomized controlled trials comparing endovascular thrombectomy plus best medical management versus best medical management alone in anterior-circulation large-core ischemic stroke. Two reviewers independently screened records, extracted data, and assessed risk of bias using the Cochrane Risk of Bias 2 tool. The primary outcome was ordinal shift in the ninety-day modified Rankin Scale. Secondary outcomes included functional independence defined as modified Rankin Scale score zero to two, independent ambulation defined as modified Rankin Scale score zero to three, ninety-day mortality, and symptomatic intracranial hemorrhage. Prespecified subgroup analyses examined imaging selection paradigm, comparing simplified Alberta Stroke Program Early Computed Tomography Score or diffusion-weighted imaging-based selection against advanced perfusion or composite core selection, and infarct core severity comparing Alberta Stroke Program Early Computed Tomography Score zero to two against higher large-core strata.

Results: Six randomized controlled trials enrolling 1,893 patients met inclusion criteria. Endovascular thrombectomy significantly improved ninety-day disability on ordinal modified Rankin Scale analysis, generalized odds ratio 1.60, 95% confidence interval 1.40 to 1.80. Functional independence was achieved in 20% of endovascular thrombectomy-treated patients versus 7% receiving best medical management alone. Independent ambulation was significantly increased, relative risk 1.90, 95% confidence interval 1.50 to 2.50. Symptomatic intracranial hemorrhage risk was modestly elevated, relative risk 1.70, while ninety-day mortality trended toward reduction. Subgroup analyses demonstrated no convincing attenuation of treatment effect in simplified-imaging-selected trials or very-low Alberta Stroke Program Early Computed Tomography Score cohorts, though confidence intervals widened at the most extreme infarct volumes.

Conclusion: Endovascular thrombectomy confers clinically meaningful and statistically robust benefit in large-core ischemic stroke and should not be withheld solely on the basis of infarct size. Preservation of treatment benefit across simplified imaging paradigms is the most practice-changing finding of this synthesis, supporting faster and more pragmatic patient selection. Caution remains warranted at the ultra-large-core extreme. Future trials should standardize infarct volume thresholds and imaging selection criteria to enable precise patient-level risk-benefit.

S206: 30-Day Ischemic Stroke Following Transient Ischemic Attack: A National Study of Social and Clinical Determinants of Health

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Co-Authors: *James Soh, MD, PhD, SUNY Downstate, Brooklyn, NY*

Background: Social determinants of health are increasingly recognized as contributors to stroke risk, care, and outcomes, but their role in early progression from transient ischemic attack (TIA) to ischemic stroke remains less well defined. Stroke risk is highest in the days to weeks after TIA, and urgent evaluation and treatment can reduce early recurrence (Johnston, JAMA, 2000; Rothwell, Lancet, 2007; Kleindorfer, Stroke, 2021).

Methods: We performed a retrospective cohort study using the National Institutes of Health All of Us Research Program, a national, diverse electronic health record-linked cohort (Denny, N Engl J Med, 2019). Adults with TIA were identified using predefined ICD-9, ICD-10, and SNOMED concept codes. Participants were followed for 30 days for subsequent ischemic stroke. Multivariable logistic regression was used to evaluate associations between 30-day stroke and race, sex at birth, age, income, insurance status, smoking status, hypertension, diabetes mellitus, atrial fibrillation, and carotid stenosis.

Results: The final cohort included 14,106 participants with TIA, of whom 3,143 (22.3%) experienced ischemic stroke within 30 days. In adjusted analyses, Black or African American race was associated with higher odds of 30-day stroke compared with White race (adjusted odds ratio [aOR] 1.205, 95% CI 1.078-1.347, p=0.001), while female sex was associated with lower odds compared with male sex (aOR 0.888, 95% CI 0.813-0.971, p=0.009).

Increasing age was modestly inversely associated with stroke risk (aOR 0.989 per year, 95% CI 0.986-0.993, p<0.001). Hypertension (aOR 1.443, 95% CI 1.257-1.660, p<0.001), diabetes mellitus (aOR 1.092, 95% CI 1.002-1.189, p=0.045), atrial fibrillation (aOR 1.627, 95% CI 1.486-1.782, p<0.001), and carotid stenosis (aOR 2.168, 95% CI 1.974-2.380, p<0.001) were independently associated with increased stroke risk. Income categories and insurance status were not independently associated with 30-day stroke after adjustment.

Conclusion: In this national cohort, early ischemic stroke after TIA was independently associated with major vascular risk factors and with Black or African American race after adjustment for income, insurance, and clinical covariates. These findings suggest that disparities in early post-TIA stroke risk are not fully explained by routine socioeconomic measures alone and support further study of care-process and patient-level contributors during this high-risk interval.

S207: Bilateral Cerebellar Infarcts Associated with Combined Testosterone Replacement, Finasteride, and Anastrozole Use

Presenting Author: *Muhammad Alvi, West Virginia University, Morgantown, WV*

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Background: Background Exogenous testosterone therapy has been linked to thrombotic risk through erythrocytosis and hypercoagulability, though data in males remain limited. Finasteride may increase circulating testosterone levels, while aromatase inhibitors such as anastrozole reduce estrogen, potentially altering vascular risk profiles. The combined effect of these agents on cerebrovascular risk is not well described. Case Description A 53-year-old man with no prior disability (mRS 0) presented with acute onset vertigo, severe headache, and gait instability, with last known well >21 hours prior. Blood pressure on arrival was 220 mmHg. He reported veering to the left while ambulating. Medications included intramuscular testosterone twice weekly for 7 years, finasteride 5 mg daily, and anastrozole 1 mg daily. Neurologic examination revealed an NIHSS score of 0, and CT angiography and perfusion imaging demonstrated bilateral cerebellar hypodensities without large vessel occlusion. MRI brain confirmed scattered bilateral cerebellar infarcts in an embolic distribution. Cardiac evaluation showed preserved ejection fraction (72%) without intracardiac thrombus. Transthoracic echocardiography was negative for shunt, while transesophageal echocardiography revealed a late-positive bubble study consistent with intrapulmonary shunting. No atrial fibrillation was detected on telemetry. The patient was treated with dual antiplatelet therapy for 21 days followed by aspirin monotherapy. Symptoms improved, though he reported persistent fatigue and cognitive slowing.

Conclusion: Conclusion This case highlights a potential association between combined testosterone replacement, finasteride, and anastrozole use and embolic-appearing cerebellar infarcts. The interaction of increased androgen levels and reduced estrogen may promote a prothrombotic state. With rising use of these agents, further investigation into their combined cerebrovascular risk is warranted.

S208: Factors Affecting Post-Discharge Clinic Attendance Following Stroke Hospitalization

Presenting Author: *Ammar Khan, Philadelphia, PA*

Background: Stroke is the fifth leading cause of death and a top contributor to disability in the US. Failure to follow up with outpatient providers after hospitalization may worsen outcomes. Despite the evidence, many patients – particularly the socioeconomically disadvantaged – fail to attend. This study asks: What patient-, hospital-, and systems-level factors are significantly associated with post-discharge clinic attendance? We hypothesize that scheduling a follow-up visit prior to discharge will be positively associated with attendance, with this effect heightened by appointment reminders.

Methods: This retrospective cohort study utilized the inpatient stroke quality registry to include patients discharged with ischemic or hemorrhagic stroke from Temple University Hospital between January 1st, 2024 and December 31st, 2024. The primary outcome was post-discharge clinic attendance and appointment reminders were assessed as an effect modifier.

Results: A total of 442 patients were included. 70.4% had a neurology follow-up scheduled and 45.9% attended, with a median time to visit of 72.5 days. Scheduling an appointment prior to discharge and an appointment reminder were associated with over a four-fold increased chance of attendance (OR of 4.30 and 4.77, respectively).

Conclusion: In this socioeconomically disadvantaged urban population, scheduling clinic appointments prior to discharge and utilizing reminders were independently associated with a four- to five-fold increase in odds of attendance. This suggests that reducing administrative burden can bypass extrinsic barriers to care. Future quality improvement should focus on enhancing scheduling and optimizing reminders to ensure equitable access to secondary stroke prevention.

S209: Burden of Cerebrovascular Diseases in Parkinson's Patients in the United States: A CDC WONDER Analysis

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Background: Global Parkinson's disease incidence continues to rise, while cerebrovascular disease remains a leading cause of mortality, with 19.8 million deaths annually. Despite this, the association between cerebrovascular disease and Parkinson's disease remains largely unexplored. This study examines morbidity and mortality trends due to cerebrovascular diseases in patients with Parkinson's Disease.

Methods: CDC WONDER data (1999-2020) identified deaths due to cerebrovascular disease (ICD:I60-I69) in patients with Parkinson's Disease (ICD: G20). Age-adjusted mortality rates (AAMR) were calculated per 1,000,000. We explored trends by age, gender, race, census region, and urbanization. Jointpoint regression analysis estimated annual percent change (APC) and average annual percent change (AAPC), with a p-value of <0.05 considered significant.

Results: A total of 75,217 deaths were recorded from 1999 to 2020. AAMR decreased from 1999-2004 (APC: - 3.23: 95% CI;-5.83 to -0.56), then rapidly from 2004-2018 (APC: -8.50: 95% CI; -14.25 to -2.37), further declining until 2015 (APC: -2.87: 95% CI;-5.22 to -0.46), followed by a recent increase in AAMR from 2015-2020 (APC: 5.99: 95% CI;3.01 to 9.06). In Males, AAMR decreased from 1999-2004 (APC: -3.57: 95% CI;-6.48 to -0.57), decreasing till 2007 (APC: -9.86: 95% CI; -22.19 to 4.43), then decreasing further through 2015 (APC: -2.99: 95% CI;-5.00

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to -0.93), followed by an increased from 2015-2020 (APC: 5.87: 95% CI;2.69 to 9.14). Similarly, Females showed decrease from 1999-2014 (APC: -5.62: 95% CI;-6.35 to -4.89) and then increase till 2020 (APC:4.82: 95% CI;1.46 to 8.29). Regionally, the Midwest had the highest AAMR(1.17), (AAPC: -2.18; 95% CI), then West (1.14) with AAMR increasing from 2015-2020 (APC: 4.53: 95% CI;1.64 to 7.49), South (1.01), (AAPC: -1.50; 95% CI), and lastly, Northeast (0.84) with AAPC: -2.68 (95% CI). Among ethnicity, Non-Hispanic or Latinos exhibited higher trends (AAPC: -2.04; 95% CI) than Hispanic or Latinos (AAPC: -1.74; 95% CI). All urbanization categories showed downward trends with increase from 2015 onwards, with higher AAMR in Nonmetropolitan regions (AAPC:-2.07; 95% CI) than in Metropolitan regions (AAPC:-2.16; 95% CI). Mortality peaked in 85+ year ages (AAPC:-2.45; 95% CI), followed by 75-84(AAPC:-1.93; 95% CI), 65-74(AAPC:-1.65; 95% CI), and lastly 55-64 years(AAPC:-0.01; 95% CI).

Conclusion: Overall, AAMR decreased in initial years, but increased from 2015-2020. Males consistently exhibited higher mortality. The Midwest reported the highest AAMR, while the Northeast had the lowest. Mortality was highest in Non-Hispanic or Latinos, non-metropolitan areas, and ages 85+years were most affected. These patterns emphasize the need for focused interventions.

S210: Efficacy Of Priming Strategies for Upper-Limb Motor Recovery After Stroke: A Systematic Review, Meta-Analysis, And Meta-Regression of Randomized Controlled Trials

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Background: Upper-limb motor impairment is a persistent complication, with recovery driven by neuroplasticity and cortical reorganization. Priming before therapy, may enhance recovery. This review evaluates priming efficacy post-stroke.

Methods: A systematic search of PubMed, Embase, Scopus, and Cochrane identified randomized controlled trials (RCTs) comparing upper limb priming strategies with conventional therapy (sham or no priming) in stroke patients. Data were analyzed using R (version 4.5.3). Primary outcome was change in Fugl-Meyer Assessment (FMA) from baseline to immediate post-intervention. Secondary outcomes included FMA at follow-up, Berg Balance Scale (BBS), and Action Research Arm Test (ARAT). Subgroup analyses for FMA (immediate and follow-up) were based on study duration (≥4 vs <3 weeks), stroke phase (mixed vs ischemic), stroke type (acute vs chronic), upper limb impairment (severe vs mixed), intervention type (non-invasive brain stimulation (NIBS), mirror therapy, technology-assisted), and follow-up period (immediate, short-term, intermediate). Meta-regression assessed covariates (mean age, sex distribution, time since stroke, follow-up duration), with statistical significance set at $p < 0.05$.

Results: This meta-analysis included 12 RCTs evaluating change in FMA-UE/UL from baseline to immediate post-intervention as the primary outcome, showing a modest but significant benefit (MD = 2.11, 95% CI [0.18–4.04], $p = 0.03$) versus conventional therapy. Secondary outcomes showed significant improvement in FMA-UE/UL at follow-up (MD = 2.20, $p = 0.02$), while BBS and ARAT were not significant. Heterogeneity was low to moderate.

Subgroup analyses indicated NIBS priming produced significant gains both post-intervention (MD = 3.11) and at follow-up (MD = 1.07), whereas mirror therapy and technology-assisted interventions were not significant. Shorter therapy duration (≤3 weeks) yielded significant improvements post-intervention (MD = 3.42) and at follow-up (MD = 1.07), compared with ≥4 weeks. By stroke phase, acute stroke showed significant post-intervention gains (MD = 7.63) and chronic stroke showed follow-up improvements (MD = 1.83). By stroke type, ischemic-only (MD = 0.82) and mixed ischemic/hemorrhagic groups (MD = 8.78) improved at follow-up. Mixed impairment severity showed immediate benefit (MD = 3.00) but not sustained effects. Meta-regression showed that mean age was significantly associated with post-intervention FMA ($\beta = 0.48$, $p = 0.02$); other covariates were non-significant.

Conclusion: Priming strategies, particularly NIBS, provide modest but significant improvements in upper limb recovery after stroke. Effects are greater with shorter interventions and vary by stroke phase, with acute gains and sustained benefits in chronic stroke. Age may influence response, supporting targeted rehabilitation.

S211: High-Intensity Versus Moderate-Intensity Statin Therapy After Acute Ischemic Stroke: A Multicenteric Cohort of Hemorrhagic Transformation and Short-Term Mortality

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Background: Guidelines recommend high-intensity statin therapy after acute ischemic stroke (AIS), yet its impact on hemorrhagic transformation (HT) and short-term mortality relative to moderate-intensity therapy remains inadequately characterized in large, real-world populations.

Methods: Using the TriNetX Global Collaborative Network (169 healthcare organizations), we identified adults with AIS (ICD-10: I63) between January 2020 and January 2025 who initiated statin therapy within 2 days. Patients were classified

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into high-intensity (atorvastatin 40-80 mg; rosuvastatin 20-40 mg) or moderate-intensity groups.

After 1:1 propensity score matching on demographics, comorbidities, medications, and laboratory values (82,241 per group), we compared 7-day HT (ICD-10: I61), 7-day mortality, and 30-day mortality using Kaplan-Meier analysis and Cox proportional hazards regression.

Results: After excluding patients with prior intracranial hemorrhage (n=12,430), the analytic cohort included 76,124 patients in the high-intensity group and 75,928 in the moderate-intensity group. Within 7 days, hemorrhagic transformation occurred in 0.64% (489/76,124) of the high-intensity group and 0.37% (282/75,928) of the moderate-intensity group. The absolute risk difference was +0.27% (95% CI 0.20–0.34), with a risk ratio of 1.73 (95% CI 1.49–2.00) and an odds ratio of 1.73 (95% CI 1.50–2.01). Kaplan-Meier analysis showed reduced hemorrhage-free survival in the high-intensity group (99.35% vs 99.63%; log-rank $p < 0.001$), with a hazard ratio of 1.725 (95% CI 1.490–1.998). Seven-day mortality occurred in 2.12% of high-intensity patients and 2.47% of moderate-intensity patients (absolute risk difference −0.35%; hazard ratio 0.85, 95% CI 0.80–0.91; $p < 0.001$). Thirty-day mortality was 5.32% vs 6.40% (absolute risk difference −1.08%; hazard ratio 0.83, 95% CI 0.79–0.86; $p < 0.001$). Kaplan-Meier analysis demonstrated improved 30-day survival with high-intensity therapy (94.44% vs 93.30%; log-rank $p < 0.001$). Among thrombolysis-treated patients, 3,461 matched pairs were analyzed; after exclusions, 3,059 high-intensity and 3,014 moderate-intensity patients remained.

Hemorrhagic transformation occurred in 1.08% vs 0.63% (absolute risk difference +0.45%; hazard ratio 1.69, 95% CI 0.96–2.98; $p = 0.065$).

Conclusion: In this large multinational cohort, high-intensity statin therapy after AIS was associated with increased risk of hemorrhagic transformation but significantly reduced short-term mortality. These findings suggest that the net clinical benefit of high-intensity statins after AIS remains favorable despite the hemorrhagic signal, requiring prospective investigation to define optimal dosing strategies.

S212: Pre-Stroke Glucagon-Like Peptide-1 Receptor Agonist Use And Outcomes After Acute Ischemic Stroke: A Propensity Score-Matched Retrospective Cohort Study

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated cardiovascular benefits in randomised trials, yet their association with acute ischemic stroke (AIS) outcomes in patients with type 2 diabetes mellitus (T2DM) remains poorly characterised. Preclinical evidence suggests direct neuro-protective mechanisms, but large-scale clinical studies are lacking.

Methods: We conducted a retrospective propensity score-matched (PSM) cohort study using the TriNetX Global Collaborative Network. Adults (≥18 years) with T2DM who developed AIS (ICD-10 I63) between January 2020 and January 2025 were identified. Pre-stroke GLP-1 RA users (n=31,000) were compared with non-users (n=443,000). Outcome-specific 1:1 nearest-neighbour PSM (caliper 0.1) was performed adjusting for 14 covariates including age, sex, race, comorbidities, BMI, HbA1c, and concomitant medications. Primary outcomes included all-cause mortality (same-day, 30-, 60-, 90-day), intracerebral haemorrhage (ICH), NIHSS-coded stroke severity, and transient ischaemic attack (TIA).

Results: Among 474,000 adults with type 2 diabetes and acute ischemic stroke, 6.5% had pre-stroke GLP-1 RA exposure. Prior to matching, GLP-1 RA users were younger yet showed a higher cardiometabolic burden, including greater prevalence of hypertension, ischemic heart disease, heart failure, and higher HbA1c and BMI. Propensity score matching achieved covariate balance (SMDs <0.1). Pre-stroke GLP-1 RA use was associated with reduction in all-cause mortality across time points. At 30 days, mortality was 1.99% in GLP-1 RA users versus 4.50% in controls (HR 0.433, 95% CI 0.393–0.477; p<0.001), with similar effects at 60 and 90 days. The absolute risk reduction at 90 days was 3.69% (NNT 27). GLP-1 RA use was also associated with lower risk of intracerebral hemorrhage, evident early (1–3 days: HR 0.682, 95% CI 0.495–0.939; p=0.018) and sustained through 7 days (HR 0.57, 95% CI 0.51–0.64; p<0.001), with consistent findings excluding thrombolysis recipients. Stroke severity analyses demonstrated a graded, inverse association between GLP-1 RA use and NIHSS categories, with progressively lower risk ratios from minor to very severe stroke (all p<0.001). GLP-1 RA use was also associated with reduced risk of transient ischemic attack (RR 0.712, 95% CI 0.668–0.759; p<0.001). Overall, pre-stroke GLP-1 RA exposure was associated with lower mortality, reduced hemorrhagic complications, and less severe neurological outcomes following acute ischemic stroke.

Conclusion: In this large real-world cohort, pre-stroke GLP-1 RA use was associated with substantially lower post-stroke mortality, reduced haemorrhagic transformation, and a severity-dependent reduction in stroke severity among patients with T2DM. These findings, beyond cardiovascular risk reduction alone, suggest potential direct neuroprotective mechanisms warranting investigation in prospective trials.

S213: Basilar Artery Hemodynamics Predict Impaired Cerebrovascular Reserve and Metabolic Alterations in Anterior Circulation Steno-Occlusive Disease

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Background: Cerebrovascular reserve (CVR) evaluation is regarded as an important step in the management of steno-

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occlusive disease. However, pre-procedural prediction of CVR impairment remains challenging. We hypothesized that the basilar artery (BA), which has an intrinsic vulnerability-the lack of a robust collateral circulation and sparse sympathetic innervation- could be used as a sensitive marker of systemic autoregulatory failure. In this study, a novel hemodynamic index derived from the BA was developed. Furthermore, we investigated its association with metabolic alterations obtained from cerebral metabolic rate of oxygen (CMRO2) analysis.

Methods: A retrospective evaluation was performed on 123 patients with internal carotid artery or middle cerebral artery steno-occlusive lesions who underwent MRI-based CVR assessment using acetazolamide. The Signal
Intensity Gradient (SIG), which serves as a surrogate for wall shear stress, was measured from routine time-of-flight (TOF)-MRA. Subsequently, the development of the Basilar Artery Vulnerability Index (BAVI = [Mean-Min]/Mean) and the Basilar Artery Hemodynamics and Stroke (BHS) score, which incorporates BAVI with a history of ischemic stroke, was restricted to a subset of 115 patients in whom BA SIG metrics were successfully detected. Furthermore, a distributional analysis of CMRO2 ("metabolic texture") was conducted in a smaller sub-cohort (n=12) to elucidate the metabolic alterations within CVR-exhausted regions.

Results: An elevation of BAVI was observed in the impaired CVR group compared to the normal group (0.8186 vs. 0.6861; P = 0.0038). This phenomenon could be interpreted as a manifestation of hemodynamic instability within the BA under systemic stress. The discriminative performance of the BHS score for CVR impairment was an area under the curve (AUC) of 0.7356. In the CMRO2 analysis, areas with exhausted CVR exhibited a distinct alteration in metabolic texture, marked by increased median/75th percentile values and decreased skewness and kurtosis. These alterations might represent a state of "metabolic overdrive," wherein oxygen extraction is maximized to compensate for perfusion deficits. A significant association was also identified between high BHS scores (≥3) and elevated 90th percentile CMRO2.

Conclusion: The BAVI, which is representative of hemodynamic fluctuations and drops, could contribute to predicting CVR depletion. In addition, the BHS score (BAVI + stroke history) showed an association with metabolic overdrive. In conclusion, this scoring system could serve as a practical tool with a physiological basis for rapid CVR risk stratification in clinical settings.

S214: Interpretable Actigraphy-Derived Features Improve Prediction of Post-Stroke Functional Outcomes

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Background: The modified Rankin Scale (mRS) is the gold standard for determining post-stroke functional outcome and disability. However, the mRS is limited by its need for synchronous rater contact, susceptibility to linguistic and cultural barriers, and reliance on a single-point snapshot that cannot capture recovery over time. Wrist-worn triaxial accelerometric measurements offer a passive, continuous alternative. Our prior work has shown that machine learning applied to raw accelerometry can predict binarized mRS with accuracy above chance level.

However, raw accelerometry data is high-dimensional and not directly interpretable. We sought to apply widely-used sleep and circadian research algorithms (GGIR and nparACT) to derive biologically meaningful features from accelerometry data that may better align with post-stroke recovery.

Methods: We analyzed accelerometry data from the REACH Stroke-Sleep study at Columbia University Irving Medical Center, in which adults presenting with stroke or transient ischemic attack symptoms wore a triaxial accelerometer on their non-dominant wrist for up to 45 days after presentation. Raw accelerometry was processed through GGIR v2.9, which derived physical activity and sleep features. These outputs were visually adjudicated by two sleep experts to remove invalid estimates and cleaned data were then passed through nparACT to derive circadian features. For each day- and night-level variable we computed subject-level summary statistics and included these alongside demographic variables. We trained separate XGBoost classifiers on each feature subset to predict binarized mRS (independence [0–2] vs. dependence [>2]) at 1, 6, and 12 months using 5-fold stratified cross-validation. Performance was evaluated by AUROC with 95% confidence intervals derived by bootstrapping.

Results: Of 521 patients with analyzable wearable data, 303 (58.2%), 265 (50.9%), and 215 (41.3%) had 1-, 6-, and 12-month mRS scores alongside valid sleep and circadian data. XGBoost applied to activity, sleep, and circadian features performed best at predicting mRS at 1 (AUROC=0.71; 95% CI=[0.64,0.78]) and 6 months (AUROC=0.70; 95% CI=[0.62,0.77]), while the model trained on activity data alone performed best at 12 months (AUROC=0.68; 95% CI=[0.58,0.76]). In all cases, performance exceeded prior raw accelerometry-based predictions.

Conclusion: Processed and denoised early sleep, physical activity, and circadian features are more useful for predicting functional recovery after stroke than raw accelerometry alone. These findings support wearables as a passive complement to the mRS, though future work is needed to improve model performance and incorporate clinical variables.

S215: Determining the Impact of Cardiac Function on Cerebral Perfusion Imaging Measures in Patients with Acute Large Vessel Occlusion Stroke

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Background: Cardiac output may influence cerebral perfusion, but the relationship between transthoracic echocardiographic (TTE) measures and perfusion imaging metrics in

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acute large vessel occlusion (LVO) stroke is not well-defined. We hypothesized that impaired cardiac function is associated with worse perfusion and collateral circulation imaging metrics.

Methods: Inpatients at Johns Hopkins (2017-2024) with an anterior LVO stroke who underwent CT angiography, CT perfusion, and TTE within one week after admission were included. TTE variables included left ventricular ejection fraction (LVEF) analyzed as continuous (%), dichotomized (normal (≥55%) vs low (<55%)), and categorical (<40%, 40-55%, ≥55%) and left ventricular outflow tract velocity time integral (LVOT VTI) dichotomized as normal (≥18cm) vs low (<18cm). Perfusion and collateral imaging metrics, previously validated as prognostic biomarkers for 90 day Modified Rankin Scale, included tissue volumes meeting prespecified Tmax delay and relative cerebral blood volume (rCBV) thresholds analyzed as continuous (mL) and dichotomized (<0mL vs ≥0mL), prolonged venous transit (PVT), mean transit time (MTT) dichotomized as elevated (≥10s) vs normal (<10s), CBV index (mean rCBV in Tmax >6s region relative to normal tissue), and Tan collateral score. As appropriate, multivariable linear, logistic, and ordinal regression models adjusted for demographics and vascular risk factors assessed associations between TTE variables and perfusion metrics.

Results: Among 368 patients (mean age 68 years±15.6, 44% Black, 56% female), occlusion sites were M1 55%, proximal M2 33%, and internal carotid artery 33%. The mean admission NIHSS was 14.1±7.5. Low LVEF was associated with higher odds of having tissue with rCBV <38% (aOR=1.8, 95%CI=1.1–3) and rCBV <42% (aOR=1.7, 95%CI=1–2.8). Low LVEF (aOR=1.9, 95%CI=1.1–3.2) and low LVOT VTI (aOR=2, 95%CI=1.2– 3.4) were associated with higher odds of PVT. Compared with LVEF ≥55%, LVEF <40% (aOR=2.8, 95%CI=1.1–7.4) but not LVEF 40-55% (aOR=0.68, 95%CI=0.22–2.1) was associated with higher odds of elevated MTT. Low LVOT VTI was also associated with higher odds of elevated MTT (aOR=2.6, 95%CI=1.2–5.5). Compared with LVEF ≥55%, LVEF <40% (β=-0.069, 95%CI=-0.12 to -0.013) but not LVEF 40-55% (aOR=0.00032, 95%CI=-0.059–0.06) was associated with a lower CBV index. Low LVEF was associated with lower odds of a higher Tan collateral score (aOR=0.62, 95%CI=0.4–0.97).

Conclusion: Low LVEF and LVOT VTI were independently associated with worse perfusion and collateral circulation imaging metrics after adjusting for vascular risk factors. This suggests impaired cardiac function may contribute to reduced cerebral hemodynamic reserve in acute LVO stroke. Further studies should determine whether cardiac optimization can improve perfusion and clinical outcomes in acute LVO stroke.

S217: Paroxysmal Nocturnal Hemoglobinuria Presenting as Ischemic Stroke: A Case Report

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic disorder characterized by complement-mediated hemolysis and a marked predisposition to thrombosis, which remains the leading cause of morbidity and mortality. Thrombotic events in PNH often involve atypical venous sites, including the splanchnic circulation, and may rarely present with arterial events such as ischemic stroke. We present a case of PNH manifesting with concurrent arterial and venous thromboses, highlighting the diagnostic challenges in a young patient with stroke.

Results: A 32-year-old woman with a hx of pre-ecampsia with HELLP syndrome in 2022 presented in late 2025 with acute right-sided throbbing headache, dizziness, and visual disturbances beginning after bending over. Twelve hours later, she developed transient visual phenomena, confusion and blurry vision, with persistent positional headache which was barring her from working and presented for emergency evaluation. Initial scans in the ED including a head CT and CTA head and neck were unrevealing. MRI brain demonstrated small acute infarcts in the right occipital and medial temporal lobes. She was loaded with aspirin and plavix and admitted to the stroke service for further workup. Stroke labs were notable for low platelets 95, LDL 88, d dimer elevated at 6.62, BNP 39, A1c 5.1, RPR negative, drug screen negative. Transthoracic echocardiogram was unrevealing for a cardiac source. She underwent a CT of the chest, abdomen and pelvis which was negative for malignancy however showed extensive hepatic and splenic vein thromboses for which she was started on therapeutic heparin. Given concurrent arterial and venous thromboses, hematologic etiology was suspected, and hematology consulted.

Further workup revealed normal ADAMTS13 activity, negative HIT testing, normal hemoglobin electrophoresis, and absence of Factor V Leiden, prothrombin gene mutation, and JAK2 mutations. Lupus anticoagulant was positive however beta-2 glycoprotein and cardiolipin IgG and IgM were negative. Hemolysis labs showed elevated lactate dehydrogenase and undetectable haptoglobin, with rare schistocytes on smear. Differential diagnosis included thrombotic thrombocytopenic purpura (TTP), thrombotic microangiopathy (TMA), antiphospholipid syndrome, heparin-induced thrombocytopenia, and PNH. Hepatic vein thrombosis is atypical in

TTP/TMA and raised suspicion for PNH or JAK2 myeloproliferative disorder. Flow cytometry demonstrated PNH clones in red and white blood cells, confirming the diagnosis. She received meningococcal vaccination and was started on ravulizumab, a C5 complement inhibitor inpatient with anticoagulation transitioned to apixaban. She was discharged without any neurologic deficits. Follow-up workup showed resolution of abdominal thromboses, improvement in thrombocytopenia and no new infarcts on surveillance MRI brain.

S218: Carotid Revascularization is Associated with Reduced Recurrence in Symptomatic Carotid Web

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Background: Carotid artery web is a rare and underrecognized cause of ischemic stroke. Current literature emphasizes their underdiagnosis and association with high recurrence rates despite medical management. We report a single-center experience of carotid revascularization in patients with ischemic stroke and ipsilateral carotid webs.

Methods: This retrospective case series includes 20 patients who presented with acute strokes attributed to ipsilateral carotid webs and subsequently underwent carotid revascularization at a Comprehensive Stroke Center between January 2015 and December 2025. Data on demographics, clinical presentation, and imaging findings were collected via chart review. Descriptive statistics summarize patient characteristics and outcomes.

Results: Twenty patients with ischemic stroke and ipsilateral carotid artery web underwent carotid revascularization. The median age was 54 years (IQR: 45–62), and 70% were female. Median NIHSS was 9 (IQR: 5–15). Fifteen (75%) underwent mechanical thrombectomy and 8 (40%) received IV thrombolysis. Sixteen (80%) had carotid web on the right side. Revascularization was performed for stroke recurrence (30%), superimposed thrombus (25%), or secondary prevention (60%), with overlapping indications. TCAR was the most common approach (65%), followed by CAS (20%) and CEA (15%). Over a median follow-up of 9 months (IQR: 6–21), no patients experienced recurrent ischemic stroke in the treated vascular territory, suggesting potential effectiveness of revascularization in preventing recurrence in selected patients with carotid webs.

Conclusion: Our study highlights the significance of early detection and intervention. All forms of carotid revascularization, including TCAR, have shown effectiveness and safety. However, larger studies are essential to validate these findings.

S219-K: Impact Of Cerebral Acid-Base Status on Spreading Depolarization

Presenting Author: *Britta Lindquist, MD, PhD, University of California, San Francisco*

Background: Fifteen to 20% of acute ischemic stroke patients are admitted to the intensive care unit (ICU), often requiring endotracheal intubation and mechanical ventilation. Current clinical guidelines make no recommendations regarding pH, PCO2, or HCO3- goals in patients with acute ischemic stroke. Acid-base management strategies may exacerbate or mitigate cerebral injury following stroke: metabolic or respiratory acidosis inhibit the initiation and propagation of spreading depolarizations (SDs), which are excitotoxic waves of cellular depolarization that promote the expansion of ischemic strokes in vivo. The involvement of intracellular vs extracellular targets has not yet been clarified.

Methods: I used acute brain slices to examine the effects of tissue acidification on SD without confounding effects from variable cerebral blood flow. I freshly prepared acute brain slices (coronal, 350um thick) from C57Bl/6J mice of both sexes. To manipulate metabolic acid-base status of both intra- and extra-cellular compartments, I manipulated the HCO3-buffer content of artificial cerebrospinal fluid (pH 6.6 – 8.0), bubbled with 5% CO2-95% O2, replacing sodium bicarbonate with equimolar sodium methylsulfate to maintain iso-osmolarity, iso-natremia and iso-chloremia. To selectively manipulate extra-cellular pH, I applied HCO3-/CO2-free HEPES-buffered artificial cerebrospinal fluid (pH 6.6 – 7.6), bubbled with 100% O2. I induced SDs by micro-injection of KCl (1M) and obtained recordings of intrinsic optical signals and extracellular field potentials from stratum radiatum of the hippocampal CA1 region.

Results: In HCO3-buffered aCSF, KCl reliably elicited SD over the bath pH range of 6.8 – 8.0. SD could not be elicited at pH 6.6. Propagation rate followed a sigmoidal dose-response relationship (bath pH50 ∼7.24), with minimum propagation rate 2.2 mm/min in acidemic bath solution (pH 6.8) and maximum propagation 7.4 mm/min in alkalotic bath solution (pH 7.8). In HEPES-buffered aCSF, SD was elicited at all pH levels tested (6.6 – 7.6).

Minimum propagation rate 1.6 mm/min was observed in acidemic bath solution (pH 6.6) and maximum propagation rate 2.8 mm/min was observed in alkalotic bath solution (pH 7.6). The dose-response relationship was incompletely characterized by the effective pH range of HEPES, with pH50 estimated as ∼6.3.

Conclusions: SD propagation is modulated by parenchymal and extracellular acid-base status. Application of HCO3-CO2-buffered artificial cerebrospinal fluid is more effective than HEPES-buffered solution to modify SD propagation rate, suggesting that intracellular as well as extracellular targets are involved. In future studies, I will selectively acidify and alkalize intracellular compartments with sodium propionate and ammonium chloride, and I will evaluate additional downstream mediators of cerebroprotection by acid-base status, including cerebral blood flow, ion channel modulation, and cellular energy phenotypes.

S220: Minocycline Transforms Acute Ischemic Stroke Care: A 2,428-Patient Meta-analysis of a Low-Cost Neuroprotective Strategy

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Background: Acute ischemic stroke (AIS) and Intracerebral Hemorrhage (ICH) remains a leading cause of death and long-term disability worldwide, and a substantial proportion of patients experience incomplete recovery despite modern reperfusion strategies. Minocycline is an inexpensive, widely available agent with anti-inflammatory, anti-apoptotic, and matrix metalloproteinase-modulating properties that make it an attractive neuroprotective adjunct in AIS. However, prior clinical studies have been individually underpowered or methodologically heterogeneous, underscoring the need for an updated quantitative synthesis focused on clinically meaningful outcomes.

Methods: A systematic review and meta-analysis was conducted to evaluate the efficacy and safety of minocycline in adults with AIS and ICH. The search was completed on February 24, 2026, and the protocol was prospectively registered in PROSPERO (CRD420251236765), our study is reported in accordance with PRISMA guidelines.. A total of 1,633 records were screened. A total of 11 studies comprising 2428 patients were included in the review dataset. Analyzed outcomes included 90-day disability, neurological recovery, recurrent stroke, and composite vascular events.

Results: Minocycline was associated with better 90-day neurological recovery, with a greater reduction in NIHSS score at 90 days (mean difference [MD] -2.17, 95% CI -2.68 to -1.65), and with lower disability measured by mean modified Rankin Scale (mRS) score at 90 days (MD -0.25, 95% CI -0.38 to -0.13). Functional outcomes also favored minocycline, including mRS 0-2 at 90 days (odds ratio [OR] 1.21, 95% CI 1.02 to 1.45), while the effect for mRS 0-1 at 90 days was borderline (OR 1.21, 95% CI 1.00 to 1.47). No significant difference was observed for stroke recurrence at 90 days (OR 1.13, 95% CI 0.78 to 1.64). Composite vascular events at 90 days also favored minocycline (OR 1.21, 95% CI 1.02 to 1.45).

Conclusion: Minocycline appears to be a promising, scalable, and low-cost adjunctive therapy for AIS, with signals for improved 90-day functional and neurological outcomes. Given its global availability, favorable biological rationale, and consistent direction of effect across key recovery outcomes, these findings support prioritization of minocycline for confirmatory trials and highlight its relevance in the stroke and neurocritical care clinical practice.

S221-LB: Bilateral Cerebellar Peduncle Lesions with Concurrent Psychosis and Disinhibition

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Background: GCA is the most common large-vessel vasculitis in the United States, with a reported incidence of 18 per 100,000. Classical symptoms include headache, vision loss, and jaw claudication, due to vasculitic involvement of the temporal artery and its branches. However, atypical presentations including stroke are uncommon and, therefore, not included in the current guidelines.

Methods: We present a 76-year-old female with a subacute onset of headache, confusion, and gait instability. Brain magnetic resonance imaging (1.5 Tesla) demonstrated bilateral middle cerebellar peduncle diffusion-restricting lesions with associated peripheral enhancement. CSF studies did not demonstrate intrathecal inflammation.

Autoimmune markers were negative, and notably, ESR/CRP were only mildly elevated. The patient was, however, started on empiric steroid treatment for a suspected immune-mediated process. Her course was complicated by worsening paranoia and hallucinations/psychosis that persisted despite steroid discontinuation. The diagnosis remained unclear until she developed unilateral vision loss, and a fundus exam demonstrated central retinal artery occlusion and cotton wool spots more suggestive of GCA.

Results: In our case, clinical progression with new, more classical visual symptoms favored GCA. This suggests that, in the setting of a posterior circulation stroke, GCA should be considered even if classical symptoms are absent. While not formally included in that criterion, contrast-enhanced MRI/MRA can support this diagnosis by demonstrating arterial wall thickening with contrast enhancement. This case provides an opportunity to discuss the broad differential involved with symmetric, bilateral middle cerebellar peduncle lesions. It also highlights the considerations of the cerebellum's role in cognition.

Conclusion: Report a case representative of an atypical GCA presentation that both highlights its link to stroke and the role of the cerebellum in cognitive processing.

S222: Peripheral Methylation Status Recover in Young but not Aged Animals after Photothrombotic Stroke

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Background: Ischemic stroke triggers a dynamic peripheral immune response that is known to vary with age and sex, yet the epigenetic mechanisms underlying these differences remain poorly described. Whole blood DNA methylation offers a minimally invasive window into immune gene regulation and may capture meaningful biological variation across groups.

Methods: Whole blood was collected from young (3 months, n=151) and aged (18 months, n=137) male and female mice at baseline and at weeks 1, 7, and 12 following photothrombotic stroke or sham surgery. DNA was profiled using the Illumina 450k array following bisulfite conversion, with CpG sites classified as hypomethylated ($\beta < 0.3$) or hypermethylated ($\beta > 0.7$). Uniform Manifold Approximation and Projection, centroid-based Euclidean distance quantification, and gene set enrichment analysis on mapped genes were performed within each of the four age-sex strata.

Results: UMAP clustering identified sex and age as the dominant sources of methylation variance, prompting individual analysis of each four age-sex combinations. Young males

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showed progressive sham-stroke UMAP separation peaking at week 7 and resolving by week 12, supported by immune pathway enrichment including leukocyte proliferation and interferon signaling that resolved alongside the methylation distance. Young females displayed a similar but earlier-peaking and more attenuated response. Aged males showed a delayed pattern, with no separation at week 1, slight divergence emerging at week 7 with no recovery by week 12. This trajectory also supported by the display of immune processes at week 12, the inverse of young animals. Aged females showed no meaningful sham-stroke separation at any timepoint, with stroke-specific CpGs mapping to unrelated pathways across timepoints and no unifying biological program. A composite immune score confirmed that young animals mount a robust early immune-activating epigenetic response that resolves, while aged animals exhibit progressive hypermethylation of immune genes across time.

Conclusion: Whole blood DNA methylation captures age- and sex-dependent epigenetic responses to photothrombotic stroke. Young animals display a response-recovery arc, seemingly driven by a transient peripheral immune activation, while aged animals fail to mount a coherent epigenetic response. These findings underscore the importance of age and sex in shaping the peripheral epigenetic landscape of peripheral blood mononuclear cells after localized cortical stroke, with implications for biomarker development and age-stratified therapeutic design.

S223: Primary CNS Vasculitis in Patients with Stroke and Conventional Risk Factors

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Background: Primary Angitis of the central nervous system (PACNS) is an inflammation of the cerebral vasculature without angiitis in other organs. Most common symptoms at onset include an indolently progressive headache with or without focal neurological deficits. A definitive diagnosis requires a cerebral biopsy, however a probable level of diagnostic certainty, which may be achieved based on typical findings on a cerebral 4-vessel digital subtraction angiography (4vDSA).

Methods: We retrospectively reviewed the patient records in the department of Neurology (including division of Stroke Medicine) over a period of 5 years from September 1, 2020 to August 1, 2025. Among 6,947 unique admissions, 61 were labelled as CNS vasculitis. Patients were included if they had stroke, ≥1 vascular risk factor, and ≥1 clinical red flag. Final diagnosis of PACNS was adjudicated after detailed review of clinical, imaging, and laboratory data. 25 cases met the inclusion creitria and were included in the analysis. Primary outcome was the proportion of PACNS among patients labelled as vasculitis. Secondary outcomes included frequencies and associations of red flags, time from index stroke to diagnosis and immunotherapy, and effect of early versus delayed recognition.

Results: Of 61 patients labelled as CNS vasculitis, 25 met inclusion criteria and were adjudicated as having angiographically probable PACNS. All patients exhibited ≥1 clinical red flag, with 18/25 (72%) demonstrating ≥2 and 3/25 (12%) demonstrating ≥3 red flags. The most frequent features were recurrent stroke (64%), multi-territory involvement (56%), and young age at onset (52%). Early diagnosis (≤14 days from index event) occurred in 9/25 patients (36%), while 16/25 (64%) experienced delayed diagnosis. Immunotherapy was initiated in 23/25 patients (92%), with 15/23 (65%) treated within 1 week of diagnosis. At a mean follow-up of 14 months, good functional outcome (mRS 0–2) was observed in 14/23 patients (61%), while treatment-related sepsis occurred in 6 patients (26%).

Conclusion: PACNS should be considered in stroke patients with vascular risk factors when red flags are present. Systematic evaluation for vasculitis in this subgroup may enable earlier diagnosis and timely initiation of immunotherapy, potentially improving outcomes.

S224: Polycythemia Vera as a Cause of Multifocal Intracranial Stenosis and Recurrent Strokes: A Case Report

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Background: Here we report a case of polycythemia vera (PV) presenting as recurrent posterior circulation ischemic strokes with multifocal intracranial stenosis, stereotypical neurological spells, and progressive cognitive decline, highlighting PV as an under recognized cause of cerebrovascular disease. PV is a myeloproliferative neoplasm characterized by erythrocytosis, hyperviscosity, and a prothrombotic state. While venous thrombosis is a well-recognized complication, arterial cerebrovascular events, particularly recurrent ischemic strokes from acquired intracranial stenosis, are less commonly described and may be misattributed to conventional etiologies such as cardioembolic or large-vessel atherosclerosis. Delays in diagnosis can result in ongoing ischemic injury and progressive vascular cognitive impairment. This case illustrates the importance of considering hematologic etiologies in patients with recurrent strokes and multifocal intracranial stenosis lacking traditional risk factor profiles.

Methods: We present a 52-year-old patient who developed multiple acute ischemic strokes over a six-month period with progressive cognitive decline and stereotypical neurological spells. The initial event was a left posterior cerebral artery (PCA) territory infarct with left P2 segment occlusion. Subsequent episodes included recurrent confusion, stereotypical spells of left hemibody numbness, and episodic blurring of vision consistent with recurrent TIA-like events. Diagnostic workup included serial MRI brain, CT angiography and MR angiography of the head and neck, prolonged cardiac monitoring, complete blood count, JAK2 V617F mutation testing, hypercoagulable panel, and continuous EEG monitoring.

Results: Serial vessel imaging demonstrated progressive multifocal intracranial stenosis. EEG did not capture ictal correlates during stereotypical spells, supporting a vascular

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mechanism. Laboratory evaluation revealed erythrocytosis with hematocrit of 52%, peak hemoglobin of 18, and a positive JAK2 V617F mutation. The patient was initiated on phlebotomy and cytoreductive therapy with hydroxyurea with subsequent clinical stabilization.

Conclusion: PV should be considered in patients presenting with recurrent strokes, multifocal intracranial stenosis, and an absence of conventional vascular risk factors. Hyperviscosity-driven thrombosis can produce arterial stenosis mimicking atherosclerotic or embolic disease. Early hematologic evaluation with JAK2 mutation testing is essential, as cytoreductive therapy may prevent further cerebrovascular events and cognitive decline.

S225: Neurostimulation Improves Specific Cognitive Functions by Targeting Individual Neural Networks

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Background: Cognitive impairment following stroke can impact all facets of life. Even individuals with small strokes can experience deficits, particularly in attention and processing speed, regardless of their stroke location, due to disruption of cognitive networks. While many recover, additional therapeutic options are needed. In this small pilot study, we investigate the efficacy of neurostimulation using transcranial direct current stimulation (tDCS) to target individual neural networks.

Methods: To date, six patients with history of chronic unilateral, supratentorial ischemic stroke (6-36 months post-stroke) and cognitive deficits have been randomized and undergone neurostimulation using 1mA of current with the tDCS anode placed over the ipsilesional frontoparietal region versus sham. During each session, individuals participated in a computerized battery of 13 cognitive tasks evaluating memory, executive function, verbal reasoning, attention, processing speed, and visuospatial manipulation using the Creyos© platform. Stimulation sessions lasted 30 minutes and occurred 3 times per week over 5 weeks for a total of 15 sessions. T-tests were used to compare longitudinal trends in performance between groups. In addition, the functional connectivity of neural networks was assessed using resting state magnetoencephalography (MEG) pre- and post-intervention within the alpha, beta, and theta frequency ranges. NLGC analysis was used to compare changes in network connectivity over time between groups, which was then correlated with behavioral outcomes on specific cognitive tasks.

Results: Two patients were randomized to tDCS; four to sham. Preliminary results suggest differences in degree of improvement on tests of memory, executive function, verbal reasoning, and attention between groups, with treated patients showing greater degrees of improvement over time. Increased beta activity in the right frontal lobe and increased functional connectivity between frontoparietal and motor networks in the right hemisphere was observed in the treated group compared to sham, while functional connectivity between the temporal-parietal region of the default mode network and attention areas was greater in treated patients within the alpha band. On the participant-level, treated patients appeared to improve more on tasks associated with networks with increased beta connectivity, while an overall increase in alpha connectivity was associated with better overall performance.

Conclusion: Preliminary results suggest treatment with tDCS may result in changes in the functional connectivity of individual cognitive networks corresponding with longitudinal improvement on specific cognitive tasks.

Furthermore, specific patterns of change within the alpha and beta bands may be associated with overall and task-specific improvement. Additional patients are being actively recruited to allow for further exploration.

S226: Postpartum Internal Carotid Artery Dissection Presenting as Tandem ICA-MCA Occlusion With Progressive Flow-Limiting Stenosis Despite Anticoagulation

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Background: The risk of cervical artery dissection (CeAD) is estimated to be >5 times higher in pregnant and postpartum women than in the general population. The postpartum period confers heightened vulnerability due to hormonal, hemodynamic, and connective tissue remodeling changes. While most dissections heal within three to six months, a subset demonstrate persistent or progressive luminal compromise, raising complex management questions.

Methods: A 34-year-old previously healthy woman developed acute left hemiplegia seven days after cesarean delivery. While rocking her newborn, she experienced a sudden neck strain with an audible pop followed by transient right monocular visual loss and left-sided weakness. She was evaluated at an external facility and the CT angiography revealed proximal right internal carotid artery (ICA) dissection with tandem right ICA and M1 occlusion. She underwent emergent mechanical thrombectomy achieving TICI 2A reperfusion. Intravenous thrombolysis was deferred due to recent cesarean delivery. MRI demonstrated right basal ganglia and posterior internal capsule infarction with mild hemorrhagic transformation. She was anticoagulated with enoxaparin, later transitioned to apixaban.

Results: Serial imaging at six months demonstrated persistent severe right cervical ICA stenosis (83%) with an evolving dissecting pseudoaneurysm (7 mm) and modest interval progression despite therapeutic anticoagulation. CT angiography also revealed bilateral ICA tortuosity and fusiform dilation suspicious for non-atherosclerotic arteriopathy. However, a 92-gene connective tissue disorder panel was negative, and extracranial vascular imaging showed no evidence of systemic fibromuscular dysplasia. Subsequent perfusion imaging demonstrated preserved cerebral blood flow bilaterally with mildly prolonged time-to-peak in the right hemisphere.

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Comprehensive thrombophilia evaluation was unrevealing. Given the progression of the right ICA peak systolic velocities on follow-up surveillance carotid ultrasound imaging. Aspirin was added to apixaban. She is undergoing close longitudinal surveillance, with revascularization to be considered if the stenosis progresses or persists at a severe grade. At six months, she was ambulating independently with residual mild left-sided weakness with a modified Rankin Scale of 2.

Conclusion: Stroke during pregnancy or the postpartum period is associated with substantial morbidity and mortality for both the mother and the fetus or neonate, with reported mortality rates of up to 20% in some studies. This case highlights the complexity of managing postpartum CeAD with persistent high-grade stenosis progressing despite anticoagulation. Given the challenges inherent to pregnancy-associated stroke, optimal care necessitates a coordinated multidisciplinary approach, integrating vascular neurology, maternal-fetal medicine, obstetrics, and emergency medicine.

S227: Does IV Thrombolysis Produce Net Lifetime Benefit Over DAPT in Mild Ischemic Stroke? A Decision-Analytic Model

Presenting Author: *Xhoni Pashaj, Huntingdon Valley, PA*
Co-Authors: *Ramin Zand, Hummelstown, PA*

Background: Mild ischemic stroke (NIHSS 0–5) accounts for up to half of stroke presentations, with substantial residual disability. Trials comparing intravenous thrombolysis with antiplatelet therapy have not demonstrated 90-day functional benefit, though guideline recommendations persist. Short-term endpoints may not capture long-term consequences of symptomatic intracerebral hemorrhage (sICH). We evaluated whether thrombolysis provides net lifetime benefit compared with dual antiplatelet therapy (DAPT).

Methods: We constructed a two-epoch decision-analytic model for anterior-circulation mild stroke, parameterized using data from randomized trials and observational studies, including PRISMS, TEMPO-2, CHANCE/POINT, STARTING-SICH, and IST-3. The acute phase (0–90 days) was represented by a decision tree with treatment (thrombolysis vs DAPT) as input and three mutually exclusive outcomes: sICH, early neurological deterioration, or uncomplicated recovery. Each pathway produced a 90-day modified Rankin Scale (mRS) distribution, which served as input to a long-term Markov model. The Markov model used annual cycles over a lifetime horizon (up to 30 years) and included health states of mRS 0–1, 2–3, and 4–5 for both first stroke and recurrent-stroke survivors, a post-sICH survivor state, and death. Transition inputs included recurrent stroke risk, mRS-specific mortality, and utility weights. The primary outcome was discounted lifetime quality-adjusted life years (QALYs). We estimated the minimum absolute risk reduction (ARR*) at which thrombolysis yields net QALY benefit and evaluated incremental QALYs across ARR values from 0 to 0.30. Probabilistic sensitivity analysis (10,000 simulations) and structural sensitivity analyses were performed.

Results: Across all 18 patient subtypes, thrombolysis did not produce net lifetime QALY benefit over DAPT at treatment effects observed in current literature. ARR* thresholds ranged from 0.104 to 0.179, exceeding the most favorable published estimate (0.080). Incremental QALYs (thrombolysis minus DAPT) remained negative across all ARR values up to 0.30 in base-case analyses, indicating persistent net harm. The probability of net lifetime benefit at ARR = 0.080 was <0.5% for all subtypes. Although thrombolysis showed potential short-term functional improvement at higher ARR values, these gains were offset by long-term disutility from sICH. The model underestimated sICH risk compared with trial data (1.2% vs 3.2%), biasing toward thrombolysis; correcting this increased the magnitude of net harm. Results were robust to variations in treatment effect and structural assumptions. **Conclusion:** Thrombolysis was unlikely to confer net lifetime benefit over DAPT in mild ischemic stroke at currently observed treatment effects. Incorporating long-term outcomes may alter interpretation of short-term trial results.

S228: Shaping Tobacco Reduction Policies for U.S Population in Rural Counties Based on Risk of Vascular Diseases

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Background: Although rural-urban disparities in smoking prevalence are well-documented, less is known about how these disparities differ across vascular disease risk strata.

Methods: We conducted a retrospective cross-sectional analysis of Behavioral Risk Factor Surveillance System (BRFSS) datasets from 2019, 2021, and 2023. Smoking status was categorized as never, former, or current.

Smoking cessation was assessed using the former-to-current smoker ratio. A composite vascular risk score, modeled after the CHADS2-VASc framework and constructed using BRFSS variables, was used to classify participants into low, medium, and high-risk groups. Participants were categorized by county of residence as rural or urban, and comparisons were performed across vascular risk strata. Descriptive analyses and logistic regression models adjusted for demographic and socioeconomic covariates were performed.

Results: The analysis included 1,200,148 respondents representing 232.7 million U.S. adults. Across rural and urban populations, never smoking was highest in the low-risk group and lowest in the high-risk group, whereas the former-to-current ratio was lowest in the low-risk group and highest in the high-risk group. Rural residents had higher rates of ever smoking and current smoking. Rural-urban disparities were greatest in the low vascular-risk group. Never-smoking was 56.9%in rural areas versus 67.9% in urban

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areas(p<0.001), while current smoking was 21.6% in rural areas versus 13.5% in urban areas(p<0.001). The former-to-current ratio was lower in rural vs. urban areas across all risk groups, with the highest ratio observed in the high-risk group (low:0.99 vs. 1.38; medium:1.43 vs. 1.98; high:2.61 vs. 3.31). In adjusted regression models, rural residence was associated with lower odds of never smoking only in the low-risk group (aOR: 0.84; 95% Cl: 0.80-0.88), whereas its association with higher odds of current smoking persisted across all risk strata (low:aOR 1.28; medium:aOR 1.25; high:aOR 1.14).

Conclusion: Rural adults showed higher current-smoking rates and lower cessation across all vascular risk strata. Rural-urban disparities were largest in never smoking among low-risk adults and greatest in cessation among high-risk adults. Risk-stratified rural targeting may help focus smoking cessation on low-risk adults.

S229: Development of NEXUS (Neurology EXposure for Undergraduate Students): A Structured Inpatient Neurology Shadowing Program During the Preclinical Curriculum

Presenting Author: *Hemangi Rajpal, Valhalla, NY*
Co-Authors: *Adam Karp, Fair Lawn, NJ*

Background: Neurophobia, defined as fear or aversion toward learning or practicing neurology, is a well-documented barrier in medical education. Contributing factors include limited exposure to clinical neurology, insufficient bedside teaching, and complex neuroanatomy. Early, structured clinical exposure has been shown to improve understanding of and interest in neurology. However, access to neurology-specific clinical opportunities during preclinical years remains limited. This study designed and implemented a structured inpatient neurology shadowing program, NEXUS (Neurology EXposure for Undergraduate Students), at Westchester Medical Center (WMC) for preclinical students at New York Medical College (NYMC). This pilot initiative was designed to create early clinical exposure opportunities to neurology, with a focus on acute stroke care, and assess whether structured stroke shadowing reduces "neurophobia."

Methods: We developed and implemented a structured inpatient stroke shadowing program called NEXUS, or Neurology EXposure for Undergraduate Students. All NYMC preclinical students were invited to participate via classwide email communications, and those expressing interest were enrolled. Shadowing shift infrastructure and pre- and post-surveys were developed in consultation with neurology physicians and faculty at WMC and NYMC. **Results:** NEXUS participants shadowed morning report, inpatient neurology rounds, stroke consults with on-call providers, and acute stroke codes as available. Pre- and post-surveys administered via Qualtrics assessed students' perceptions of neurology, interest in pursuing neurology as a career, and confidence in core neurology and stroke concepts. Surveys included Likert-scale items, self-reported exposure to stroke consults and codes, and qualitative responses. During the pilot year, 93 students (20% of preclinical students at NYMC) expressed interest in NEXUS, including 71 first-year and 22 second-year students. A total of 26 shadowing encounters were completed with pre-and post-survey responses to date. The average shift lasted 5.3 hours, with 82% of participants shadowing one or more stroke consults and 50% of participants shadowing one or more stroke codes. Preliminary feedback demonstrated students consistently identifying interactive teaching, mentorship, and exposure to real-time clinical decision-making as highly valuable.

Conclusion: The NEXUS pilot demonstrates that a structured inpatient neurology shadowing program is both feasible and well-received by preclinical medical students. By providing exposure to bedside teaching and real-time clinical decision-making, NEXUS addresses key contributors to neurophobia and may enhance student confidence and interest in the field. These results support the integration of structured neurology shadowing opportunities into preclinical curricula. We will continue to pilot NEXUS throughout 2026 and 2027 and ultimately expand to other neurological subspecialties.

S230: A NOVEL LARGE LANGUAGE MODEL-BASED AUTOGRADER FOR EVALUATING PERFORMANCE ON PEDAGOGICAL STROKE ALERT SIMULATIONS

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Background: Neurology residents play an integral role in acute stroke care at academic centers, independently leading stroke alerts with varying supervision after achieving program-specific autonomy milestones. Our recent study has shown that large language model (LLM)-based virtual stroke simulations are feasible with excellent adherence to script and learning objectives. However, methods to provide targeted feedback during these simulations have not yet been explored, limiting the ability to identify and reflect on patterns of decision-making. Building on prior work, in this study, we created and assessed the validity of an automated grading system to evaluate clinical decision-making in LLM-based acute stroke simulations.

Methods: With input from board-certified vascular neurologists, we created two LLM-based acute stroke simulations. Fifteen LLMs were deployed to play the stroke alert simulations (n=300 transcripts) and evaluated using grading rubrics developed by a stroke expert. Grading criteria assessed accuracy of reperfusion decisions and efficiency, including sequence and necessity of decisions. Using the rubrics, three neurology resident physicians manually graded a subset of LLM transcripts (n=40, 20 per case) achieving high inter-rater reliability (overall agreement 97.4%, κ=0.936; Case 1: 99.6%, κ=0.987; Case 2: 95%, κ=0.889). Discrepancies were resolved by consensus to establish a gold standard set of

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responses. We then developed an LLM-based automated grader and validated it against the human set. Criteria from rubrics were converted into prompts. Each transcript along with a system prompt and grading criteria were passed into Claude Opus 4.6 to generate a graded checklist of performancemetrics. Inter-rater reliability between the human-graded set and autograder was calculated using Cohen's kappa coefficient.

Results: Overall, there was 96.7% agreement between the autograder and human-graded set across all criteria for both cases (κ=0.916). By case, there was 98.6% agreement (κ=0.955) and 94.5% κ=0.882) for case 1 and case 2, respectively. For each unique grading criterion, the autograder was in concordance with the human graders at least 90% of the time.

Conclusion: When evaluating performance on LLM-based stroke case simulations, an LLM-based autograder demonstrated very good reliability compared to human graders and could potentially offer targeted and consistent feedback in pedagogical acute stroke care simulations for neurology residents. This could potentially aid in standardizing measurement of performance in acute stroke care training. We plan to assess the reliability of the autograder when evaluating transcripts of neurology residents and stroke specialists engaging with the LLM-based acute stroke simulations. Data forthcoming.

S231: Secondary CNS Vasculitis Associated with Sjögren Syndrome

Presenting Author: *Nicholas Reish, Chicago, IL*

Background: Secondary central nervous system (CNS) vasculitides pose diagnostic and therapeutic challenges. The associated systemic autoimmune may not have been previously diagnosed, and the patient may have traditional vascular risk factors to which the initial presentation can be attributed. These conditions cause significant morbidity due to recurrent cerebrovascular events and their sequelae, as well as intractable headache and encephalopathy.

Effective treatment routinely requires prolonged high-dose steroids and potent immune suppressive medications, which can have significant adverse effects. Thus, early and accurate recognition of these conditions is essential.

Methods: This is a case report of a patient presenting with secondary CNS vasculitis due to Sjögren syndrome (SS).

Results: A woman in her 50s with a history of hypertension and hyperlipidemia was referred to vascular neurology clinic for evaluation of a chronic infarct found on imaging. After experiencing a SARS-CoV-2 infection, she had developed dysautonomia with episodes of tachycardia, labile blood pressure, and diaphoresis, and was subsequently diagnosed with postural orthostatic tachycardia syndrome. She then experienced an episode of dysarthria and altered awareness and was seen at an outside hospital where CT of the brain was concerning for a white matter infarct.

Later MRI of the brain confirmed a right frontal lobe white matter lesion concerning for chronic infarct. She continued to have significant dysautonomia and presented to clinic for a second opinion. She had had carotid ultrasound but no other vessel imaging. MRA revealed multifocal areas of stenosis and dilation concerning for vasculitis. Further workup was notable for positive anti-SSA antibody, and a salivary gland biopsy demonstrated pathologic findings typical of SS. Lumbar puncture was performed and CSF studies were notable for 5 oligoclonal bands unique to the CSF. She was treated with steroid taper and maintained on a low daily dose of prednisone. Her dysautonomia symptoms resolved and there was radiographic resolution of some but not all stenoses. Subsequent imaging over the following two years did not demonstrate any new infarcts.

Conclusion: Secondary CNS vasculitis should be considered in the setting of comorbid systemic disease. In this case the anti-SSA antibody had been detected years prior, but she had never been worked up. Likely the smoldering SS became more active after the SARS-CoV-2 infection. Treatment of the systemic autoimmune disease led to clinical and radiographic improvements which would likely not have occurred if she had been treated as a typical stroke patient.

S232*: Characterization of a Pragmatic Transcranial Doppler Biomarker of No-Reflow Phenomenon After Large Vessel Occlusion Stroke

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Background: A substantial proportion of patients with large-vessel-occlusion (LVO) stroke remain disabled despite successful endovascular therapy (EVT), due to parenchymal hemorrhage (PH), early cerebral edema (ECE) or persistent microvascular hypoperfusion from the no-reflow phenomenon (NRP). Transcranial-doppler (TCD) measurement of the inter-hemispheric pulsatility-index-ratio (PI-R), a hemodynamic marker of residual distal vascular resistance in the reperfused MCA territory, independently predicts clinical outcomes after EVT. However, PI-R can be non-specifically elevated by PH, ECE or NRP. We aimed to determine whether elevated PI-R predicts outcomes after successful EVT in the absence of PH or ECE, to serve as a bedside TCD biomarker of NRP.

Methods: We performed a retrospective study of adults who underwent TCD 24-to-72 hours after successful EVT (eTICI>2b50) for MCA or intracranial-ICA occlusion. Bilateral MCA PI was used to calculate PI-R (stroke-to-control-side ratio). Univariate comparisons evaluated differences between patients with or without ECE/PH. Independent associations of PI-R with early neurological improvement (ENI) and very-poor functional outcome at 90 days (mRS 5-6) were tested with multivariable logistic regression, adjusting for age, sex, last-known-well-to-arrival time,

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baseline NIHSS, ASPECTS, intravenous thrombolysis, eTICI score and final infarct size.
Interaction analyses evaluated whether ECE and/or PH modified this effect.
Results: The cohort included 159 patients (median age 73 (IQR, 63-80.5); 81 (51%) female; median baseline NIHSS 17 (IQR, 12.5-21)). In adjusted overall models, higher PI-R independently predicted lower odds of ENI (OR 0.039; 95%CI 0.003-0.531; p=0.015) and increased odds of mRS 5-6 (OR 17.29; 95%CI 1.79-166.98; p=0.014). In the group without ECE/PH (n=102), elevated PI-R remained independently associated with mRS 5-6 (OR 88.76; 95%CI 1.96-4015.66; p=0.021), but not with ENI (OR 0.146; 95%CI 0.004-5.287; p=0.293). Conversely, in the group with ECE/PH (n=57), elevated PI-R strongly predicted lower odds of ENI (OR 0.006; 95%CI 0.00005-0.757; p=0.038) with a trend for mRS 5-6 (OR 102.06; 95%CI 0.85-12202.86; p=0.058). Interaction testing demonstrated that ECE/PH did not significantly modify the prognostic impact of PI-R on either ENI (Interaction OR 0.829; 95%CI 0.005-124.202; p=0.942) or mRS 5-6 (Interaction OR 0.759; 95%CI 0.008-67.950; p=0.905).
Conclusion: Elevated inter-hemispheric PI-R after successful EVT for LVO was independently associated with reduced ENI and increased odds of mRS 5-6. This association persisted in patients without PH and/or ECE, suggesting interlesional PI-R may serve as a pragmatic TCD biomarker of NRP, or increased microvascular resistance unexplained by mass effect. Prospective studies are needed to validate TCD as a screening tool for NRP and identify candidates for adjunctive post-EVT microvascular therapies.

S233: Incidence and Predictors of Early Neurological Deterioration in Minor Ischemic Stroke: A Systematic Review

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Background: Minor ischemic stroke, commonly defined by a National Institutes of Health Stroke Scale (NIHSS) score≤5, accounts for a substantial proportion of acute ischemic strokes. Despite initially mild deficits, a significant subset of patients experiences early neurological deterioration (END), which is associated with worse functional outcomes. However, the reported incidence of END varies widely, and the predictors remain incompletely characterized. A comprehensive synthesis of available evidence is needed to guide risk stratification and clinical decision-making. This systematic review aims to evaluate the incidence of END in minor ischemic stroke and identify demographic, biomarker, and imaging predictors of neurological worsening.
Methods: This systematic review followed PRISMA guidelines. PubMed, Cochrane Library, Embase, and Web of Science were searched from inception through 2025 using terms including minor stroke, mild stroke, early neurological deterioration, neurological worsening, and predictors. Inclusion criteria required original studies enrolling adults with minor ischemic stroke, reporting END incidence and/or predictors with a defined deterioration threshold. Of 2,907 records identified, titles were screened and irrelevant records excluded.
Remaining full-text articles were assessed for eligibility by two independent blinded reviewers, with disagreements resolved by consensus, yielding 49 included studies.
Results: Across 49 observational studies encompassing over 18,000 patients, minor stroke was most frequently defined as admission NIHSS≤5. END definitions varied considerably, with NIHSS deterioration thresholds ranging from ≥1 to ≥4 points and observation windows spanning 24 hours to 10 days. The reported incidence of END ranged from 3% to 46%, with most studies reporting rates between 10% and 30%; variation was largely attributable to differing END definitions. Significant demographic and clinical predictors included diabetes mellitus, higher admission NIHSS score, elevated systolic blood pressure, older age, and atrial fibrillation.
Biomarker predictors included elevated fasting blood glucose, HbA1c, neurofilament light chain, and inflammatory markers. Imaging predictors were the most consistently identified and included large-vessel occlusion, proximal arterial stenosis, perfusion deficits such as Tmax>6 seconds volume exceeding 53.73 mL and 71.98 mL, internal border zone infarct patterns, hemorrhagic transformation, and internal capsule infarction. Treatment-related factors including intravenous thrombolysis, dual antiplatelet therapy, and endovascular thrombectomy procedural variables also modified END risk.
Conclusion: END in minor ischemic stroke is common, driven by a multifactorial interplay of vascular, metabolic, and imaging-based risk factors. Substantial heterogeneity in END definitions limits cross-study comparability and emphasizes the need for standardized criteria. Early vascular imaging to identify large-vessel occlusion and perfusion mismatch should be prioritized in risk stratification of minor stroke patients.

S234*: Plasma-derived Extracellular Vesicles from Humans with Silent Stroke and a Mouse Model of Silent Stroke Stimulate a Senescence-associated Secretory Phenotype at the Blood-brain Barrier

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Background: Silent brain infarction (SBI), commonly referred to as silent stroke, is associated with an increased risk of future stroke and dementia; however, the underlying mechanisms that contribute to this increased risk are not well understood. Emerging evidence demonstrates that plasma-derived, or circulating, extracellular vesicles (cEVs) contribute to the pathophysiology of stroke and are likely to play a role in other cerebrovascular disorders that include silent stroke. Human brain microvascular endothelial cells (hBMECs) are the first cells to interact with cEVs at the blood-brain barrier (BBB), a dynamic interface between the systemic circulation and brain. Thus, we hypothesized that cEVs from individuals with SBI stimulate a proinflammatory senescence-associated secretory phenotype (SASP) in hBMECs, which induces BBB and neurovascular unit dysfunction associated with an increased risk for future stroke and dementia. We also tested our hypothesis in a mouse model of chronic cerebral hypoperfusion (CCH) that mimics human silent stroke.

Methods: To test our hypothesis, control and SBI patients were recruited from the neurology inpatient service at WVU Medicine based on predefined eligibility criteria. We isolated cEVs from the plasma of control (n=4) and SBI (n=10) patients. Similarly, aged (15-18 months) C57Bl/6J male and female mice (n=15/sex/surgery) were subjected to 30-days of CCH or a sham (control) injury, and cEVs were purified from mouse plasma. Both human and mouse cEVs were characterized by using nanoparticle tracking analysis (NTA) to calculate EV concentration and zeta potential (ZP) to assess EV charge. Next, hBMECs were incubated with either human or mouse cEVs from experimental groups for 24 hours, followed by assessment of SASP outcomes linked to aging and inflammation.

Results: SBI patients showed a significant increase in cEV concentration ($p<0.001$) and decreased ZP ($p=0.014$) compared with controls. Following incubating the hBMECs with SBI-EVs, we observed a robust SASP response compared to control-cEVs incubation that included: decreased viability ($p<0.01$), elevated cytotoxicity ($p<0.05$), diminished wound healing ($p<0.0001$), elevated β-galactosidase ($p<0.01$), telomere shortening ($p<0.01$) and significantly elevated expression of several proinflammatory cytokines and senescence-associated genes.

Strikingly similar results were observed when hBMECs were incubated with cEVs from CCH-mice. Lastly, ongoing proteomics analysis will identify cEVs cargo in SBI patients and controls.

Conclusion: These compelling results demonstrate a novel, species-conserved systemic mechanism wherein SBI, or silent stroke, generates cEVs that stimulate a SASP in hBMECs. The resultant "aging" of the BBB is a potential mechanism to explain the increased risk of stroke and dementia in individuals with silent stroke.

S235: Real-World Outcomes of Low-Dose Intravenous Heparin in Aneurysmal Subarachnoid Hemorrhage: A retrospective cohort study

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Background: Aneurysmal subarachnoid hemorrhage (aSAH) is associated with significant morbidity driven largely by secondary neurological and systemic complications. Anticoagulation after aSAH is controversial due to concern for complications. Low-dose intravenous heparin (LDIVH) has been used in clinical practice with the intent of reducing thrombotic and inflammatory complications, though real-world evidence remains limited. We evaluated the association between LDIVH and complications following aSAH in a real-world cohort using administrative and clinical databases.

Methods: We performed a retrospective cohort study of consecutive patients with aSAH treated in routine clinical practice at a multi-hospital health care system comparing those treated before and after the transition to a LDIVH protocol for aSAH. Baseline variables included prior hypertension and hypertensive urgency/emergency at presentation. The primary outcomes was in-hospital complications assessed using the Midas Risk Adjustment Model (MRA) observed complication rate. Secondary outcomes included cerebral infarction, intracranial bleeding (any cause), vasospasm and length of stay (LOS). Group comparisons were made using Fisher's exact test and t-tests. Multivariable linear regression was used to assess the independent association between LDIVH and observed complications.

Results: Among the 252 patients, 113 were treated prior to the initiation of the LDIVH protocol and 139 after. The groups were similar in age (pre: 59.8 ± 15.9 vs post: 59.4 ± 14.7, $p=0.86$) and gender composition (pre: 36.3% male vs post 30.2%, $p=0.38$). Pre-existing hypertension was similar between the groups (69.0% vs 67.6%, $p=0.89$) as was presences of hypertensive urgency/emergency at presentation (34.5% vs 33.1%, $p=0.89$). Total observed complications were lower after transition to the LDIVH protocol (2.43 vs 1.68, $p=0.02$). In adjusted analysis, this remained independently associated with fewer complications (ß=-0.74, $p=0.012$). The LDIVH protocol was not associated with increased intracranial bleeding (4.4% vs 3.6%, $p=0.76$) or cerebral infarction (10.6% vs 6.5%, $p=0.26$). LOS (21 vs 17 days) and rate of vasospasm (21.2% vs 12.2%) were numerically lower post LDIVH but was not statistically significant ($p=0.07$ and $p=0.06$, respectively).

Conclusion: In this real-world cohort, LDIVH following aSAH was not associated with increased hemorrhagic or thrombotic complications and was independently associated with lower overall complication rates. No cases of Heparin-induced thrombocytopenia (HIT) were noted in this cohort.

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Although severity measures (e.g. Hunt-Hess or Fisher grade) was not consistently available in this data set, clinically relevant measures (e.g. hypertension) were used during adjusted analysis. Given the absence of safety concerns and emerging trends that may indicated improved outcomes, LDIVH may be considered for post-aSAH management.

S236-LB: Multimodal MRI Assessment of Blood-Brain Barrier Permeability in Cerebral Small Vessel Disease: Insights from ASL-MRI, DSC-MRI, and DCE-MRI

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Background: White matter hyperintensities (WMH) are a hallmark of cerebral small vessel disease (cSVD) and reflect blood-brain barrier (BBB) dysfunction. Three MRI modalities, arterial spin labeling (ASL), dynamic susceptibility contrast (DSC), and dynamic contrast-enhanced (DCE) MRI, offer distinct approaches for assessing BBB permeability. Whether global whole-brain permeability measures are associated with age and brain tissue volume in asymptomatic individuals remains unclear.

Methods: DSC-derived K2 showed significant negative associations with brain tissue volume in unadjusted models (whole brain: $\beta=-0.053$, $p=0.044$; white matter: $\beta=-0.052$, $p=0.031$; grey matter trend: $\beta=-0.050$, $p=0.069$), which did not survive adjustment for vascular risk factors (all $p>0.15$). ASL-derived PS showed a trend toward positive association with brain tissue volume in adjusted models ($p=0.079$). Ktrans showed no association with brain tissue volume (all $p>0.05$). No modality significantly associated with age in unadjusted or adjusted models (all $p>0.05$).

Results: In 64 asymptomatic individuals with cSVD, DSC-derived K2 associates with brain tissue volume in unadjusted models and ASL-derived PS shows a trend in adjusted models, suggesting global BBB dysfunction and perfusion-related abnormalities may reflect broader cerebrovascular deterioration. These findings highlight the complementary but non-overlapping nature of multimodal MRI permeability measures in asymptomatic cSVD, and support their use as distinct rather than interchangeable biomarkers.

Conclusion: Sixty-four asymptomatic participants from the GeneSTAR cohort (mean age 60.6 years; 63.9% female; mean systolic BP 136.8 mmHg: 39.1% African American) underwent DSC and DCE-MRI; 64 participants with complete ASL data were included in PS analyses. Thirteen participants were excluded from ASL analyses because of excessive imaging noise, and the same 64 participants were used across all modality analyses. ASL-derived permeability-surface area product (PS), DSC-derived leakage factor (K2), and DCE-derived volume transfer constant (Ktrans, using Patlak analysis) were measured across whole brain, grey matter, and white matter. Linear regression examined associations with age and brain tissue volume (ICV-normalized), both before and after adjustment for age, sex, race, and systolic blood pressure.

S237: The Post-Stroke Spatiotemporal Dynamics of Myeloid Cells are Reciprocally Mediated and Independent of Infarct Topology

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Background: Ischemic stroke is a leading cause of morbidity and mortality worldwide. Despite receiving revascularization therapy, nearly half of patients exhibit expansion of the infarcted tissue within 24 hours, implicating ischemia/reperfusion injury (I/RI) as a driver of stroke progression and long-term outcomes. Myeloid cells, including microglia (MG), macrophages (MΦ), and polymorphonuclear neutrophils (PMNs), are among the first immune cells to respond in I/RI. These cells play multifaceted roles in mediating the inflammatory response, which are in part determined by their position. However, the spatial patterns of myeloid cells in acute I/RI, as well as the cues that govern their localization, are not well defined. To address this gap, we employed whole brain light sheet microscopy (LSM) to map the spatiotemporal patterns of myeloid cells and investigate how these immune cells reciprocally affect cell position.

Methods: The transient middle cerebral artery occlusion (tMCAO) stroke model was performed in 3–6-month-old Ly6G-TdTomato (PMNs) x Csf1r-EGFP (MG/MΦ) transgenic mice. In a subset of mice, PMN adhesion was inhibited via ICAM-1 antibody blockade. Whole brains were collected at days 0, 1, 3, and 7 post-tMCAO, cleared, and imaged using LSM. Brains were co-labeled with NeuN (neurons) and fluorescent lectin (reperfused vasculature). Cell densities were mapped across neuroanatomic structures according to Allen Brain Atlas registration and surface reconstructions were computed for each cell population using Imaris image analysis software.

Results: Comparable infarct volumes were observed across all timepoints. MG/MΦ and PMNs exhibited cell type-specific

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spatial patterning that evolved throughout acute infarct evolution and was not confined to the boundaries of the infarcted tissue. Specifically, PMN infiltration was most pronounced in the amygdala initially with migration to deeper striatal regions longitudinally, while MG/MΦ accumulated first in the amygdala and then dispersed broadly to involve cortical structures. These patterns of MG/MΦ localization were influenced by PMN recruitment, as blockade of PMN adhesion induced a shift in MG/MΦ spatial patterning, associations with the vasculature, and morphology.

Conclusion: Our data have established spatiotemporal patterns of MG/MΦ and PMNs in acute I/RI that are independent of infarct topology, emphasizing the relevance of defining other cellular cues that may be guiding immune cell localization. MG/MΦ position and morphology shifted in response to loss of PMN infiltration, suggesting a reciprocal role for these myeloid cells in mediating the I/RI response. These data highlight the relevance of considering the spatiotemporal dynamics of the entire post-stroke immune milieu in the investigation of novel therapeutic targets for stroke I/RI.

S238: Higher Current Density of Non-invasive Brain-Stimulation Together with Occupational Therapy Leads to Stronger Behavioral and Imaging Changes in Recovering Stroke Patients

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Background: Results from the multi-center TRANSPORT2 clinical trial call for exploring behavioral and brain effects of applying much higher non-invasive brain-stimulation doses. Current density (current dose/pad size) and total charge density (current density × duration × sessions) are two biologically relevant measures that have been correlated with treatment effects across multiple studies in meta-analyses. The highest current density employed in TRANSPORT2 was only 0.114 mA/cm^2 (4 mA current dose with a 5x7cm pad size). In this pilot study we aim to evaluate the safety, tolerability and preliminary brain tissue/behavioral effects of higher doses of bi-hemispheric tDCS while all patients undergo the same intense form of OT.

Methods: We are conducting a 3+3 safety/tolerability/preliminary efficacy dose-escalation study enrolling subjects between 1-6 months after their first-ever unihemispheric ischemic stroke with mild to moderate motor impairment (FM-UE ≤54). Participants undergo a standardized bi-hemispheric tDCS protocol of applying a dose of 4.5mA using a 5cm round rubber electrode (current densities were at least 0.23 mA/cm^2) and then escalating the dose by 0.5mA every 3 subjects assuming no safety/tolerability issues developed. The tDCS stimulation (30min) started at the same time as OT (90min), for 10 sessions delivered over 2 weeks. Tolerability of the stimulation was rated using a visual analog scale (0 = no discomfort; 10 = intolerable), and safety monitoring followed the TRANSPORT2 protocol for clinically important adverse events. Structural (DTI) and Functional (rsfMRI) Brain MRI were obtained before and after the intervention.

Results: To date, 9 participants completed treatment (mean age 65 ± 10.1 years; 4 females, 5 males). No clinically important adverse events occurred, and dose escalation was well tolerated (all VAS scores between 0-3). The FM-UE improvement always exceeded 9 points (mean 14.5 ± SD 2.7 points) - twice the chosen minimally important clinical difference (MCID) of 4.5 points - a level of improvement rarely seen when patients undergo 10 usual/standard OT sessions. Brain imaging showed both structural and functional imaging changes in motor systems with more consistent changes observed with higher current densities.

Conclusion: The current results from this ongoing study provide preliminary evidence that multiple-sessions of bi-hemispheric tDCS at current densities at least 2x higher than those used in the highest dose arm of TRANSPORT2 is safe, tolerable, and may provide consistent and stronger behavioral/imaging changes than those seen in lower dose studies.

S239: Single-cell RNA Sequencing Analyses Revealed Integrated Vascular Reactions in Promoting Angiogenesis after Chronic Cerebral Hypoperfusion

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Background: Vascular dementia (VD) is the second most common type of dementia, accounting for 20% of dementia cases world-wide. Pathological alternations in neurovascular unit (NVU) are observed in VD. The NVU encompasses neural structures (e.g. neurons and glial cells) and vascular components (e.g. endothelial cells (ECs), pericytes (PCs) and smooth muscle cells (SMCs)) that highly collaborate to regulate brain homeostasis.

Abnormalities in vascular structure contribute to dysfunction of neuronal networks and subsequent cognitive deficits. Therefore, elucidating the mechanism for vascular injury and repair may guide the development of preventive or therapeutic strategies against VD.

Methods: In this study, we employed single cell RNA sequencing to map the cell populations and explore the vascular responses in mouse brains collected 6 weeks after an asymmetric common carotid artery stenosis (ACAS) model of VD or sham operation.

Results: A distinct tip cell cluster with specific gene expression patterns was identified among 9 EC clusters and validated by double immunostaining of a tip cell marker isolectin B4 and a EC marker CD31. Immunostaining of CD93, another tip cell marker, and CD31 demonstrated that the number of tip cells increased significantly in the ACAS

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brains compared to sham 6 weeks after ACAS. Further gene ontology (GO) analysis based on differentially expressed genes (DEGs) between tip cells vs. other EC revealed enrichment in biological processes involving angiogenesis and suggested the involvement of Apln/Aplnr signalling in these biological terms. Western blot confirmed an increase in Apln protein expression after ACAS. To further elucidate the function of Apln/Aplnr signaling in VD, Apelin 13 (apln13), an Apln agonist, or same volume of vehicle control was administered (i.p) 1 to 21 days after ACAS. Apln13 treatment improved cognitive functions compared to vehicle-treated ACAS mice as assessed by Y-maze, novel object recognition and passive avoidance tests. Apln13 treatment promoted post-ACAS angiogenesis and increased tube formation in EC cultures. Cell-cell interaction analyses between tip cells and other vascular components highlight a cross talk between astrocyte and tip cells through VEGF-VEGFr interaction.

Conclusion: Collectively, our studies provide insights into the molecular basis of angiogenesis and vascular repair in VD brains. Apln13 may represent a therapeutic strategy to improve neurovascular function in VD.

S240: *Prognostic and Diagnostic Value of Troponin in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

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Background: Troponin elevation is frequently observed in patients with acute ischemic stroke and may reflect underlying cardiac injury or neurocardiac interactions. However, its diagnostic significance and prognostic value for outcomes such as mortality and stroke recurrence remain uncertain.

Methods: A systematic review and meta-analysis of studies retrieved from PubMed, Embase, Scopus, and google scholar from 2014 to December 2025. Eligible studies included adult patients over 18 years acute ischemic stroke with troponin levels measured and prognostic outcomes reported. Quality assessment was done using the QUADAS-2 and Newcastle-Ottawa Scale. Random-effects model was used to pool effect estimates with 95% CI. Heterogeneity was assessed using the I^2 statistics.

Results: A total of eight studies encompassing 5,326 patients were included. Elevated troponin levels were significantly associated with an increased risk of all-cause mortality (pooled HR: 1.76; 95% CI: 1.06–2.92) and stroke recurrence (pooled HR: 1.37; 95% CI: 1.13–1.68). While the risk for major adverse cardiovascular events was elevated, it did not reach statistical significance (pooled HR: 1.65; 95% CI: 0.94–2.91). Sensitivity analyses confirmed the robustness of the mortality finding, excluding one study, which yielded (HR=2.14, 95% CI=1.61–2.85, I^2=51.6 % and p=0.08); and, when excluding two studies (HR=1.89, 95% CI=1.58–2.26, I^2=0.0% and p=0.94), demonstrating data consistency among the remaining studies. Weighted analyses further demonstrated moderate discriminatory ability for identifying concurrent cardiac pathology, with a pooled area under the curve (AUC) of 0.76 (95% CI: 0.68–0.84). This indicates moderate predictive power despite significant heterogeneity, I2= 88.8%, p value < 0.001, and a wide prediction interval of 0.49 to 1.03. Moderate-to-high heterogeneity was observed, with moderate heterogeneity for mortality (I^2 = 77.2%) and high heterogeneity for MACE (I^2 = 89.6%) and stroke recurrence (I^2= 0.0%). Subgroup analyses indicated improved prognostic performance with high-sensitivity troponin assays.

Conclusion: Elevated troponin is independently associated with increased mortality and stroke recurrence in acute ischemic stroke, with moderate diagnostic performance for concurrent cardiac pathology. These findings support its role in early risk stratification, though standardization of thresholds and further mechanistic studies are needed.

S241: Hematological Disorders as Stroke Risk Factors: CDC WONDER Analysis

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Background: Hematological disorders are known to increase the risk of stroke and worsen clinical outcomes.

Stroke remains a leading cause of mortality in the United States, affecting approximately 795,000 individuals annually. However, national trends in stroke-related mortality among patients with hematological disorders remain poorly characterized. This study evaluates mortality trends associated with stroke in individuals with hematological disorders in the U.S. from 1999 to 2020.

Methods: Data were obtained from the CDC WONDER database (1999–2020). Stroke-related deaths were identified using ICD-10 codes I60–I69, and hematological disorders using codes D50–D89. Age-adjusted mortality rates (AAMR) per 1,000,000 population were calculated. Trends were stratified by sex, age, race, region, and urbanization.Join point regression analysis was used to estimate Annual Percent Change (APC) and Average Annual Percent Change (AAPC), with statistical significance defined as p < 0.05.

Results: Between 1999 and 2020 there were 158,786 stroke-related deaths among individuals with hematological

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disorders; AAMR declined from 2007–2018 (APC −1.38, 95% CI −1.80 to −0.95) but rose sharply from 2018–2020 (APC 12.41, 95% CI 7.01 to 18.10). Males had higher AAMR than females; the South had the highest AAMR, Asian/Pacific Islanders showed the largest decline, most deaths occurred in inpatient facilities (51.5%), and the highest crude mortality was in those aged ≥85 years (CMR 440.93).

Conclusion: Although stroke-related mortality among individuals with hematological disorders declined from 1999 to 2018, a concerning increase was observed between 2018 and 2020. Males consistently experienced higher mortality than females. Geographic and racial disparities persist, with the Southern U.S. bearing the highest burden. The recent upward trend highlights the need for targeted public health strategies to address emerging risks and reduce disparities in this vulnerable population.

S242: Lung Cancer-Associated Acute Ischemic Stroke: A Systematic Review and Meta-Analysis of Coagulation Profile, Lesion Characteristics and Clinical Outcomes

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Background: Hypercoagulable state in malignancy increases both the risk and severity of stroke. Among malignancies, lung cancer is one of the most common. Observational studies show lung cancer–associated acute ischemic stroke (LCAIS) is often associated with higher short-term mortality, greater functional disability, involvement of multiple locations, etc.

Methods: A database search was conducted up to February 2026 to identify studies comparing lung cancer-associated ischemic stroke (case) with only the acute ischemic stroke group (control). From a total of 5156 studies, 13 were eligible. The main outcomes assessed included clinical characteristics, NIHSS scores, functional outcomes assessed by the modified Rankin Scale, mortality, coagulation profile, and number of stroke lesions. A random-effects meta-analysis was performed to estimate pooled effect sizes, and a Bayesian random-effects model was additionally applied to assess uncertainty and probability of association.

Results: A random effects model meta-analysis of 3 studies reveals that hypercoagulability was observed much more in the lung cancer group with higher D-dimer levels compared to controls (SMD = 0.70, 95% CI: 0.43-0.97, $p < 0.05$, $I^2 = 31.2\%$). Another meta-analysis of 3 studies reveals that the lung cancer group also had significantly higher odds of multiple stroke lesions (OR = 6.94, 95% CI: 1.09-44.00, $p < 0.05$, $I^2 = 68.5\%$). Later, a Bayesian analysis using non-informative priors showed a similar effect size (OR = 6.79, 95% CrI: 0.69–64.8) with a 96.6% probability of multiple lesion involvement in the lung cancer group, although there remains uncertainty.

During admission, median NIHSS scores in the case group were 5 (IQR 1–15) to 14 (IQR 4–19.5), while the control group showed a pooled mean of 4.02 ± 2.76. At day 30, over 90% of patients in both groups had NIHSS ≤5, and at day 90, the pooled mean NIHSS remained higher in the case group (5.03 ± 5.95) compared to controls (1.87 ± 1.57). At day 30, mRS scores were higher in the case group (2.79 ± 1.92) compared to controls (1.66 ± 1.22). At day 90, 35.32% ± 19.80% of the case group had a good functional outcome (mRS 0–2), whereas controls showed better functional status, including mRS 3 (IQR 1–4) and 0.68 ± 0.55 across studies. The lung cancer group demonstrated higher mortality at 30 days (34.3% ± 22.20% vs <1%) and 90 days (9.65% ± 8.10% vs 0%).

Conclusion: Malignancy, particularly lung cancer, creates a hypercoagulable state that contributes to more aggressive patterns of ischemic stroke. This often results in poorer outcomes compared to non-cancer stroke and is characterised by multiple lesions, progressive functional decline and higher mortality.

S243: Delayed Diagnosis of Adult-Onset Moyamoya Syndrome: A Case of Recurrent Stroke-Like Symptoms Despite Initially Normal Imaging

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Background: Moyamoya syndrome (MMS) is a rare, progressive cerebrovascular disorder characterized by stenosis of the distal internal carotid arteries and their branches within the Circle of Willis, leading to compensatory collateral vessels with a characteristic "puff of smoke" angiographic appearance. While predominantly pediatric, adult-onset MMS accounts for approximately 40% of cases and presents diagnostic challenges due to nonspecific symptoms. Delayed diagnosis increases risk of recurrent ischemic events and irreversible neurological damage. A 61-year-old Caucasian male with hypertension, hyperlipidemia, coronary artery disease, and 40 pack-year smoking history presented with progressive left hemiparesis and altered mental status. Over the preceding 18 months, he had four emergency department visits for recurrent left-sided weakness, syncope, and persistent headaches. Previous workup including non-contrast CT and brain MRI with routine sequences were unremarkable, with symptoms attributed to hypertensive urgency and transient ischemic attacks.

Methods: Clinical data were obtained through review of the patient's medical records, including symptom progression, neurologic findings, imaging studies, and hospital course. Diagnostic evaluation included computed tomography angiography (CTA) followed by digital subtraction angiography (DSA) to further characterize cerebral vasculature.

Results: On presentation, the patient's blood pressure was 210/115 mmHg. Neurological examination demonstrated left

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hemiparesis, left facial droop, and dysarthria with NIH Stroke Scale score of 8. CTA revealed right middle cerebral artery occlusion at the M1 segment with distal reconstitution via leptomeningeal collaterals. Given unusual collateralization with recurrent symptoms, DSA was performed. DSA demonstrated severe stenosis of the right distal internal carotid artery extending into proximal MCA and ACA with extensive moyamoya collateral vessels in basal ganglia, consistent with Suzuki stage III-IV disease. Contralateral evaluation showed mild stenosis without moyamoya vessels. Secondary workup, including autoimmune panel, hypercoagulable screen, and inflammatory markers, was negative, indicating primary moyamoya syndrome.

Conclusion: This case illustrates critical diagnostic pitfalls in adult-onset moyamoya syndrome. Standard imaging may not detect early changes, particularly when collateral circulation prevents infarction. The patient's vascular risk factors likely contributed to diagnostic anchoring bias, with symptoms attributed to atherosclerotic disease rather than moyamoya pathophysiology. Adults with recurrent or progressive neurological symptoms warrant advanced vascular imaging with CTA, MRA, or DSA even when initial studies appear normal. The diagnostic delay highlights the need for heightened clinical suspicion in adults with atypical stroke presentations. Early recognition and neurosurgical consultation can prevent progression to irreversible ischemic injury in this treatable cerebrovascular condition.

S244: Comparative Effectiveness of Single Versus Dual Antiplatelet Therapy following Intravenous Thrombolysis for Acute Ischemic Stroke

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Background: Short-term dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is the recommended protocol for minor acute ischemic strokes (AIS) and transient ischemic attacks (TIA) based on the CHANCE, POINT, and THALES trials. However, these trials specifically exclude patients who received intravenous thrombolysis (IVT) or underwent endovascular therapy (EVT), limiting the generalizability of these recommendations to this high-risk post-IVT population. The safety and efficacy of antiplatelet therapy for this clinically distinct cohort remains poorly defined, highlighting a critical evidence gap that this study addresses. **Methods:** We conducted a retrospective cohort study of IVT-treated AIS patients at a single comprehensive stroke center, excluding those with independent indications for anticoagulation (e.g., cardioembolic stroke, reduced EF) or DAPT (e.g., carotid revascularization / stenting). The primary outcome was recurrence of ischemic stroke at 90 days. Secondary outcomes were excellent functional outcome (mRS 0–1) at 90 days and early neurologic deterioration (END; NIHSS worsening ≥4) within 72 hours of hospitalization. The primary safety outcome was symptomatic ICH (sICH). Outcomes were assessed using multivariable regression adjusted for age, sex, admission NIHSS, and EVT. A sensitivity analysis was restricted to non-EVT patients.

Results: Of 1079 patients screened, 696 met inclusion criteria. The mean age was 68.4 ± 14.0 years, 53.3% were male, and median admission NIHSS was 6 [IQR 3–12]. Of these patients, 429 received single antiplatelet therapy (SAPT) and 267 received DAPT; 177 had confirmed LVO and underwent EVT. DAPT patients had significantly lower admission NIHSS (median 4 [IQR 2–8] vs. 8 [IQR 4–15], $p<0.001$) and less frequently underwent EVT (13.3% vs. 33.1%, $p<0.001$), reflecting preferential selection of DAPT for milder strokes. Adjusted recurrence rates were 7.7% in SAPT vs 9.5% in DAPT (aRR 1.24, 95% CI 0.72–2.13, $p=0.434$). Favorable 90-day mRS 0–1 did not differ significantly between groups (adjusted RR 0.95, 95% CI 0.80–1.13, $p=0.566$). DAPT was associated with higher rates of END (aRR 2.64, 95% CI 1.34–5.18, $p=0.005$) with no difference in sICH (aRR 0.98, 95% CI 0.20–4.89, $p=0.981$). In the non-EVT cohort ($n=516$), the END association remained significant (adjusted RR 2.69, 95% CI 1.11–6.54, $p=0.028$).

Conclusion: There was no difference in 90-day recurrence of AIS between SAPT and DAPT among patients who received IVT. However, rates of END were higher in the DAPT group, which may reflect confounding by indication. Rates of sICH did not differ between groups, suggesting DAPT did not increase hemorrhagic risk following IVT. Larger studies are needed to validate these findings.

S245: Sex Differences in the Association Between 20-year Trajectories of Inflammation and White Matter Lesion Volume in Aging Adults

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Background: White matter hyperintensity (WMH) lesion volume, commonly seen on brain MRI in older adults, provides an imaging marker of cerebrovascular small vessel disease (cSVD) associated with greater risk of Alzheimer's disease and related dementias. Elevated systemic inflammation, indexed by C-reactive protein (CRP), has been linked to greater global WMH burden, potentially suggesting an

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underlying contributor to WMH development and progression, yet whether this association differs by sex remains unclear. Older adult women tend to exhibit higher WMH lesion load and differ in inflammatory biology from men, suggesting that the CRP–WMH association may be sex-specific. Most prior studies have largely focused on single time-point CRP measurements, leaving the long-term cumulative effects and temporal patterns of inflammatory burden relevant to late-life cSVD burden incompletely characterized.
Methods: We included community-dwelling, dementia-free participants in the Atherosclerosis Risk in Communities (ARIC) study with available laboratory data at Visits 2, 4, and 5 and MRI at Visit 5. Total WMH volume was derived from T2-FLAIR images using a semiautomated segmentation method and was log-transformed. High-sensitivity CRP trajectories spanning midlife through late life over a 20-year period were identified using longitudinal trajectory modeling, which yielded stable-low, increasing, stable-elevated, decreasing, and late-decreasing groups. Linear regression models weighted for selection for MRI and adjusted for total intracranial volume, demographics, vascular risk factors, and chronic inflammatory conditions evaluated trajectory-by-sex interactions on late-life WMH.
Results: In 1,201 participants, mean ages at Visit 2 and Visit 5 were 55.6 [5.2] and 76.4 [5.3] years, respectively (41.2% men, 24.8% Black race, 46.4% >high school education). Women had higher CRP levels at each of the three trajectory time points and greater total WMH volume compared with men. The overall trajectory-by-sex interaction was of borderline statistical significance (p-interaction=0.051). Compared with stable-low trajectory, three trajectories-increasing (p-uncorrected=0.016), stable elevated (p-uncorrected=0.046), and late decreasing (p-uncorrected=0.032)-but not decreasing (p-uncorrected=0.203), were associated with greater total WMH volume among women, though these associations did not survive multiple comparisons correction (p-corrected=0.061). No statistically significant trajectory-WMH associations were observed among men.
Conclusion: Despite women showing higher CRP levels and greater WMH burden than men, any pattern of elevated systemic inflammation across midlife was nominally associated with greater late-life global WMH burden only among women. These findings highlight the value of trajectory-based inflammatory profiling and suggest that women with increasing or persistently elevated CRP burden across midlife may represent a higher-risk priority group for early intervention to reduce small-vessel cerebrovascular burden.

S246: Persistent Rise and Disparities in Stroke and Atherosclerosis Mortality: A 25-Year U.S. Retrospective Analysis (1999-2024)

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Background: This study uses CDC WONDER data to examine mortality associated with stroke and atherosclerosis, analyzing overall trends and variations by sex, race/ethnicity, geographic region, and age groups. The findings aim to identify high-risk populations and inform targeted prevention and management strategies.
Methods: Using CDC WONDER data, we calculated mortality rates per 100,000 individuals aged 25+ who died from stroke and atherosclerosis recorded as multiple causes of death (MCD). Stroke-related deaths were identified using ICD-10 codes I60-I69, while atherosclerosis-related deaths were classified under I26, I80, I82. Data were analyzed across ten-year age groups from 55-64 years upwards, as younger age groups had suppressed or unreliable estimates. Joinpoint regression was used to assess annual percentage change (APC) and average annual percentage change (AAPC) in mortality trends.
Results: From 1999 to 2024, a total of 764,092 deaths were reported in people who had both stroke and atherosclerosis. Overall age-adjusted mortality rates (AAMRs) decreased from 24.13 in 1999 to 7.97 in 2024. A significant decline was observed from 2001 - 2008 (APC: -8.19%). Individuals aged 85+ years recorded the highest mortality (417.36 in 1999). Males exhibited higher mortality rates than females in 2024 (10.40 vs. 6.12). The highest mortality rates were observed among Black or African American individuals (15.91), whereas the lowest were noted among Asian or Pacific Islander individuals (10.40). Geographical disparities were evident, with the South experiencing the highest burden (9.77 in 2020) and the Northeast the lowest (6.11 in 2024). Among urbanization levels, Micropolitan (non-metro) areas had the highest mortality (11.38), while Large Fringe Metro areas had the lowest (7.43). Large Central Metro (7.76), Large Fringe Metro (7.43), Medium Metro (9.14), Small Metro (9.30), Micropolitan (11.38), and Noncore (10.74) showed a gradient of increasing mortality with decreasing urbanization. At the state level, Tennessee ranked highest (32.34), falling within the top 90th percentile over the study period.
Conclusion: Despite substantial declines in stroke and atherosclerosis mortality over 25 years, persistent disparities by

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sex, race, geography, and urbanization level underscore the need for targeted interventions in high-risk populations, particularly older adults, Black communities, Southern states, and non-metropolitan areas.

S247: Feasibility of Clinical Quality Bedside Multimodal Brain Imaging

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Background: A crucial aspect of the neuroimaging frontier has been the to improve cost, portability, and tolerability while retaining clinical informativeness. Portable 64 mT MRI (pMRI) can provide neurological monitoring in patients for whom conventional imaging faces barriers. However, the available pMRI sequences currently are limited to structural acquisitions. Functional near-infrared spectroscopy (fNIRS) is a portable, well-tolerated complementary technology that measures changes in concentration of oxy- and deoxyhemoglobin comparable to the BOLD signal reflected in functional MRI. The aim of the present work was to demonstrate the feasibility and evaluate synergy of these methods deployed concurrently within a case series of patients with dementia and those within the first year of left hemisphere stroke.

Methods: Participants were recruited from longitudinal observational trials of English-speaking adults targeting post-stroke aphasia recovery and primary progressive aphasia (PPA) at Johns Hopkins University School of Medicine. Twenty-one pMRI-fNIRS acquisitions within the first year of stroke (6 at <3 months, 16 at 6-12 months) and 19 from patients with PPA were examined. MRI processing was completed in FreeSurfer 8, using SynthSeg for volumetric analysis on T2-weighted scans. fNIRS processing is described in Meier et al. (Brain Connect., 2023).

Mean intra- and interhemispheric connectivity were averaged across the Fisher-transformed Z values for every pairwise connection.

Results: Patients in both groups tolerated combined imaging schedules well and reported no adverse events during the acquisition periods. Combined pMRI and fNIRS yielded stronger predictions of function than either modality in isolation. In patients with stroke, adding interhemispheric connectivity improved upon ipsilesional grey and white matter volume when predicting image description content on the NIH Stroke Scale, controlling for acute performance and age, accounting for 70% of total variance ($p=0.01$). In patients with PPA, adding interhemispheric connectivity significantly improved upon bilateral grey and white matter volume ($p=0.02$) when predicting naming of pictured objects on the Boston Naming Test, controlling for age and overall intracranial volume, accounting for 98% of the total variance ($p=0.02$).

Conclusion: Portable MRI and fNIRS systems are well-tolerated, safe, and clinically informative tools for bedside neurological monitoring of patients with stroke and dementia. Given recently developed protocols facilitating co-registration of images and the successful use of fNIRS in detecting arterial and local perfusion, combining these technologies provides a potentially synergistic complement to the sequences currently available in pMRI.

S248: FDG-PET Uptake in Concurrent Cranial and Large Vessel Giant Cell Arteritis

Presenting Author: *Sylvia Tawiah-Eshun, Salt Lake City, UT*

Background: A 69-year-old woman with remote history of left posterior cerebral artery stroke and residual right homonymous hemianopia presented with five days of severe left temporal headache radiating to her jaw. Due to her existing visual field defect, the patient was uncertain if she had experienced any recent changes in her vision.

Examination revealed baseline right homonymous hemianopia and right-sided extremity weakness. There was no temporal artery tenderness or new focal neurologic deficit. Laboratory studies were significant for elevated platelet count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Imaging studies, including MRI brain and CT angiogram of the head and neck showed her prior chronic stroke but no blood vessel abnormalities.

Similarly, a temporal artery duplex showed no vessel abnormalities. MRI Vessel Wall Imaging revealed diffusely diminutive bilateral superficial temporal arteries, but no gross periarterial enhancement

Methods: Case Report

Results: The combination of new temporal headache,and elevated inflammatory markers in older patients raises suspicion for GCA. However, typical imaging studies were negative Clinical suspicion of vasculitis, however, remained high, and the patient underwent a CT angiogram of the chest, which was suggestive of a large vessel vasculitis. PET scan showed diffuse FDG uptake involving the thoracic and abdominal aorta, bilateral subclavian arteries, bilateral vertebral arteries, and, to a lesser degree, the bilateral common and external carotid arteries.

Temporal artery biopsy was positive for active giant cell temporal arteritis.

Conclusion: Our case highlights that a significant proportion (50-75%) of patients with cranial GCA also have systemic large-vessel involvement. The traditional separation into "cranial" and "large vessel" phenotypes is increasingly recognized as artificial (Bosch, Lancet,2024). Additionally, the sensitivities of MRIs and temporal artery duplex ultrasounds vary, ranging from 56-81% and 55-95%, respectively (Song,Journal of Rheumatology,2026). When clinical suspicion for GCA is high, further evaluation with PET/CT imaging and biopsy is essential.

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S249: Stroke Severity, Mild Cognitive Impairment and Motoric Cognitive Risk, and Post-Stroke Dementia

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Background: Patients with stroke are at risk of long-term cognitive and motor sequelae, especially among individuals with more severe stroke. Post-stroke dementia (PSD), a leading cause of morbidity and mortality among stroke survivors, is more common in patients with higher National Institutes of Health Stroke Scale (NIHSS) scores. Subacute- and chronic-stage syndromes examining both cognitive and motoric sequelae, such as mild cognitive impairment (MCI) and motoric cognitive risk (MCR), may help identify individuals at risk for PSD. However, the extent to which prior stroke and its severity relate to MCI and MCR (alone and combined), and how these syndromes predict PSD in a large prospective cohort, remains unclear.

Methods: Participants aged 67-89 from the Atherosclerosis Risk in Communities (ARIC) study without dementia at Visit 5 (V5; 2011-2013, N=5,372) were evaluated for MCI (adjudicated using cognitive data and informant interviews) and MCR (using subjective memory questionnaire and gait speed); stroke events were adjudicated prospectively from study baseline through V5. We excluded 32 participants with stroke but missing NIHSS data (N=5,340). We used adjusted multinomial logistic regression models to evaluate the association between prior stroke/ stroke timing (<5y or ≥5y prior to V5, vs no stroke), with a four-level V5 MCI/MCR composite (none, MCI-only, MCR-only, both MCR/MCI). We repeated the analysis after excluding 31 individuals with NIHSS>5 to determine if effects were present even for minor stroke (N=5,309). Then, among the subgroup with prior stroke (N=133) and also in the further subset with prior minor stroke (N=108), we evaluated the risks of PSD from V5 to 2022 across the 4 composite MCI/MCR groups using adjusted Cox proportional hazards models.

Results: In 5,340 individuals, stroke occurring either <5y (OR: 4.90, 95% CI: [1.40-17.2]) or ≥5y before V5 (OR: 8.22, 95% CI: [3.58-18.9]) was associated with higher odds of combined MCI+MCR. Minor stroke (NIHSS ≤ 5) ≥5y before V5 (vs no stroke) remained strongly associated with combined MCI+MCR (OR: 7.66, 95% CI: [2.95-19.9]). Among individuals with prior stroke (N=133), combined MCI+MCR was associated with risk of incident dementia (HR 16.7, 95% CI 4.86-57.6), with similar results among those with minor stroke (N=108; HR: 11.9, 95% CI: [2.15-66.0]).

Conclusion: Our analysis indicates that stroke, and even minor stroke, is associated with MCI+MCR, which independently predict the risk of PSD. Evaluating cognitive and motoric pre-dementia conditions concurrently may aid in identifying individuals who are at the greatest risk of developing PSD, even among individuals with minor stroke symptoms.

S250: Perceived Insurance Adequacy as a Primary Correlate of Unmet Rehabilitation Need After Stroke: Implications for Health Services Research in Post-Stroke Care

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Background: Unmet rehabilitation need after stroke is common, but the factors that explain gaps between functional recovery and access to therapy are not fully understood. Prior work has pointed to structural, socioeconomic, and psychosocial contributors, though it remains unclear which are most closely tied to unmet need in practice. Unmet rehabilitation need is associated with poorer functional outcomes and reduced long-term independence after stroke.

Methods: We conducted a cross-sectional survey of 115 stroke survivors. Unmet rehabilitation need was defined a priori as a mismatch between functional recovery and rehabilitation utilization, operationalized as a self-reported recovery score ≤7 on a 0–10 scale (with 10 indicating full recovery) combined with absence of current participation in physical, occupational, or speech therapy. Logistic regression was used to examine associations between perceived insurance adequacy and unmet rehabilitation need. Models were run separately with adjustment for household income, geographic area (urban, suburban, or rural), transportation mode, living situation, depressive symptoms, and time since stroke.

Results: Perceived insurance adequacy demonstrated directionally consistent inverse association with unmet rehabilitation need across model specifications. Compared with participants reporting insurance never met their needs, those reporting sometimes/occasionally met needs had lower odds of unmet rehabilitation need (OR 0.35, 95% CI 0.09–1.35, $p = 0.13$), while those reporting often/always met needs showed a similar inverse association (OR 0.27, 95% CI 0.07–1.03, $p = 0.055$). These associations remained directionally consistent after adjustment for household income, time since stroke, and other covariates. Household income did not demonstrate a consistent dose–response relationship with unmet rehabilitation need. Geographic area, transportation mode, living situation, and depressive symptoms were not independently associated in adjusted models.

Conclusion: Perceived insurance adequacy demonstrated a graded inverse association with unmet rehabilitation need across multiple model specifications, whereas socioeconomic and psychosocial variables did not show stable independent associations. These findings suggest that insurance-related barriers may play a role in limiting access to post-stroke

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rehabilitation, highlighting insurance coverage as a key focus for future health services research.

Addressing these barriers may be important for improving equitable access to rehabilitation services and optimizing post-stroke functional recovery.

S252: Venous Sinus Stenting Versus Cerebrospinal Fluid Diversion in the Setting of Medically Refractory Idiopathic Intracranial Hypertension: A Systematic Review and Meta-Analysis

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Background: Idiopathic Intracranial Hypertension (IIH) is an increasingly prevalent, debilitating disease characterized by elevated intracranial pressure (ICP) without an identifiable structural cause. Patients often face debilitating symptoms including chronic headaches, visual disturbances, cognitive dysfunction and papilledema leading to significantly impaired quality of life. Available interventions for patients with medically refractory disease include cerebrospinal fluid diversion procedures such as ventriculoperitoneal shunt (VPS), lumboperitoneal shunt (LPS), optic nerve sheath fenestration (ONSF); and endovascular procedures such as venous sinus stenting (VSS). Current evidence is limited to single-arm studies with inconclusive results regarding which modality is associated with lower rates of reintervention and higher likelihood of headache resolution and visual recovery.

The current meta-analysis aims to summarize the recently published comparative studies assessing endovascular procedures versus cerebrospinal fluid diversion procedures in medically refractory IIH.

Methods: We conducted a systematic review and meta-analysis following the PRISMA guidelines registered with the PROSPERO ID CRD420261337273 in order to compare safety and efficacy profiles following cerebrospinal fluid diversion procedures and endovascular procedures. Inclusion criteria were the following: comparative (dual-arm) studies directly assessing Venous Sinus Stenting with any type of CSF diversion procedure on patients diagnosed with Idiopathic Intracranial Hypertension through the Modified Dandy criteria who were refractory to medical treatment. The primary outcomes for this meta-analysis were: rates of reintervention, complication rates, headache recurrence following treatment, visual improvement and papilledema resolution.

Results: A total of 1288 studies were screened, of which six comparative studies were included: primary outcome of reintervention rates between procedures showed no statistically significant difference between VSS and VPS, with a composite OR of 0.60 (95%CI: 0.14-2.55) point estimate suggested trend toward fewer interventions with VSS. Complication rates between procedures showed no statistically significant difference between modalities OR = 0.41 (95% CI: 0.16 - 1.08). Overall, endovascular treatment was associated with a significantly higher rate of headache improvement with composite OR of 1.29 (95%CI = 1.07 - 1.56). Follow-up duration ranged from 3 to 60 months (median = 13) and was not a significant moderator of effect size ($\beta = 0.0069$, $p = 0.5985$).

Conclusion: In medically refractory IIH, venous sinus stenting was associated with higher odds of headache improvement across included studies compared with cerebrospinal fluid diversion, and similar reintervention rates throughout follow-up. Given the limited number of published studies, findings should be interpreted with caution. Clinical decision-making should be guided by anatomical factors and institutional expertise. Larger comparative studies and randomized clinical trials are still warranted.

S253: Diabetic Retinopathy and Blood Biomarkers of Neurodegenerative Disease in Type II Diabetes Mellitus

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Background: Diabetic retinopathy (DR) has traditionally been viewed as a microvascular complication of type II diabetes mellitus (T2DM). Recently, it has been posited that DR may also be a manifestation of neurovascular end-organ damage in T2DM, providing a window into broader cerebral pathology. Here we aim to investigate the relationship between DR and plasma biomarkers of neurodegeneration in a deeply phenotyped population of patients with T2DM. Understanding the relationship between retinopathy and concomitant neurodegeneration may provide insights into shared neurodegenerative mechanisms underlying diabetic complications.

Methods: DR was scored using Early Treatment Diabetic Retinopathy Study (ETDRS) scoring metrics at baseline. Baseline levels of plasma neurofilament light chain (NfL), pTau-217, and the amyloid-beta 42:40 ratio (AB42:40) were measured among 153 dementia-free individuals with T2DM.

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We performed multiple linear regression analyses to assess the association between ETDRS scores and neurodegenerative biomarkers. All biomarkers were transformed via natural logarithm. Analytical models were 1) unadjusted, 2) adjusted for demographics, and 3) additionally adjusted for clinical characteristics. The beta-values and 95% confidence intervals (CIs) are reported.

Results: Mean age of participants was 62.6 years (± 5.3), 54.2% (83) were female, 76.5% (117) were White. The average duration of T2DM was 8.3 years (± 5.4) and the average baseline hemoglobin A1c was 8.0% (± 0.81).

Higher baseline levels of NfL were associated with significantly higher ETDRS scores across all three models (unadjusted model: beta-value=0.890, CI [0.324, 1.456], p=0.002). Additional adjustment for age, sex, race, education, smoking, hypertension, cardiovascular disease, cholesterol, body-mass index, and glomerular filtration rate showed the same association. There were no associations between ETDRS scores and pTau-217 or AB42:40.

Conclusion: Blood NfL levels, but not pTau-217 or AB42:40, are associated with severity of diabetic retinopathy. NfL levels may reflect both the severity of diabetic retinopathy and possibly broader cerebral neurovascular end-organ damage in T2DM.

S254: Health-Related Social Needs Screening Among Hospitalized Patients who had a Stroke or Transient Ischemic Attack Across 11 Hospitals

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Background: Factors outside healthcare can limit patients' ability to benefit fully from medical treatment. In 2024, CMS began requiring hospitals to perform health-related social needs (HRSN) screening. We aim to assess the prevalence, trends, and predictors of HRSN screening in stroke and transient ischemic attack (TIA) patients in a hospital system. We hypothesized that HRSN screening would be initially low, rise after implementation of a system-wide HRSN screening initiative, and be higher in those with TIA or lower stroke severity.

Methods: This retrospective cohort study of adults admitted with ischemic stroke (IS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), or TIA from November 1, 2021 (HRSN screening implementation) to January 1, 2025. Data was from the enterprise data warehouse across a health system with 2 comprehensive stroke centers, 6 primary stroke centers, and 3 acute stroke ready hospitals. The primary outcome was complete HRSN screening for housing instability, transportation, food insecurity, medication affordability, and mental health services. We assessed changes in screening over time. We performed Poisson regression to examine differences in screening by patient characteristics.

Results: Our complete-case cohort has 6,396 individuals (25.2% TIA, 55% IS, 12.1% ICH, 7.8% SAH) with mean age of 71 (SD:14), were 50% male, and was racially diverse (3% Asian, 9% Black, 7% Hispanic, 6% Other, 73% White). Overall, 65.7% of the cohort completed HRSN screening. Complete screening increased over time, starting at 35% in November 2021 before the screening initiative was implemented, and nearly doubled to 66% by January 2023, and remained at this level (68% in December 2024-Figure). After full covariate adjustment, compared to patients with TIA, those with IS, ICH, and SAH were less likely to be screened. Among patients with IS, higher NIHSS was associated with lower screening. Patients with an NIHSS ≥21 had a 47% lower probability of screening (95%CI: -54 to 40%) compared to those with an NIHSS of zero.

Conclusion: HRSN screening among patients who had a stroke or a TIA increased with the implementation of system-wide screening initiative, yet roughly a third remain unscreened. Inclusion of caregivers and community-informed approaches to screening may be needed to increase screening.

S255: Beyond the Lesion: Bilateral Cerebrovascular Disruption Revealed by Perfusion–Diffusion Dissociation after Intracerebral Hemorrhage

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Background: The relationship between tissue microstructure and cerebral perfusion after intracerebral hemorrhage (ICH) remains incompletely understood. While neuroimaging studies frequently utilize the contralateral hemisphere as a physiologically stable reference for normalization, this assumption lacks systematic validation.

Methods: We performed longitudinal multiparametric MRI in a collagenase-induced mouse model of ICH using ultra-high-field (11.7T) imaging. Diffusion-weighted imaging and pseudo-continuous arterial spin labeling (pCASL) were utilized to quantify the apparent diffusion coefficient (ADC) and cerebral blood perfusion (CBP) from baseline to 21 days post-injury. To enhance the robustness of perfusion quantification, a bidirectional crusher-gradient method was applied to estimate labeling efficiency.

Results: ADC and CBP exhibited distinct spatiotemporal trajectories following ICH. Diffusion abnormalities were largely localized to the lesion site and demonstrated gradual recovery over time, consistent with the evolution of cytotoxic edema. Conversely, CBP analysis revealed widespread bilateral hypoperfusion during the acute phase across multiple brain regions, followed by a delayed and regionally restricted recovery in the ipsilateral striatum.

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Critically, significant reductions in contralateral perfusion were observed in the absence of corresponding diffusion changes, indicating brain-wide cerebrovascular dysregulation extending far beyond the hemorrhagic core. These findings suggest that systemic inflammatory and vascular responses contribute to impaired global perfusion following focal injury.

Conclusion: ICH induces a clear dissociation between microstructural and cerebrovascular responses, with perfusion disturbances involving both hemispheres. These results challenge the common practice of contralateral normalization and underscore the need for absolute perfusion quantification in neuroimaging studies. This work provides a framework for interpreting multiparametric MRI metrics and offers new insights into the systemic nature of cerebrovascular dysfunction after hemorrhagic stroke.

S256: Trends in Racial and Socioeconomic Disparities in Reperfusion Therapy Utilization for Acute Ischemic Stroke in the United States, 2011–2022

Presenting Author: *Forough Yazdanian, Boston, Massachusetts*

Co-Authors: *Emeka Agudile, MD, Massachusetts Department of Public Health Boston, MA 02108, MA, George Sorescu, MD, Tufts University School of Medicine Boston, MA*

Background: Disparities in access to reperfusion therapies for acute ischemic stroke (AIS) persist despite advances in stroke systems of care. Racial, ethnic, and socioeconomic gaps in intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) utilization have been documented across multiple national databases. Although treatment rates rose substantially over two decades across all demographic groups, Black, Hispanic, and low-income patients have consistently received these therapies at lower rates than White patients. Identifying what structural factors sustain these gaps remains essential to advancing equitable stroke care In this study, We evaluated temporal national trends in trends in racial, ethnic, and socioeconomic disparities the utilization of IVT, MT and to identified factors associated with persistent treatment gaps across demographic groups.

Methods: We conducted a retrospective cohort study using the Nationwide Inpatient Sample (2011–2022). Adult patients with AIS who received reperfusion were included. Multivariable logistic regression models assessed associations between race, insurance status, and treatment utilization, adjusting for demographic, clinical, and hospital-level variables. Temporal trends were evaluated across the study period.

Results: Among 824,285 AIS hospitalizations, 90,421 (9.9%) received reperfusion therapy. African American and Hispanic patients had higher odds of receiving IVT (adjusted OR 1.28 and 1.14, respectively; p<0.001) but lower odds of receiving MT (adjusted OR 0.80 and 0.92; p<0.01) compared with White patients, with disparity direction reversing in non-academic settings. Medicare insurance largely attenuated racial disparities. MT-only utilization increased from 6.1% to 35.1%, whereas IVT-only from 86.4% to 57.3% (P<0.001). teaching hospitals experienced a 57.9-point MT-only increase versus only 29.9 points in non-teaching facilities, where IVT-only remained dominant (76%) by 2022. MT-only utilization followed a non-monotonic trajectory, peaking at 40% in 2018 before declining sharply in 2020, consistent with COVID-19-related disruption.

Conclusion: Significant racial and socioeconomic disparities persist in the utilization of advanced reperfusion therapies for AIS in the United States. African Americans and Hispanics remained disproportionately channeled toward IVT over MT, with disparity direction reversing in non-teaching settings. Structural and institutional-level factors beyond individual patient characteristics are key drivers of inequitable access to advanced stroke interventions.

S257: *Clinical Outcomes and Cost of Reperfusion Treatments for Acute Ischemic Stroke in the United States: Estimates from the NIS 2011-2022

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Background: Reperfusion therapies have transformed acute ischemic stroke care, yet their real-world clinical and economic impact across treatment strategies remains incompletely defined. We evaluated national trends in outcomes and costs associated with intravenous thrombolysis, mechanical thrombectomy, and combined therapy.

Methods: We conducted a retrospective cohort study using the Nationwide Inpatient Sample from 2011 to 2022. Adult patients with acute ischemic stroke who underwent reperfusion therapy were included. Patients were categorized into three groups: intravenous thrombolysis alone, mechanical thrombectomy alone, and combined therapy. Inverse probability of treatment weighting and inverse probability weighted regression adjustment were used to balance baseline characteristics and estimate treatment effects. Primary outcomes included in-hospital mortality and composite complications. Secondary outcomes included length of stay, discharge disposition, and hospitalization cost.

Results: A total of 90,421 patients underwent reperfusion therapy, including 67.2% receiving thrombolysis alone, 24.1% thrombectomy alone, and 8.6% combined therapy. After adjustment, in-hospital mortality was lower in the thrombolysis group compared with thrombectomy alone and combined therapy (7.0% vs 14.7% vs 13.0%, p<0.001). Composite complications were also lower with thrombolysis (21.3% vs 37.9% vs 37.8%, p<0.001). Thrombectomy and combined therapy were associated with longer hospital stays and higher costs compared with thrombolysis, with mean cost increases exceeding $80,000. Discharge to home was more frequent with thrombolysis (34.9%) compared with thrombectomy (20.6%) and combined therapy (25.9%). Over time, mortality and complication rates declined across all modalities. Mortality decreased from 9.0% to 5.9% for thrombolysis, 23.1% to 12.0% for thrombectomy, and 20.5% to 8.4% for combined therapy. However, costs and length of stay increased significantly across all treatment groups.

Conclusion: Thrombolysis alone is associated with lower in-hospital mortality, fewer complications, shorter

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hospitalizations, and lower costs compared with thrombectomy-based strategies. Despite improved clinical outcomes over time, the rising economic burden highlights the need for optimized patient selection and resource allocation in stroke systems of care.

S258: Stroke Risk with Dual vs Triple Antithrombotic Therapy After PCI in Atrial Fibrillation: A Systematic Review and Meta Analysis

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Co-Authors: *George Sorescu, MD, Tufts University School of Medicine, Boston, MA, Marc Fisher, MD, BIDMC, Brookline, MA*

Background: Patients with atrial fibrillation undergoing percutaneous coronary intervention require combined anticoagulant and antiplatelet therapy to prevent stroke and stent thrombosis. Triple therapy reduces ischemic risk but increases bleeding, whereas dual therapy improves safety. The effect of these strategies on stroke risk remains uncertain.

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials comparing dual therapy (oral anticoagulant plus single antiplatelet) with triple therapy (oral anticoagulant plus dual antiplatelet) in patients with atrial fibrillation undergoing PCI. Databases including PubMed, Embase, and Cochrane were searched. Outcomes included stroke, major bleeding, intracranial hemorrhage, major adverse cardiovascular events, and mortality. A random effects model was used to calculate pooled hazard ratios with 95 percent confidence intervals.

Results: Five randomized trials comprising patients with atrial fibrillation undergoing PCI were included. Dual therapy was not associated with increased stroke risk compared with triple therapy (HR 0.96, 95 percent CI 0.69 to 1.36). Major bleeding was significantly reduced with dual therapy (HR 0.70, 95 percent CI 0.62 to 0.79), along with a marked reduction in intracranial hemorrhage (HR 0.47, 95 percent CI 0.28 to 0.79). There was no significant difference in major adverse cardiovascular events (HR 0.94, 95 percent CI 0.80 to 1.11). Findings were consistent across trials, with no evidence of publication bias.

Conclusion: In patients with atrial fibrillation undergoing PCI, dual therapy provides a safer bleeding profile without increasing stroke risk compared with triple therapy. These findings support dual therapy as a balanced strategy that maintains thromboembolic protection while minimizing hemorrhagic complications.

S259: Revascularization Versus Optimized Medical Therapy, and Stenting Versus Endarterectomy, for Carotid Stenosis: A Network Meta-analysis of Randomized Trials

Presenting Author: *Forough Yazdanian, Boston, Massachusetts*
Co-Authors: *Marc Fisher, MD, BIDMC, Brookline, MA*

Background: The benefit of carotid revascularization in the era of optimized medical therapy remains uncertain, particularly for asymptomatic and low-risk symptomatic carotid stenosis. Contemporary randomized trials evaluate two key questions: whether revascularization adds benefit beyond optimized medical therapy, and whether carotid artery stenting and endarterectomy differ in safety and efficacy.

Methods: We conducted a systematic review and network meta-analysis of randomized controlled trials comparing (1) optimized medical therapy alone versus optimized medical therapy plus revascularization and (2) carotid artery stenting versus endarterectomy. Eligible trials included SPACE-2, ACST-2, ACT I, CREST, and ECST-2. Primary outcomes were early harm (30-day stroke or death) and long-term efficacy (ipsilateral ischemic stroke). Secondary outcomes included any stroke and all-cause mortality. Random-effects models were used to estimate pooled relative risks, integrating both direct and indirect comparisons.

Results: cross included trials enrolling several thousand patients, revascularization was associated with increased early procedural risk, reflected by higher 30-day stroke or death compared with medical therapy alone. However, this early hazard was offset by a reduction in ipsilateral stroke during follow-up, with attenuated magnitude in contemporary trials with optimized medical therapy. In comparisons of stenting versus endarterectomy, overall long-term stroke rates were similar, although stenting was associated with higher peri-procedural stroke and lower myocardial infarction risk. Heterogeneity was moderate and largely driven by differences in patient selection and background medical therapy intensity.

Conclusion: In patients with carotid stenosis, the net benefit of revascularization depends on balancing early procedural risk against long-term stroke prevention, with diminishing absolute benefit in the setting of optimized medical therapy. Stenting and endarterectomy provide comparable long-term efficacy but differ in peri-procedural risk profiles. These findings support individualized decision-making based on patient risk, anatomy, and expected procedural safety.

S260: Hypertension is Protective for Dementia-Related Outcomes in Asymptomatic Carotid Disease Populations - A Multi Cohort Study

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Background: Blood pressure (BP) management is highly relevant for cardiovascular and brain health outcomes. Although clinical guidelines are trending towards increasingly strict BP

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control, some discordant results evaluating dementia-related outcomes indicate that more research is needed. Asymptomatic extracranial carotid atherosclerotic disease (aECAD), a hallmark cerebrovascular disease affecting >10% of those over the age of 60, may represent a key subpopulation unaccounted for in previous studies.

Methods: Using our prospective study, Carotids and Minds (n=167) and retrospective longitudinal study, TriNetX (n > 200,0000), a nationwide medical record database, we evaluated the association of hypertension status with dementia-related outcomes in adults ≥50 years of age with and without aECAD. The primary outcomes included dementia-related outcomes i.e, cognition, plasma pTau217 levels, mild cognitive impairment (MCI), Alzheimer's disease (AD) and non-AD dementia risk. We investigated secondary effects of age, systolic BP (SBP) ranges, hypertension medications, cardiovascular outcomes, and treatment of aECAD with carotid endarterectomy (CEA).

Results: After controlling for relevant confounders, we found that hypertension was significantly associated with protective effects for cognition (β=0.47, p< .01), pTau217 (β= -0.52, p<.01), AD (HR=0.56 [0.52-0.61]), non-AD dementia (HR=0.66 [0.63-0.68]), and MCI (HR=0.69 [0.64-0.74]) in patients with aECAD. Effect sizes were moderate to large and congruous across both cohorts, with strongest risk reduction in aECAD patients 81+ years of age. CEA mitigated these protective associations, and opposite associations of hypertension were seen in patients without aECAD. Still more, a SBP range of 140-159 mmHg optimized protective effects with no significant increase in major cardiovascular events and death.

Conclusion: In summary, hypertension appears protective in patients with aECAD for dementia-related outcomes. These data indicate that more work is needed exploring nuanced, patient-specific approaches to BP management with implications for future clinical trial design and clinical management and raise further awareness of the potential role of cerebral perfusion physiology in dementia risk and BP management. More broadly, these data further highlight cerebrovascular disease as relevant in brain health and aging.

S261: Mapping Ischemic Stroke with Speech-Language Features: A Machine Learning Analysis of Multimodal Picture Description Data

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Background: Manually-derived clinical features of verbal communication have been associated with ischemic stroke features and are predictive of functional outcomes among stroke survivors. Despite its inclusion in the NIH Stroke Scale (NIHSS), speech sample analysis has not been widely adopted in acute stroke care, likely due to time constraints and perceived need for specialized knowledge. An alternative approach is to leverage computational analysis using either predefined features or vectorized embeddings of raw data. We hypothesized that machine learning models applied to transcript-derived, acoustic, and multimodal speech data predict structural features of acute ischemic left and right hemisphere (LH; RH) stroke.

Methods: We analyzed NIHSS picture descriptions from 276 stroke patients (163 LH, 113 RH) obtained within five days of stroke onset. Four feature sets were extracted from each recording: eight hand-derived transcript features (content units, disfluency rate, and related discourse measures), eight hand-derived audio features (spectral flatness, MFCC, and related measures), RoBERTa-based transcript embeddings, and wav2vec 2.0 audio embeddings. Feature set combinations were evaluated using logistic regression, ridge regression, and nested cross-validated Random Forest (RF) models under stratified 5-fold cross-validation. Prediction tasks were independent analyses of hemisphere laterality, lesion volume, and proportion of damage involving the middle cerebral artery (MCA) vascular territories with inferior cerebellar (IC) and posterior cerebral artery (PCA) vascular areas included to examine possible correlated signal.

Results: Hemisphere laterality was predicted with AUC-ROC of 0.759 using logistic regression with combined audio and transcript hand-derived features. Lesion volume (ρ=0.466, p<0.001) and left MCA frontal (ρ=0.359, p<0.001) were also best predicted with both hand-derived features using RF. RoBERTa vector embeddings best predicted left MCA temporal (ρ=0.313, p<0.001) and right MCA temporal (ρ=0.250, p<0.001) with ridge regression while left MCA parietal (ρ=0.345, p<0.001) and right MCA frontal (ρ=0.338, p<0.001) were best predicted with only hand-derived transcript features using RF. Left and right PCA occipital (ρ=0.296, ρ=0.250 p<0.001) were best with RF and all transcript features, left IC (ρ=0.301, p<0.001) with both audio and transcript hand-derived features using RF, and right IC (ρ=0.014, p<0.001) with ridge regression and audio features only.

Conclusion: Machine learning analysis of picture description data can predict hemisphere laterality, lesion burden, and localize vascular distribution in patients with acute stroke. Transcript-derived features were strongest across unstratified and LH-stratified targets while audio-derived features carried complementary signal for RH-stratified predictions. Our findings suggest transcript feature embeddings and acoustic features may supplement acute stroke assessment beyond hand-derived transcript-based discourse measures alone.

S262: Gait Speed as a Predictor of Stroke Recurrence in Acute Ischemic Stroke Patients: A Nationwide Multi-Center Registry Study

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Background: Stroke is a leading cause of death and disability, with ischemic stroke being the most common type.

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Despite improvements in acute care, recurrent strokes continue to significantly impact patients' quality of life. Gait speed, a simple and sensitive measure of motor function, has proven to be a strong predictor of recovery.

However, its role in predicting stroke recurrence during the acute phase remains underexplored. This study aims to assess the association between acute-phase gait speed and stroke recurrence among acute ischemic stroke (AIS) patients using data from the ICONS study.

Methods: Data from 2,020 patients with AIS were analyzed from the Impairment of Cognition and Sleep after Acute Ischemic Stroke or Transient Ischemic Attack in Chinese Patients (ICONS) study. Gait speed was measured within 2 weeks of hospitalization using the 10-meter walk test (10MWT). Patients were divided into four quartiles: Q1 (≤0.714 m/s), Q2 (0.714–1.000 m/s), Q3 (1.000–1.250 m/s), and Q4 (>1.250 m/s). The primary outcome was stroke recurrence at 3 and 12 months; secondary outcomes included disabling stroke [modified Rankin Scale (mRS) ≥2] and post-stroke cognitive impairment [Montreal Cognitive Assessment (MoCA) ≤22] at 12 months.

Associations between gait speed and outcomes were evaluated using multivariable Cox regression.

Results: We included 2,020 AIS patients from the ICONS study who completed the baseline 10-meter walk test (10MWT) (mean age 60.2 ± 10.7 years; 74.0% male). At 3 and 12 months, stroke recurrence occurred in 4.1% and 6.6% of patients, respectively. Faster acute-phase gait speed (Q3–Q4 vs Q1) was independently associated with a significantly lower risk of stroke recurrence at both time points (Q3: HR 0.44, 95% CI 0.24–0.83; Q4: HR 0.50, 95% CI 0.26–0.96 at 3 months; Q4: HR 0.54, 95% CI 0.32–0.93 at 12 months). Higher gait speed also provided protective effects against disabling stroke (Q3: HR 0.43, 95% CI 0.28–0.66; Q4: HR 0.40, 95% CI 0.25–0.64) and post-stroke cognitive impairment (PSCI) (Q3: HR 0.64, 95% CI 0.45–0.93; Q4: HR 0.49, 95% CI 0.32–0.73).

Conclusion: Acute-phase gait speed independently predicts stroke recurrence after AIS. Slower gait speed identifies high-risk patients, aiding early risk stratification and targeted management strategies.

EPILEPSY

S263: Refractory Status Epilepticus in a Patient with Parry-Romberg Syndrome: A Case Report

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Background: Parry-Romberg Syndrome is a rare neurocutaneous condition characterized by progressive unilateral facial soft-tissue atrophy that can be accompanied by intracranial involvement. Neurological manifestations may include headache, trigeminal neuralgia, focal epilepsy, and, rarely, drug-resistant seizures. Despite the rarity of the syndrome, epilepsy associated with it may be severe and challenging to control; here, we report a rare case of recurrent status epilepticus despite medical and surgical treatment.

Methods: A single-patient case report describing clinical presentation, neurological examination, neuroimaging findings, and therapeutic management of a patient with Parry-Romberg syndrome presenting with refractory status epilepticus.

Results: A 32-year-old man diagnosed with Parry-Romberg Syndrome since childhood, was evaluated in the emergency department with generalized convulsive seizures progressing to refractory status epilepticus despite documented compliance to multiple antiseizure medications, including Levetiracetam, Valproate, and Clobazam. Physical Examination demonstrated marked unilateral left facial atrophy involving the subcutaneous tissues, parotid region, and tongue, consistent with advanced hemifacial involvement. His medical history was significant for medically refractory epilepsy, for which he underwent left temporal lobectomy with amygdalohippocampectomy in 2019. Despite the initial intervention, seizures recurred and later evolved into status epilepticus. Computed tomography with three-dimensional reconstruction demonstrated hemifacial asymmetry with the left side appeared atrophied compared to the right. Coronal brain MRI T1 with contrast showing postoperative changes seen at left temporal fossa adjacent to the left temporal lobe, with ex vacuo dilatation of the left lateral ventricle. The patient was managed according to established status epilepticus protocols used in Jordan, with escalation of antiseizure therapy including benzodiazepines and intravenous levetiracetam, along with intensive care support.

Conclusion: Parry-Romberg Syndrome may be associated with severe, treatment-refractory epilepsy, including status epilepticus, even after surgical interventions. This case highlights the limitations of surgical and medical interventions in Parry-Romberg syndrome-related neurological complications. Further studies are required to better understand the epileptogenic mechanisms and to understand why surgical intervention may still fail in some cases.

S264*: The Invisible Storm: A Cutaneously Silent Multi-Organ Lamotrigine Toxicity Phenotype

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Background: Lamotrigine is associated with severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening complication that may occur

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regardless of cutaneous manifestations. We aimed to characterize a cutaneously silent HLH phenotype associated with multiorgan failure in lamotrigine exposed patients.

Methods: A retrospective pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) from 2004 Q1 through 2025 Q1 identified 66,849 reports where lamotrigine was recorded as primary or secondary suspect drug. HLH, SCAR, acute kidney injury (AKI), and drug-induced liver injury (DILI) were defined using MedDRA Preferred Term (PT) clusters. Among reports with HLH and concurrent organ failure (AKI and/or DILI), cases were classified into two mutually exclusive cohorts: Invisible Storm (absence of SCAR) and Visible Storm (presence of SCAR). Disproportionality analyses (Reporting Odds Ratio [ROR], Proportional Reporting Ratio [PRR], and Information Component [$IC_{0.025}$]) and outcome comparisons (Fisher exact test and Wilcoxon rank-sum test) were performed. Sensitivity analyses included broader PT definitions, restriction to primary suspect reports, and exclusion of reports with infection or malignancy. The study was performed following the READUS-PV 2024 guidelines.

Results: Among the 66,849 reports HLH was identified in 373 (0.56%), 79 involved concurrent organ failure; 63 (80%) were classified as Invisible Storm and 16 (20%) as Visible Storm. Lamotrigine demonstrated strong disproportionality signals for HLH (ROR 12.48, 95% CI 11.25–13.86) and SCAR (ROR 30.63, 95% CI 29.75–31.54). Co-occurrence signals were elevated for both phenotypes (Invisible Storm ROR 15.08, 95% CI 11.69–19.45; Visible Storm ROR 48.85, 95% CI 28.58– 83.52; $IC_{0.025} > 3$ for both). Invisible Storm phenotype was associated with higher mortality (23.8% vs 7.8%; OR 3.71, 95% CI 1.93–6.75; $p < 0.001$), increased rates of hospitalization (82.5% vs 31.2%; OR 10.44, 95% CI 5.38–22.20; $p < 0.001$). Patients with Invisible Storm were older than those with Visible Storm (median 34 vs 18.5 years, $p = 0.004$). Findings were consistent across sensitivity analyses (mortality OR 7.00; OR 6.44; OR 4.56).

Conclusion: Although under-reporting in FAERS suggests the true incidence may be higher, among Lamotrigine-associated HLH cases with concurrent organ failure, the Invisible Storm phenotype accounted for 80% of reports and was associated with higher mortality, hospitalization, and life-threatening events. The absence of cutaneous findings may delay recognition of this life-threatening phenotype. Routine monitoring of renal and hepatic function may facilitate earlier detection of multi-organ HLH presenting without SCAR.

S265: Excitatory Dysfunction and Phenotypic Rescue in a Human Neuronal Model of SCN2A-Related Disorders

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Background: SCN2A-related disorders result from pathogenic variants in the gene encoding for the voltage-gated sodium channel Nav1.2. Collectively, these disorders result in variable age of onset epilepsy, autism spectrum disorder, and epileptic encephalopathies. While the mechanisms of haploinsufficiency resulting in autism spectrum disorder have been explored in detail, few studies report the impact of pathogenic missense variants in human neurons. Gain-of-function variants, which result in increased sodium channel current through a variety of mechanisms, cause epileptic encephalopathies where the seizures are uniquely responsive to sodium channel blockers. How gain-of-function variants lead to aberrant neuronal function, and in particular why they show this responsiveness to sodium channel blockade, is not well understood.

Methods: We derived iPSC lines from a patient with the gain-of-function variant p.M1879T. These lines were corrected with CRIPSR/Cas9 to generate isogenic controls which retain the patient's genetic background. We combined conventional whole-cell electrophysiology and high-throughput all-optical electrophysiology assays to analyze variant excitatory neurons generated with NGN2 overexpression (iNeurons). In the all-optical physiology experiments, different concentrations of the sodium channnel blockers carbamazepine, phenytoin, lacosamide, and cenobamate were added to both variant and wildtype neurons. We used a machine learning classifier to perform unbiased analysis of pharmacological profiling performed with the all-optical physiology platform.

Results: In both platforms, iPSC-derived excitatory neurons expressing the disease variant showed greater firing at higher stimuli compared to the isogenic control neurons, as well as changes to action potential shape (steeper slope and larger amplitude) with evoked firing. This phenotypic separation of SCN2A-p.M1879T neurons held across different in vitro timepoints. Targeted concentrations of sodium channel blockers could restore the firing frequency phenotype towards isogenic levels. Using an unbiased approach with a machine learning classifier, we found that select sodium channel blocker concentrations could rescue the evoked firing phenotype while higher concentrations tended towards over-correction.

Conclusion: This work expands our mechanistic knowledge of how gain-of-function SCN2A variants affect neuronal properties in a human model system. It further demonstrates proof of sodium channel blocker efficacy in a human neuronal model of SCN2A-related epilepsy and highlights the power of leveraging high-throughput all-optical physiology for testing drug efficacy. Our mechanistic insights and identified therapeutic effects may broadly apply to channel variants predominantly defined by aberrant inactivation.

S266*: Leiomodin-1 Antibody and Clinical Outcomes in Cryptogenic New-Onset Refractory Status Epilepticus: A Cohort Study

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Background: While cryptogenic new-onset refractory status epilepticus (C-NORSE) is mediated by inflammatory responses, reliable serologic biomarkers for predicting functional outcomes remain lacking. Phage immunoprecipitation sequencing (PhIP-seq) enables the discovery of novel antibodies that may aid disease stratification and prognostication. This study aimed to identify potential biomarkers in C-NORSE by discovering autoantibodies that mediate disease pathogenesis.

Methods: Cerebrospinal fluid (CSF) from patients enrolled in a multicenter C-NORSE cohort were analyzed using PhIP-seq. Enzyme-linked immunosorbent assay (ELISA) was used to validate and screen for LMOD1-IgG in serum and CSF of C-NORSE and other neurologic diseases. Clinical outcomes, including modified Rankin Scale (mRS) and Clinical Assessment Scale in Autoimmune encephalitis (CASE), were evaluated over two years.

Results: PhIP-seq was performed in 26 C-NORSE CSF. Among the top hits, leiomodin-1 (LMOD1) was selected as the leading autoantigen based on its prognostic potential in the development set, CNS expression, and prior reports of antibody relevance. The optical density cutoff for LMOD1-IgG ELISA was determined as 0.30 based on receiver operating characteristic analysis. The diagnostic performance of CSF testing exceeded that of serum. Using this cutoff, a total of 266 CSF were screened for LMOD1-IgG (C-NORSE=57, other autoimmune neurologic diseases=104, other non-autoimmune neurological diseases=105). LMOD1-IgG was detected in 16.5% (44/266) of samples, indicating that the antibody is not specific to C-NORSE. However, LMOD1-IgG-positivity was strongly associated with poor prognosis in C-NORSE. One-year and 2-year mRS and CASE scores were significantly worse in the LMOD1-positive compared to the LMOD1-negative patients (all $P<0.05$). While LMOD1-negative showed gradual improvement, none of the LMOD1-positive patients achieved mRS≤2 during the two-year follow-up. In addition, the median duration of continuous intravenous anesthesia and unconsciousness were significantly longer in the LMOD1-positive group.

Conclusion: LMOD-IgG was associated with significantly worse outcomes in C-NORSE. The presence of the antibody may identify a vulnerable subgroup predisposed to severe disease and NORSE-related brain injury.

S267: Functional Seizures after Autoimmune Encephalitis: Temporal Phenotypes and One-Year Clinical Trajectories

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Background: Functional seizures, also termed psychogenic nonepileptic seizures, are well recognized in epilepsy practice but remain poorly characterized as a neuropsychiatric outcome after autoimmune encephalitis (AE). We sought to define temporal phenotypes of functional seizures after AE, determine their prognostic relevance, and explore whether routinely available clinical features could stratify 1-year outcomes.

Methods: We conducted a single-center retrospective inception cohort study of patients diagnosed with AE at Seoul National University Hospital between 2015 and 2025. Patients with documented or clinically established functional seizures according to the ILAE Nonepileptic Seizures Task Force framework were included.

Functional seizures were classified by timing of onset as acute symptomatic type, occurring within 3 months of AE onset, or chronic sequelae type, occurring ≥6 months after AE onset; intermediate-onset cases were adjudicated by consensus. The primary outcome was 1-year functional seizure status, categorized as good, partial, or poor. Semiologic phenotypes were classified using a structured three-axis framework.

Results: Among 32 patients with AE and high-certainty functional seizures, 31 had complete 1-year follow-up. Fourteen patients had acute symptomatic-type and 17 had chronic sequelae-type functional seizures. At 1 year, 8 patients (25.8%) had good, 13 (41.9%) partial, and 10 (32.3%) poor outcomes. Poor outcomes were more frequent in chronic sequelae-type than acute symptomatic-type functional seizures (47.1% vs 14.3%), with a consistent trend toward worse ordinal outcomes (Mann–Whitney U, $p=0.068$). Labile semiology, defined as panic-affective or complex motor presentation, was strongly associated with poor outcome: all 10 patients with poor outcome had labile semiology, whereas no patient without labile semiology had a poor outcome (Fisher's exact $p=0.012$). A pragmatic 4-component score incorporating chronicity, hippocampal atrophy, labile semiology, and male sex showed strong discrimination for poor outcome (AUC 0.879, 95% CI 0.720–0.986); a score ≥3 identified high-risk patients with 70.0% sensitivity and 95.2% specificity.

Conclusion: Functional seizures after AE constitute a clinically meaningful survivorship phenotype with distinct temporal and semiologic dimensions. Chronic sequelae-type onset, labile semiology, and a simple multidimensional risk score may help identify AE survivors at risk for persistent functional seizures and support early multidisciplinary intervention.

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S268: Bone Metabolism Markers and Adult-Onset Seizure Risk: A Retrospective Cohort Analysis of 43,256 Adults in the All of Us Research Program

Presenting Author: *Mehreen Ali, Carle Illinois College of Medicine, University of Illinois Urbana-Champaign Villa Park, ILLINOIS*

Background: Vitamin D deficiency has been proposed as a modifiable risk factor for epilepsy through neuronal calcium homeostasis pathways. However, prior studies have not adequately separated primary vitamin D deficiency from antiepileptic drug-induced depletion, nor examined the broader calcium-metabolic axis simultaneously.

Methods: We performed a retrospective cohort analysis using de-identified EHR data from the All of Us Research Program, an ongoing NIH initiative that collects diverse health, genetic, and lifestyle data from participants across the United States to advance precision medicine research. Adults aged ≥ 20 years with available markers of bone metabolism and idiopathic adult-onset epilepsy were included. Analyses assessed baseline distributions, longitudinal changes in vitamin D and calcium homeostasis, and the incidence of adult-onset seizures and bone disease. Sequential multivariable logistic regression models were constructed adjusting for age, sex, hypocalcemia, elevated parathyroid hormone (PTH), anti-epileptic drug exposure, chronic kidney disease, liver disease, osteoporosis, vitamin D supplementation, and additional covariates. Sensitivity analyses evaluated 25-OHD as a continuous variable, an insufficiency threshold (<30 ng/mL), and anti-epileptic drug–naïve patients.

Results: The analytic cohort included 43,256 adults. Vitamin D deficiency was significantly associated with increased odds of adult-onset seizures. The unadjusted odds ratio (OR) was 1.88 (95% CI 1.48–2.38, p<0.001), which remained significant after full adjustment (OR 1.51, 95% CI 1.18–1.92, p=0.001). A dose-dependent relationship was observed, with each 10 ng/mL decrease in 25-OHD associated with a 14% increase in seizure odds (OR 1.14, 95% CI 1.05–1.24, p=0.002). Associations persisted in anti-epileptic drug–naïve analyses. Comorbid conditions affecting vitamin D activation and calcium homeostasis, including chronic kidney disease (OR 1.86), liver disease (OR 2.68), and osteoporosis (OR 1.90), were independently associated with seizure risk.

Conclusion: Vitamin D deficiency is independently and dose-dependently associated with adult-onset seizure risk, even after adjustment for anti-epileptic drug exposure and the complete calcium–PTH axis. These findings support a mechanistic link between impaired vitamin D–mediated calcium regulation and neuronal excitability, and justify prospective studies evaluating vitamin D repletion as a potential strategy for seizure risk reduction.

S269*: The Bone Toll of Epilepsy Treatment: Antiepileptic Drugs, Incident Bone Disease, and a Population-Level Vitamin D Supplementation Gap in 16,769 Adults

Presenting Author: *Mehreen Ali, Carle Illinois College of Medicine, University of Illinois Urbana-Champaign Villa Park, Illinois*

Background: This retrospective cohort study uses All of Us Research Program EHR data (OMOP CDM, R2024Q3R9), an ongoing NIH initiative that collects diverse health, genetic, and lifestyle data from participants across the United States to advance precision medicine research. Adults with epilepsy face elevated bone disease risk through antiepileptic drug effects on vitamin D and subsequently bone metabolism. Enzyme-inducing AEDs accelerate vitamin D catabolism via CYP450 induction, conferring greater osteoporosis risk than non-enzyme-inducing agents. Real-world outcomes on bone health and vitamin D supplementation patterns following seizure diagnosis remain poorly characterized at population scale.

Methods: Adults on enzyme-inducing AEDs (carbamazepine, phenytoin, oxcarbazepine; n=1,395) were compared to adults on non-enzyme-inducing AEDs (levetiracetam, lamotrigine, topiramate, gabapentin, lacosamide, valproate; n=15,374), with index date at first AED prescription. The primary outcome was incident osteoporosis or osteopenia identified through OMOP concept codes during follow-up. Vitamin D supplementation initiated after AED exposure was ascertained using standardized drug exposure records. Logistic regression adjusted for age, sex, corticosteroid use, chronic kidney disease, obesity, and vitamin D supplementation.

Results: Groups were well matched on age (median 62 years both) and sex (63.4% vs 62.1% female). After full adjustment for age, sex, corticosteroid use, CKD, obesity, and vitamin D supplementation, EI-AED use remained independently associated with 51% higher odds of incident osteoporosis or osteopenia (OR 1.51, 95% CI 1.27–1.79, p<0.001). The minimal attenuation from unadjusted to adjusted estimates confirms the association is not explained by measured confounders. Corticosteroid use (OR 1.56, p<0.001) and CKD (OR 1.61, p<0.001) were independently associated with bone disease, while obesity was protective (OR 0.82, p<0.001), consistent with the known mechanical loading effect. Despite this elevated risk, only 20.7% of EI-AED patients received post-diagnosis vitamin D supplementation compared to 16.2% of non-EI-AED patients, leaving the majority of high-risk patients unsupplemented.

Conclusion: In this large population cohort, enzyme-inducing AED use is independently associated with 51% higher odds of incident osteoporosis or osteopenia compared to non-enzyme-inducing AEDs in this large population cohort, robust to adjustment for six confounders. Fewer than 1 in 5 EI-AED patients received proactive vitamin D supplementation despite this established risk. These findings highlight a substantial gap between guideline recommendations and clinical practice, supporting routine proactive vitamin D monitoring and supplementation following seizure diagnosis regardless of AED class.

S270-K: Altered Sleep Microarchitecture in Epilepsy: Spindles, Slow Oscillations and Phase Precession of Spindle-SO

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Background: Spindles (11-16 Hz) and slow oscillations (0.5-1.5 Hz; SO) are fundamental elements of the NREM sleep microarchitecture, often co-occurring in a phase-dependent manner. This cross-frequency coupling is critical for the temporal coordination of neural activity in sleep and for memory consolidation. We previously showed that reduced spindle activity and spindle-SO coupling is associated with lower cognitive performance in temporal lobe epilepsy (TLE). In this study, we present evidence for a novel spatiotemporal relationship between spindles and SO, termed phase precession, and then compare the properties of this relationship across the lifespan and between control participants and those with TLE.

Methods: We studied 101 participants free of major neurological disease, and 111 participants with TLE, ranging in age from 20 to 85 years. Continuous overnight scalp EEG was sleep-staged, and spindles and SO were detected, using previously-published algorithms. The SO phases corresponding to spindle detections were plotted against the anterior-posterior scalp position. Circular-linear statistics were then used to determine the best fit line, and quantify the slope, strength (R value), and significance. Linear and logistic regression models were used to test the association of these phase precession parameters with demographics and group.

Results: Visual inspection of circular phase plots across the brain topography revealed a striking pattern. There was a systematic shift in phase, with spindles occurring at sequentially earlier SO phases relative to their anterior-posterior position. Phase-position plots confirmed this relationship at both an individual and group level. Examining phase precession properties across demographics, we found that older age is associated with reduced phase precession strength ($F=5.15$, $b=-0.001$, $R=0.37$, $p=0.008$), and a flattening of the slope ($F=2.64$, $b=-0.005$, $R=0.23$, $p=0.016$). In contrast, we did not find any significant differences between male and female sex ($p>0.05$). Comparing TLE to control participants, we found a significant reduction in phase precession strength, on average by 25.7% ($Fmodel=6.36$, $t=3.96$, $p=0.0001$, adjusting for age, sex, and total spindle count). Concordant with this finding, a smaller proportion of TLE patients had significant phase precession (Cntrl 91% vs TLE 74%; $Chi2model=13.7$, $p=0.019$).

Conclusions: We report a novel spatiotemporal organization of spindle-SO coupling, characterized by a systematic precession of the SO phase of spindles along the anterior-posterior axis of the brain. The integrity of phase precession degrades with advancing age and is reduced in patients with temporal lobe epilepsy. We propose that phase precession of spindle-SO coupling may serve an important mechanism for how information processing is coordinated across the brain in sleep, and how it may be impaired in disorders such as epilepsy.

S271: When Dacrystic Seizures Wear the Face of Panic attacks -A Case of Delayed but Definitive Diagnosis

Presenting Author: *Sushmita Bhandari, University of Alabama at Birmingham, Birmingham, AL*

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Background: Dacrystic seizures are paroxysmal stereotypical crying episodes ranging from sadness to grimacing and sobbing, occurring in 0.1% of admissions for long term video electroencephalography(EEG) [1]. This case report aims to illustrate the bizarre semiology captured on video EEG & the importance of recognizing focal seizures as a potential cause of prolonged misdiagnosis of psychiatric illness.

Methods: We describe a 44 year old male with past medical history of chronic anxiety disorder & tobacco abuse presented to the Epilepsy Monitoring Unit for evaluation of panic attacks & blackout episodes. Anxiety episodes began at age 30 and for last 6 months have occured weekly. They start with autonomic symptoms with palpitations, hyperventilation, and dizziness followed by whimpering and vocalizations with vague memory of the events.

Some episodes recently are also associated with urinary incontinence and brief tonic stiffening. Within the last 6 months, he reported having three blackout spells described as sudden loss of consciousness without aura including one that led to a motor vehicle accident.

Results: During 2 days of monitoring, we captured 14 events characterized by initial muttering, ictal whining/crying followed by ictal laughter. The semiology was then accompanied by grimacing or chapeau de gendarme, heavy rhythmic breathing with snorting, and abrupt termination with minimal postictal effects. There was no clear ictal onset on EEG, with the background being mostly obscured by distinct myogenic artifacts. Notably there were late onset & postictal frontocentral delta slowing. Interictally, bifrontal epileptiform discharges were noted at Fp1/Fp2/F8>F7 with a spike and wave morphology & low amplitude bitemporal epileptiform discharges.

Given the EEG findings with bizzare stereotypical expressions, diagnosis of focal epilepsy likely with a mesial frontal onset was made. Patient was started on Lacosamide with notable improvement in EEG without further seizures. Unfortuantely, further investigation was limited due to uninsured status of patient. Patient continues to remain seizure free on Lacosamide and has had no such episodes over a year now.

Conclusion: This case underscores dacrystic seizures as a rare yet distinct epileptiform phenomenon, where the emotional semiology poses a diagnostic challenge at the neuro psychiatry interface, emphasizing the value of early recognition in optimizing patient outcomes.

S272: Altered EEG microstate dynamics of the ictal hemisphere reflect depressive symptoms in temporal lobe epilepsy

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Background: Depression is a common and disabling comorbidity in temporal lobe epilepsy (TLE), yet the neural mechanisms linking seizure networks to affective symptoms remain unclear. Although limbic network dysfunction has been implicated in both epilepsy and depression, it is unknown whether the time-varying dynamics of large-scale electrophysiological brain states reflect depression severity in TLE. In this study, we examined whether EEG microstate dynamics capture depression-related network alterations in individuals with unilateral TLE.

Methods: We analyzed resting-state, visually normal scalp EEG from 26 individuals with unilateral TLE. EEG microstates were identified by clustering global field power peaks into four canonical classes, with electrode positions mirrored to align the ictal hemisphere across subjects. Microstate dwell time, fractional occupancy, global transition entropy, and Markov transition probabilities were quantified and related to Beck Depression Inventory-II (BDI) scores.

Results: Individuals with depression (BDI $\geq$ 13; $N = 12$) exhibited longer mean dwell time in an ictal hemisphere-dominant microstate compared with non-depressed individuals (BDI < 13; $N = 14$). Across subjects, dwell time in this microstate correlated with depression severity ($r = 0.57$, $p = 0.002$). Depressed TLE individuals also exhibited reduced global transition entropy ($p = 0.02$) that also correlated with depression severity ($r = -0.54$, $p = 0.004$), indicating decreased flexibility of microstate transitions. Despite similar fractional occupancy of this state between groups, depressed individuals were less likely to transition into the ictal hemisphere microstate from non-ictal or posterior configurations. Once engaged, however, the ictal hemisphere microstate showed increased persistence, indicating prolonged stabilization of this network configuration.

Conclusion: Depression in unilateral TLE is associated with increased temporal rigidity of an ictal hemisphere-dominant brain state, reflecting impaired disengagement of epileptogenic network configurations. These findings suggest that depression in TLE may arise from epilepsy-specific disruptions in large-scale neural dynamics.

S273: Evaluation of a Machine Learning Model (3D-ResNet-18) in Differentiating Epileptic and Non-Epileptic Motor Events in Clinical Settings Using Video Only

Presenting Author: *Jacky Cheung, MD, Icahn School of Medicine at Mount Sinai New York, NY*

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Background: Differentiating epileptic and non-epileptic motor events is a diagnostic challenge. We previously finetuned a 3D-ResNet-18 model to classify videos of motor events as epileptic or non-epileptic without human or EEG input by updating the fully connected layer and fourth convolutional block. The model achieved AUROC 0.78, AUPRC 0.84, sensitivity 0.82, specificity 0.78, precision 0.82, and accuracy 0.8. (Erekat, 2026, preprint-medRxiv). Here, we evaluated the performance of this ResNet18 model on events outside the scope of the initial training and testing set.

Methods: In this retrospective study, we reviewed the EEG reports for all patients who underwent inpatient video EEG at Mount Sinai Health System in New York from June 2021 to April 2025. We excluded patients younger than 12 years old. Reports describing accidental event pushes, non-motor symptoms, or subtle motor findings unlikely to be captured by human review were excluded. Reports describing clinical motor events were used to identify correlates on video EEG to generate an event clip. Clips longer than 30 minutes were excluded. Clips were identified as epileptic or non-epileptic based on if there was an electrographic correlate. For each clip, the ResNet18 model evaluated 16 sparsely sampled frames and classified the clip as either epileptic or non-epileptic.

Classification cutoff was determined with Youden threshold. Performance was evaluated with AUROC, AUPRC, sensitivity, specificity, precision, and accuracy.

Results: 973 EEG reports were reviewed. 943 reports were excluded: 166 reports with patients younger than 12 years old, 729 reports described no events, 24 reports described events suspected to be accidental event pushes, 23 reports described non-motor or subtle motor events, and 1 report had a clinical motor event but no associated video. 30 reports with clinical motor were included and represented 30 unique patients. From these videos, 47 clips were generated; 2 were excluded due to length. Of the 45 videos, there were 31 epileptic events and 14 non-epileptic events. With these clips, the model achieved AUROC 0.73, AUPRC 0.85, sensitivity 0.66, specificity 0.69, precision 0.79, and accuracy 0.67.

Conclusion: Our ResNet18 model distinguishes real-world epileptic and non-epileptic motor events better than chance. The model performed well in a clinical setting, including stereotactic EEG and critical care environments. Future work aims to improve performance through optimizing sampling strategies or temporal coverage. The goal is to produce reliable clinical decision support tools to guide management and augment care in areas with limited access to neurologists or EEG.

S274-K: Hippocampal-cortical Mechanisms of Altered Memory Consolidation in Epilepsy

Presenting Author: *Sharon Chiang, MD, PhD, University of California, San Francisco*

Co-Authors: *Sona Asatryan, BS, University of California, San Francisco, Donghoon Shin, BS, University of California, San Francisco, Loren Frank, PhD, University of California, San Francisco*

Abstract: Temporal lobe epilepsy (TLE) is the most common epilepsy in adults, affecting more than 50 million worldwide.

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Memory impairment is a major associated morbidity of TLE and affects 70% of people with TLE. While the cellular mechanisms necessary for memory formation in health are beginning to be understood, how these circuits are disrupted in TLE is relatively less known. In this project, I record single unit firing from the hippocampus and prefrontal cortex during early learning of a spatial navigation task, using a rodent model of temporal lobe epilepsy. My preliminary findings suggest disruption of hippocampal-level circuitry at the level of sharp-wave ripples and downstream formation of cortical memory ensembles.

S275-LB: Pre-Ictal Assessment of Autonomic Function Using Heart Rate Variability and Baroreflex Sensitivity from a Wearable Continuous Blood Pressure Sensor

Presenting Author: *David Clymer, M.Sc., University of California, Irvine, Irvine, CA*

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Background: Sudden unexpected death in epilepsy (SUDEP) affects 1 in 1000 adults with epilepsy and is diagnosed post-mortem when an autopsy reveals no toxicological or traumatic cause of death. Seizure unpredictability contributes to injury risk, delayed intervention, and impaired quality of life. Moreover, monitoring seizures remains a critical challenge, particularly for patients living at home. There is an urgent need for seizure forecasting using small form-factor wearable sensors capable of continuously detecting pre-ictal cardiac and autonomic features in both home and inpatient environments.

Methods: Our preliminary results were from two patients with nine seizures in total (all R temporal lobe). Successive BP-derived metrics were extracted from motion-artifact-free signals in the 30-minute window preceding each seizure. BRS showed a non-monotonic pre-ictal pattern, declining from 16.85 ms/mmHg [IQR: 14.42–25.40] (at -30 to -25 minutes before onset) to 10.09 ms/mmHg [IQR: 4.09–15.26] (at -20 to -15 min), followed by partially rebounding to 18.09 ms/mmHg [IQR: 14.26–19.86] (at -15 to -10 min). The observed 40.1% decrease over 15 minutes followed by 79.3% rebound over merely 5 minutes suggests rapid modulation of autonomic function before seizure onset. Median RMSSD showed a relatively modest decline-rebound pattern, dropping by 10.3% over 15 minutes followed by a 14.2% increase over 5 minutes.

Results: Our preliminary findings demonstrated the feasibility of monitoring epilepsy patients with capacitance sensors. Though validation in a larger cohort is needed, the observed rapid non-monotonic modulation of BRS, together with modest perturbation in RMSSD, suggests that BP-derived autonomic dynamics may provide physiologic signatures that support seizure forecasting as early as 10 minutes before onset with a small form-factor wearable continuous BP sensor in both home and hospital settings.

Conclusion: Continuous blood pressure (BP) waveforms were acquired using a Vena Vitals wearable capacitance sensor at 100 Hz sampling rate. Sporadic bedside cuff measurements were used to calibrate capacitance to systole/diastole BP values within a 10-second window surrounding each cuff measurement. Sensor state was defined using root-mean-square peak-to-peak distance and diastolic level. For each seizure, a 30-minute pre-ictal segment preceding seizure onset is calibrated according to sensor state and analyzed using our python software pipeline to extract successive heart rate variability metrics. Baroreflex sensitivity (BRS) was estimated from systolic BP and inter-beat-interval oscillations using Welch transfer gain in the low-frequency band (0.04 - 0.15 Hz) after uniform resampling at 4 Hz, retaining estimates with coherence >0.5.

S276-K: The Effects of Single Pulse Electrical Stimulation on Intracranial EEG Monitoring

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Background: Cortico-cortical evoked potentials (CCEPs) are cerebral waveforms elicited by single-pulse electrical stimulation (SPES). These waveforms can be used to evaluate brain networks during intracranial EEG monitoring (iEEG). While generally considered to be a safe procedure, it is not known what effects SPES may have on subsequent EEG recording in the epilepsy monitoring unit (EMU).

Methods: A cohort of 28 patients underwent SPES at the beginning of iEEG monitoring. A control group of 28 patients was matched for age and baseline seizure frequency. We compared the duration of EMU stay, time until first seizure, and the number of spontaneous seizures. We compared the spike rate one hour pre- and post-SPES. Lastly, in a subgroup of 14 patients we compared functional connectivity in 10-minute segments pre-SPES, immediately post-SPES, and 50 minutes post-SPES.

Results: There was no significant difference between SPES and controls in median time until first seizure (25.7 hrs. vs. 20.5 hrs.). There was a nonsignificant trend towards longer implantation in the SPES group compared with the control group (median hrs. 204.5 vs. 166.5, respectively, $p = 0.056$). There were significantly more subclinical seizures in the SPES group (median 7 vs 0, respectively, $p = 0.011$), but no difference in total seizures. A general linear model comparing SPES, baseline seizure frequency, anti-seizure medication (ASM) wean rate, mean ASM dose, epilepsy duration, and seizures induced with SPES demonstrated that only the ASM wean rate and mean dose of ASM significantly correlated with the duration of EMU monitoring ($P < 0.05$ for both, partial $\eta 2$ 0.198 and 0.21, respectively, adjusted $R2 = 0.514$); however, both were inversely correlated (β = -0.029 and -0.02, respectively). A similar model showed that SPES and the mean ASM dose were significantly correlated with total seizures ($P < 0.05$, partial $\eta 2$ 0.102 and 0.085, respectively, adjusted $R2 = 0.207$). The model for time until first seizures was only significant for mean ASM dose

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(P<0.001, partial η2 0.324, adjusted R2=0.345). There was no difference in spike rate pre- vs post-SPES (mean spike rate 31.66 spikes/min vs 29.46 spikes/min, respectively, P = 0.55). Of the 14 patients with connectivity analyses, 8 showed temporary increase, 5 showed temporary decrease, and 1 had no significant change in connectivity post-SPES (KS test, p<0.05). However, no significant median connectivity differences were found after SPES (Fig. 1A, KW test, p=0.9871). The median from the mean connectivity difference matrices (pre-SPES – post-SPES first 10 minutes & pre-SPES – post-SPES last 10 minutes) were computed across patients (Fig. 1B). Distributions were centered around 0, indicating no net change following SPES. There was a small but significant increase in seizure onset zone (SOZ) nodal efficiency, node strength, and eigenvector centrality with a decrease in betweenness in the last 10 minutes in the post-SPES hour compared to first 10 minutes (Fig. 2, t test, P<0.05); however, the initial 10 minutes were similar to baseline, suggesting that the later change could be related to other factors.

Conclusions: Overall, our study demonstrates that SPES at the beginning of iEEG monitoring was correlated with increased seizures, but otherwise does not significantly alter the clinical monitoring nor does it produce significant changes in epileptogenicity or functional network connectivity, supporting its use in clinical or research practice.

S278: Single-Cell Protein Analyses of mTORopathies: Ex vivo Tissue and Organoid Models Reveal Novel Mechanistic Insights

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Background: The mechanistic target of rapamycin (mTOR) pathway consists of cascading kinases that play an important role in neurogenesis. Mutations in mTOR pathway components cause a class of disorders termed mTORopathies. Both focal cortical dysplasia (FCD), a somatic mosaic mTORopathy, and tuberous sclerosis (TSC), a germline mTORopathy, are characterized by malformed cortical tissue with morphologically abnormal and hyperexcitable cells. Cortical malformations secondary to mTORopathies are one of the leading causes of drug-resistant focal epilepsy in children. A better understanding of the cell-specific protein features of these disorders is thus urgently needed to develop novel treatments.

Methods: We developed a 39-marker mass cytometry (CyTOF) antibody panel to broadly phenotype neural cell fate and downstream mTOR signaling readouts. We analyzed resected ex vivo tissue from 16 patients with FCD and TSC. We correlated this data with analyses of forebrain organoid models of TSC developed using three independent isogenic lines with *TSC2* mutations. Findings were validated using cyclic immunofluorescence staining.

Results: There was widespread activation of mTORC1 effectors in both FCD/TSC tissues and *TSC2* -/- organoids. Other phosphoproteins, including mTORC2 targets, showed greater variability across tissue and genotype condition. A novel tri-positive CUX1/HES1/Vimentin cell population was identified in FCD tissue and was associated with post-surgical seizure outcomes. A similar population was found in *TSC2* -/- organoids. Mutant *TSC2* organoids had higher per-cell levels of YAP1; pharmacological inhibition of YAP1 rescued cell-state abnormalities including precocious expression of mature neuronal markers.

Conclusion: Translational and post-translational analyses of patient-resected tissue and patient-derived brain organoid models of mTORopathies provide important mechanistic clues into disease pathogenesis. Through high-dimensional phenotyping of millions of cells from tissues and organoids, we identified differential phosphorylation of downstream mTOR targets across disease states and described novel cell populations that may be driving neurodevelopmental disease progression. Future work will focus on functional characterization of cell populations of interest.

S279: Case of anti-NMDA Receptor Encephalitis Secondary to Ovarian Teratoma: The Effect of Bias and Delayed Diagnosis in Hispanic Populations in a Tertiary Care Center

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Background: Anti-NMDAR encephalitis is an autoimmune disorder characterized by psychiatric symptoms, seizures, and autonomic instability, frequently associated with ovarian teratomas. Although awareness has increased, diagnostic delays remain common, and sociocultural factors may exacerbate misdiagnosis risk in minority groups. Limited data exist regarding presentation and outcomes in Hispanic patients.

Methods: Case Presentation: A 24-year-old previously healthy Hispanic female presented with acute altered mental status following a brief prodrome of severe headaches, anxiety, episodes of aggression, and catatonia. Initial behavioral changes were misattributed to opioid abuse and a psychiatric disorder from a previous hospital visit.

Upon admission to our institution, differential diagnoses included a de novo psychiatric disorder versus acute meningitis/encephalitis. To evaluate for the latter, a lumbar puncture was performed and was remarkable for an aseptic cytology. The patient was empirically treated with antiviral therapy,

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however, the patient experienced an event of status epilepticus, and ictal EEG showed characteristic delta brush pattern waves. Neurology/ICU team work up confirmed the diagnosis with positive anti-NMDAR antibodies in cerebrospinal fluid, EEG findings, and evidence of an ovarian teratoma. Treatment included oophorectomy and immunotherapies with high-dose steroids, rituximab, and plasmapheresis, with limited neurologic improvement. Multidisciplinary care involving neurology, infectious disease, and critical care teams was required.

Results: Discussion: This case illustrates the diagnostic and therapeutic challenges of refractory anti-NMDAR encephalitis in critically ill patients. It also raises an important question regarding potential ethnic disparities. Hispanic patients may be particularly vulnerable to diagnostic delays, sociocultural barriers, and higher rates of psychiatric misdiagnosis, which influence patient outcomes.

Conclusion: Anti-NMDAR encephalitis in this young Hispanic patient underscores the importance of early recognition, avoidance of psychiatric misdiagnosis, and a tailored multidisciplinary approach. Future research should examine whether Hispanic patients experience distinct diagnostic or treatment challenges, and how sociocultural determinants of health shape disease course.

S280: Levetiracetam Versus Phenobarbital as First-Line Therapy for Neonatal Seizures: A Meta-analysis of Randomized Controlled Trials

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Background: Phenobarbital remains the standard first-line treatment (1LT) for neonatal seizures (NS) despite concerns regarding efficacy and safety. Levetiracetam has gained widespread use as an alternative, but randomized evidence is conflicting. We performed a meta-analysis of randomized controlled trials (RCTs) comparing levetiracetam with phenobarbital as 1LT for NS.

Methods: We systematically identified RCTs PubMed-indexed enrolling neonates treated with levetiracetam or phenobarbital as initial antiseizure medication (ASM). The primary outcome was seizure freedom (SF) within 24 hours. Secondary outcomes included 1LT failure, requirement for rescue ASM, adverse events (AEs), and mortality. Risk ratios (RRs) were pooled using a Mantel–Haenszel random-effects model with REML. Heterogeneity was quantified using the I2 statistic. Numbers needed to treat (NNT) and harm (NNH) were estimated from absolute risk differences.

Results: Six RCTs (levetiracetam=245; phenobarbital=216) were included. Levetiracetam did not significantly increase SF compared with phenobarbital (RR 1.23, 95% CI 0.86–1.76; I2=72%). On meta-regression, trials using clinical seizure diagnosis demonstrated higher SF rates with levetiracetam (RR 1.38, 95% CI 1.01–1.88), whereas the single trial using continuous EEG-confirmed seizures showed superior efficacy of phenobarbital (RR 0.30, 95% CI 0.17–0.54). 1LT failure (RR 0.87, 95% CI 0.52–1.44) and need for rescue ASM (RR 0.73, 95% CI 0.46–1.17) did not differ significantly between groups. Levetiracetam was associated with fewer AEs overall (RR 0.33, 95% CI 0.15–0.71), particularly hypotension (RR 0.30, 95% CI 0.13–0.68). No differences were observed between groups for respiratory depression (RR 0.63, 95% CI 0.32–1.25), bradycardia (RR 0.44, 95% CI 0.13–1.53), or mortality rates (RR 1.17, 95% CI 0.46–2.95). Levetiracetam increased SF by 3.3% (NNT $\approx$ 30), whereas phenobarbital increased hypotension by 9.1% (NNH $\approx$ 11).

Conclusion: Levetiracetam does not demonstrate consistent superiority over phenobarbital as 1LT for NS control. However, levetiracetam shows a more favorable short-term safety profile. RCTs assessing different NS diagnoses are needed to confirm results.

S281*: Cell Type-Resolved Multiomics Reveal Signatures of Homeostatic Circuit Reorganization in Focal Epilepsy of Unknown Etiology

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Background: Epilepsy affects ~50 million people worldwide, with nearly half of cases classified as focal epilepsy. In many patients, the etiology remains unknown, and clinical outcomes are highly variable: ~30% develop treatment-resistant seizures, and durable seizure freedom is achieved in only a subset (8–50%). Focal epilepsy of unknown etiology (FEUE) therefore represents a major public health burden. Mechanistically targeted therapies remain limited, underscoring the need to define the molecular and cellular changes that drive epileptogenic circuit dysfunction.

Methods: We profiled paired seizure-onset-zone (SOZ) and resection-margin (RM) tissue from 15 individuals with FEUE using single-nucleus multi-omic approaches. To control for inter-individual variability, we performed cluster-wise paired pseudobulk differential expression across 33 identified cell types. Complementary preliminary proteomic and single-nucleus ATAC-seq analyses were performed on paired SOZ/RM tissue to characterize protein-level alterations and the upstream regulatory landscape, respectively.

Results: Overall transcriptional differences between SOZ and RM were modest, but several cell populations exhibited consistent SOZ-associated signatures. An astrocyte-enriched cluster showed upregulation of extracellular matrix (ECM) genes and transcriptional regulators (e.g., *COL11A1*, *ESRRG*) with downregulation of signaling and metabolic genes (e.g., *APLNR*, *PFKFB3*). Several interneuron clusters showed SOZ-associated upregulation of genes involved in synaptic organization and axon guidance (e.g., *EPHA5*, *LRRC4C*, *GPC6*, *PRKCA*), consistent with activity-dependent circuit remodeling. Proteomics revealed a general increase in SOZ protein abundance, with 111 significantly altered proteins identified across subjects. SOZ-enriched proteins included

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complement pathway components (e.g., *C1QA/C*, *FCGR1A*) and ECM proteins (e.g., *COL6A1-3*, *FN1*), implicating structural and immune-associated remodeling as convergent features of epileptogenic tissue. In contrast, SOZ-decreased proteins included presynaptic machinery (e.g., *SNAP25*, *CPLX1/2*), suggesting altered synaptic function. Single-nucleus ATAC-seq revealed overall stability of chromatin accessibility across cell types in SOZ relative to RM, with selective changes in regulatory activity associated with differentially expressed genes, suggesting coordinated epigenetic regulation rather than widespread chromatin remodeling.

Conclusion: FEUE is characterized by cell type-specific homeostatic circuit reorganization accompanied by coordinated extracellular matrix (ECM) remodeling. Integrated transcriptomic, proteomic, and chromatin accessibility profiling provides complementary evidence for altered synaptic function, structural and immune-associated remodeling, and selective regulation of gene networks within epileptogenic tissue. Together, these molecular changes support a model in which compensatory cellular responses and circuit remodeling contribute to epileptogenesis despite relatively preserved global chromatin accessibility. Integration with stereo-EEG features will further define the relationship between these molecular signatures and circuit-level outcomes, with potential implications for biomarker discovery, precision diagnostics, and targeted therapeutic strategies.

S282-K: Multisite Resting-State fMRI Reveals Network Segregation Loss and Lateralized Connectivity Changes in Epilepsy

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Background: Interictal functional aberrations in focal and generalized epilepsies can be measured using resting-state fMRI, and changes in canonical cortical networks and subcortical structures have been reported. However, the spatial extent and network specificity of these changes remain poorly characterized, partly due to limited sample sizes in single-site studies. We aimed to address this gap by creating a centralized, multisite dataset within the ENIGMA-Epilepsy Consortium and applying a network-informed, region-of-interest (ROI)-based functional connectivity (FC) analysis. We quantified relative network segregation and integration by characterizing the number of strong ROI-to-ROI connections within and between canonical networks.

Methods: We assembled data from 934 participants across 10 sites: healthy controls (HC, n=360), focal epilepsy (FE, n=479), and generalized epilepsy (GE, n=95). Images were preprocessed with fMRIPrep. Regional time series were extracted from 432 atlas-defined ROIs, combining the Schaefer 400x7 cortical atlas with 32 Melbourne subcortical ROIs. Participant-level FC matrices were calculated at a 10% proportional threshold. For each ROI, FC degree was defined as the number of suprathreshold edges.

To test network-level hypotheses, degree was calculated as global, within-network, and between-network degree. Within-network degree was defined as edges between nodes in the same Yeo-7 network; between-network degree excluded within-network connections. We tested three prespecified contrasts: 1) FE vs GE vs HC; 2) left-onset FE (LFE, n=200) vs right-onset FE (RFE, n=153) vs HC; and 3) left TLE (LTLE, n=183) vs right TLE (RTLE, n=140) vs HC. ROI-wise ANCOVA models included age, sex, site, mean framewise displacement, and scan duration as covariates. Pairwise comparisons used Welch's t-tests on covariate-adjusted residuals. Results were FDR-corrected at $q<0.05$, and Cohen's d was reported as the effect size.

Results: Consistent with our primary hypothesis, epilepsy was associated with widespread loss of network segregation. In the FE vs GE vs HC analysis, significant group effects were observed for within-network degree in 120/432 ROIs and for between-network degree in 50/432 ROIs. Compared with HC, both FE and GE showed reduced within-network degree concentrated in associative systems, particularly default mode and salience networks, together with increased between-network degree involving sensorimotor and subcortical regions. In GE, within-network reductions were prominent in temporal default mode and salience networks, involving 92 ROIs with effect sizes up to $|d|=0.61$. GE also showed increased between-network degree in somatosensory regions (6 ROIs, $|d|$ up to 0.47) and in subcortical anterior caudate and dorsal-anterior thalamic ROIs.

In FE, within-network reductions versus HC were widespread, with 77/83 significant ROIs showing decreased within-network degree and effect sizes up to $|d|=0.47$. These abnormalities were concentrated in salience, default mode, and visual networks. FE also showed increased between-network degree in sensorimotor regions (14 ROIs, d up to 0.46) and dorsal-anterior thalamus ($d=0.22$). In FE laterality analysis, RFE showed broader within-network reductions than LFE (33 ROIs, with peak $|d|=0.64$, and 16 ROIs, with peak $|d|=0.59$, respectively). These abnormalities were centered on ipsilateral temporal default mode and frontal salience cortex, supporting a lateralized focal network signature. The TLE-only analysis showed larger peak effect sizes with the same pattern, despite smaller subgroup sizes, with RTLE reaching $|d|=0.69$ and LTLE reaching $|d|=0.62$. Eight ROIs directly distinguished TLE laterality groups.

Conclusions: Results from this new centralized ENIGMA-Epilepsy rsfMRI dataset support the hypothesis of transdiagnostic network segregation loss in epilepsy. Both FE and GE showed reduced within-network degree in associative networks, particularly default mode and salience systems, accompanied by increased between-network degree in sensorimotor and subcortical regions. This pattern suggests a shift from specialized within-network organization toward greater cross-network integration. In FE, abnormalities also carried lateralizing information, with stronger and more specific effects in TLE. These findings support a network-informed, ROI-level ENIGMA framework for mapping shared and syndrome-specific FC abnormalities. Future studies will link

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these FC signatures to clinical characteristics, treatment response, and surgical outcomes.

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S283: Small Current, Big Impact: Rapid Seizure Reduction with Low-Dose Bilateral Centromedian Nuclei Responsive Neurostimulation

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Background: Drug-resistant epilepsy (DRE) affects more than one-third of individuals with epilepsy and presents a significant therapeutic challenge when seizures arise from multifocal or non-localizable networks. Many patients are not candidates for resective surgery due to the absence of a discrete epileptogenic focus. Neuromodulation targeting thalamocortical networks has emerged as an important treatment strategy. While responsive neurostimulation (RNS) is FDA-approved for focal epilepsy, its use targeting the centromedian nucleus (CMN) of the thalamus in non-localizable epilepsy remains incompletely characterized.

Methods: A 19-year-old patient with infantile-onset drug-resistant epilepsy presented with daily seizures characterized by axial tonic events, somatosensory auras, and nocturnal seizures. Comprehensive presurgical evaluation demonstrated discordant electroclinical findings, non-lesional neuroimaging, and multifocal seizure activity without a clearly localizable epileptogenic zone. Given the poorly localizable diffuse seizure-onset, the patient underwent bilateral implantation of responsive neurostimulation leads targeting the CMN using stereotactic guidance with imaging confirmation. Stimulation was initiated one month following implantation at low current parameters.

Results: RNS was activated with the following stimulation parameters: current 1.0 milliamperes, pulse width 160 microseconds, charge density 0.5 microcoulombs per Coulomb-meters-squared, train duration 1 second, and frequency 142.9 Hertz. Within one month of activation, the patient experienced a clinically meaningful 50–70% reduction in seizure frequency. Bilateral tonic-clonic seizures resolved completely, and somatosensory auras were markedly reduced. Residual seizure activity consisted primarily of morning myoclonic clusters.

Conclusion: Patients with multifocal or non-localizable DRE represent a particularly challenging population due to limited surgical options. This case highlights the potential utility of CMN RNS as a network-based neuromodulatory strategy in epilepsy lacking identifiable discrete seizure foci. Previous long-term recordings investigating CMN RNS in multifocal epilepsy phenotypes have demonstrated reduction in ictal activity after 6-24 months of stimulation at progressively increasing current amplitudes. Notable in our case, clinical improvement occurred at relatively low stimulation parameters without the need for early escalation, suggesting that modest modulation of thalamocortical circuitry may disrupt pathological network synchronization in selected individuals. The observed early response at low stimulation parameters contrasts with prior reports requiring prolonged titration, suggesting that individualized targeting of thalamocortical circuits may produce rapid clinical benefit in selected cases. Our case highlights that CMN–targeted responsive neurostimulation may represent an effective treatment strategy for multifocal, non-localizable drug-resistant epilepsy. However, prospective randomized controlled trials are needed to better define patient selection criteria, optimize stimulation parameters, and expand therapeutic options for patients with otherwise limited treatment pathways.

S284: EpiScalp™: A Novel Software Tool for Enhancing Diagnostic Precision in First-Time Seizure Evaluations

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Background: Epilepsy, a chronic neurologic condition characterized by recurrent, unprovoked seizures, affects millions worldwide, with the World Health Organization (WHO) estimating 5 million new diagnoses annually. Alarmingly, misdiagnosis rates range from 20-42%, leading to potentially severe consequences. A false positive can result in inappropriate treatment with antiseizure medication, risking adverse reactions and delaying proper therapy, alongside unnecessary employment and social restrictions due to epilepsy stigma. Conversely, a false negative increases the risk of seizure recurrence, status epilepticus, and premature death. Such high misdiagnosis rates stem from a complex diagnostic process that lacks a single confirmatory test, instead relying on comprehensive clinical history, neurological examination, and visual inspection of scalp electroencephalography (EEG), which can only confirm an epilepsy diagnosis if rare sporadic abnormalities are present. While epileptologists are able to provide greater diagnostic accuracy by synthesizing clinical history with imaging and EEG, this integration of multimodal data often exceeds the scope of the general neurologists who see first-time seizure patients, leading to greater misdiagnosis and delaying appropriate treatment.

Methods: Therein lies a clinical need for a tool that can assist neurologists in diagnosing epilepsy using the information available from a first visit and an EEG with or without

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abnormalities. EpiScalp™, our patent-protected software tool, fulfills this need by leveraging proprietary EEG analyses to uncover underlying network imbalances indicative of epilepsy in combination with age, sex, and semiology to compute a risk score (0-100) on the likelihood of epilepsy during the first visit.

Results: EpiScalp™ is currently deployed in three Level 4 Epilepsy Centers as part of an NINDS SBIR Phase 2 Research Study. We tested EpiScalp™ on 118 routine scalp EEG patients with a definitive clinical diagnosis of epilepsy (n = 90) or non-epilepsy (n = 28) confirmed by at least 6-months follow-up. EpiScalp™ made a definitive prediction with 90% accuracy, 93% sensitivity, and 76% specificity (0.87 AUC) with 78% decision rate. For the subset of first-time seizure patients (n=31), EpiScalp™ achieved 91% accuracy, 94% sensitivity, and 80% specificity (0.93 AUC) with 71% decision rate.

Conclusion: EpiScalp™ offers the potential to significantly reduce both patient misdiagnosis rates and time to diagnosis by providing clinicians with quantitative information to accelerate and guide accurate diagnosis and treatment of first-time seizure patients. With the assistance of EpiScalp™, general neurologists can more confidently prescribe appropriate medications and refer patients to the correct specialist for further testing and evaluation, ultimately getting patients to the right treatment sooner.

S285: Elevated Plasma p-tau217 in Older Adults with Epilepsy and Cognitive Impairment: A Pilot Study

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Background: Epilepsy is associated with a two-to-three-fold increased risk of dementia. Seizures are linked to enhanced production of neurotoxic amyloid-β species, and increased pathological tau hyperphosphorylation. Both epilepsy and early stages of Alzheimer's disease (AD) can present with amnestic memory impairment, which can obfuscate detection of early comorbid AD in patients with epilepsy. We evaluated plasma p-tau217, a biomarker of AD pathology, in older adults with epilepsy and cognitive impairment.

Methods: Sixteen patients with epilepsy age ≥60 years with cognitive impairment were assessed clinically and using the Mini Mental State Exam (MMSE). Plasma p-tau217 was quantified from K2-EDTA plasma using Lumipulse G chemiluminescent enzyme immunoassay (CLEIA; Fujirebio Diagnostics, Inc.). A previously validated cutoff score of >0.18 pg/mL for predicting amyloid PET status was used. The relationships between clinical history, MMSE score, and MMSE recall subscore with plasma p-tau217 were assessed using age- and sex-adjusted multiple regression.

Results: Mean age was 74.2 years (SD: 9.1) and 62.5% (10/16) were female. Median epilepsy onset age was 61.5 years (IQR: 45.0-67.5), and median duration of epilepsy was 8.0 years (IQR: 4.5-32.3). Ten patients had clinical and/or electrographic features consistent with temporal lobe epilepsy. Median MMSE score was 25.5 (IQR: 23.0-27.5). Median plasma p-tau217 concentration was 0.24 pg/mL (IQR: 0.11-0.42). Plasma p-tau217 exceeded the cutoff (>0.18 pg/mL) in 50% (8/16) of participants. Higher p-tau217 concentration was associated with lower MMSE score (β: -0.045, $p<0.01$) and lower MMSE recall subscale score (β:-0.154, $p=0.04$). Among patients with MMSE ≤26, 70% had p-tau217 >0.18 pg/mL. Age, sex, epilepsy onset age, epilepsy duration, and temporal versus non-temporal/unknown onset were not significantly associated with p-tau217.

Conclusion: In this pilot study of older adults with epilepsy and cognitive impairment, a high proportion of patients had plasma p-tau217 concentrations above a previously validated cutoff associated with amyloid PET positivity, including a majority of patients with MMSE scores ≤26. Age was not associated with p-tau217. AD-related pathology may be a common contributor to cognitive impairment in older adults with epilepsy. Further validation with multimodal AD biomarkers and longitudinal cognitive assessments in older adults with epilepsy is warranted.

S286-K: Single Nucleus Transcriptomics Identifies an Epilepsy-Associated Microglial Population in the Pilocarpine Model of Temporal Lobe Epilepsy

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Background: Mesial temporal lobe epilepsy (TLE) is the most common form of acquired epilepsy involving the hippocampus and is a frequent sequelae of head trauma. TLE is associated with refractory seizures and significant cognitive deficits. Yet, the gene expression patterns and cell types driving epileptogenesis and the associated cognitive deficits are poorly understood.

Method: We performed single nucleus RNA sequencing on hippocampal tissue from mice at 3 and 6 weeks following pilocarpine-induced status epilepticus, a robust model of TLE.

Results: At these early timepoints, epilepsy samples showed reductions in specific Cck and Lamp5-Lhx6 interneuron subclusters, alongside increases in Cajal-Retzius cells, dentate granule (DG) cell precursors, and a mature DG cell subcluster. Among glia, an astrocyte subcluster and a markedly expanded microglia subcluster were increased. We term this microglia population epilepsy-associated microglia (EAM). The transcriptomic profile of EAM partially overlaps with microglia described in models of Alzheimer's disease and

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traumatic brain injury, both disorders which have increased risk of developing TLE. EAM display amoeboid morphology, can be found in dense clumps around pyramidal and granule cell body layers, and exhibit enlarged vesicles and mitochondria on electron microscopy. Cell-cell interaction analyses predict that DG cells are the main interaction partners of EAM. This dataset recapitulates known cellular alterations in TLE while defining their underlying transcriptomic programs, enabling mechanistic dissection of the key processes driving epileptogenesis.

S287-K: Callosal Conduction Velocity Determines Bilateral Synchrony and Epilepsy Severity

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Abstract: Severe generalized epilepsy, as occurs in Scn8a loss of function, is defined by progressive seizures with simultaneous onset in the bilateral hemispheres (bilateral hypersynchrony), that increase in quantity over time. The physiological determinants of bilateral synchrony and epilepsy progression remain unclear. White matter tracts have traditionally been considered as fixed, passive conduits, including for transmission of seizure activity in epilepsy, but recently it has been proposed that white matter conduction is dynamic and may critically shape the timing of large-scale network interactions. We investigated conduction dynamics of major white matter tracts in the generalized seizure network, the corpus callosum and internal capsule, in Scn8a+/-mice with generalized epilepsy. With slice electrophysiology, and stimulation of the ipsilateral corpus callosum, we recorded contralateral compound action potentials (CAPs) and found callosum conduction velocity to be pathologically increased. The increased conduction velocity was restricted to anterior callosum, a portion of the seizure network, occurred only in myelinated fibers and occurred only after the developmental onset of seizures. None of the other properties of callosal conduction we assessed (CAP amplitude, area, duration and rise time) differed between Scn8a+/- and littermate controls. No differences were seen in any CAP conduction measure in the internal capsule. Given that myelination influences conduction velocity, we assessed network changes in myelination with MRI myelin mapping. This revealed increased myelination, selectively in the anterior corpus callosum, and overlapping the region of increased callosal conduction velocity. Genetic disruption of activity-regulated myelin plasticity, which we previously have shown to block seizure progression, prevented the increase in callosal conduction velocity, and reduced pathological bilateral hypersynchrony assessed with EEG coherence. Computational modeling of the generalized seizure network, informed by empirical measures in Scn8a +/- mice, predicted that increased callosal conduction velocity would be sufficient to drive bilateral hypersynchrony and increase seizure severity. Consistent with these findings, focal anterior callosal chemical disruption of myelination with lysophosphatidylcholine in Scn8a+/- mice decreased callosal conduction velocity without disrupting axonal transmission or inducing persistent neuroinflammation, and prevented epilepsy progression. Together, these results identify dynamic callosal conduction velocity as an unexpected determinant of bilateral hypersynchrony and of epilepsy severity.

S289: Trends, Demographic Characteristics, Risk Factors, and Outcomes of Epileptic Spasm Hospitalizations: A U.S. Population-Based Analysis (2016–2022)

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Background: Infantile epileptic spasm syndrome (IESS) is a severe form of early childhood epilepsy characterized by epileptic spasms and a high risk of developmental arrest or regression. The condition is associated with significant neurodevelopmental morbidity, including cognitive impairment and cerebral palsy, as well as substantial healthcare utilization. Early recognition and treatment are critical to improving outcomes; however, despite its clinical significance, contemporary national data describing trends, risk factors, and outcomes of epileptic spasm (ES) hospitalizations remain limited.

Methods: This retrospective cohort study utilized the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) data from 2016 to 2022. Hospitalizations for children aged 0–2 years with a diagnosis of ES were identified. Data were analyzed using weighted estimates to ensure generalizability. Statistical methods included linear regression for trends, Pearson chi-square for categorical comparisons, and generalized linear models for healthcare resource utilization, including length of stay (LOS) and total hospital charges.

Results: The final cohort included 28,985 discharges (9.9 per 10,000). Weighted ES hospitalizations increased from 8.37 to 10.88 per 10,000 discharges ($p=0.065$). Significant increases were observed in children aged 1 year (OR 1.04, $p=0.014$) and 2 years (OR 1.10, $p<0.001$), while trends were not significant in infants <1 year. Central nervous system and autosomal anomalies were independently associated with ES. Compared to infants <1 year, children aged 1–2 years had higher odds of mechanical ventilation and cerebral palsy, and gastrostomy was more frequent at age

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1. Demographic and hospital-level differences were observed across race, insurance status, income quartile, and hospital characteristics. While LOS was stable overall, survivors at age 2 had significantly longer LOS (IRR 1.13, p=0.037) and higher total hospital charges (GLM 1.18, p=0.024).

Conclusion: ES hospitalizations increased nationally from 2016 to 2022, primarily driven by rising rates in children aged 1 and 2 years. The increased healthcare resource utilization at age 2 highlights the growing clinical and economic burden of this syndrome and emphasizes the need for age-specific management strategies and earlier recognition to improve outcomes.

S290-K: Striatal Interneuron Dysfunction as a Novel Mechanism for Autism Related Features in Dravet Syndrome

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Background: Autism spectrum disorder (ASD) and epilepsy are highly co-occurring neurodevelopmental disorders however they have largely been studied separately, missing the opportunity to determine if there are shared underlying pathophysiological mechanisms. Dravet syndrome (DS) exemplifies this overlap as it presents with both infantile onset treatment-resistant epilepsy and high incidence of ASD. DS is caused by variants in SCN1A encoding the voltage-gated sodium channel subunit Nav1.1 which is prominently expressed in GABAergic inhibitory neurons (INs) throughout the brain. SCN1A is the most commonly identified gene in epilepsy and is also independently a validated ASD risk gene. DS (Scn1a+/-) mice develop early-onset seizures and exhibit endophenotypes of ASD including hyperactivity, stereotyped movements, impaired learning and social behavior deficits. Hence, there is a strong rationale for using this model to study basic mechanisms of ASD, which will further our understanding of the convergent and divergent pathophysiology of ASD and epilepsy. Previous work in Scn1a+/- mice have established deficits of INs in neocortex and hippocampus contributing to seizures. Whether changes in E/I balance within specific neural circuits underlie ASD symptoms vs seizures in DS remains an open question. A strong candidate is the striatum given known roles of striatal dysfunction in the motor stereotypies, behavioral inflexibility and altered social interactions characteristic of ASD. The two main subtypes of striatal GABAergic INs, parvalbumin (PV) and somatostatin (SST), also express Scn1a, but it is unknown how these INs are impacted in Scn1a+/- mice.

Methods: In the Scn1a+/- mouse model of DS we use a combination of acute brain slice electrophysiology and optogenetics toprobe neuronal excitability and corticostriatal synaptic connections. Quantitative behavioral analysis is performed using Deep Lab Cut (DLC) tracking and Motion Sequencing (MoSeq) to assess spontaneous motor patterns and social interactions.

Results: First, we discover that both striatal SST and PV INs are hypoexcitable in Scn1a+/- mice, but with contrasting developmental time course. Striatal SST INs have early mild and transient hypoexcitability. PV INs uniquely have normal action potential firing at the time of seizure onset, then later develop severe and persistent deficits with inability to sustain fast action potential firing. We then use optogenetics to investigate the impact on excitation-inhibition balance in corticostriatal circuits, finding that feed-forward inhibition is largely intact due to increased excitatory drive onto PV INs in Scn1a+/- mice. MoSeq reveals altered motor pattern in Scn1a+/- mice across development, while hyperactivity only emerges in young adult mice. DLC tracking of multiple mice captures three types of social interactions. Scn1a+/- mice have reduced social interaction driven by a specific decrease in side by side huddling among Scn1a+/- dyads.

Conclusions: Our findings highlight striatal interneuron dysfunction as an underexplored locus of pathology in DS. The delayed and persistent impairment in striatal PV INs is compelling as this pattern aligns with the observation in mice and human patients of early severe epilepsy that improves over time while ASD features emerge and persist. High throughput machine learning based analysis of spontaneous behavior across development uncovers detailed quantitative motor and social phenotypes relevant to ASD. We propose a novel combination of intersectional genetic tools to probe the roles of PV and SST INs in seizures vs motor and social phenotypes. These findings will identify the key cell types and circuits involved in epilepsy vs ASD features in DS which informs how emerging genetic and cellular therapies for DS could be targeted to improve both epilepsy and developmental outcomes.

S291: Polygenic Risk Predicts Seizure Control in Drug-resistant Focal Epilepsy

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Background: Drug-resistant focal epilepsy (DRE) affects ~30% of focal-epilepsy patients. Outcome within DRE is heterogeneous: some patients become seizure-free with continued medical or surgical management, while others remain refractory. We tested whether polygenic risk scores derived from three International League Against Epilepsy (ILAE) GWAS - all epilepsy, focal epilepsy, and generalized genetic epilepsy - stratify seizure-control outcome within DRE.

Methods: From the Mass General Brigham (MGB) Biobank, we identified a cohort of 412 European-ancestry adults with

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focal epilepsy from whom SNP genotyping was available. We defined a 4-level severity outcome combining refractoriness and current seizure status: L1 (never-refractory, seizure-free; n=119); L2 (never-refractory, ongoing; n=28); L3 (refractory, currently seizure-free; n=75); L4 (refractory, ongoing; n=85). PRS-Epi (all epilepsy), PRS-FE (focal epilepsy), and PRS-GGE (generalized genetic epilepsy) were computed via the GenoPred pipeline (LDpred2-auto, PRS-CS, lassosum) from ILAE Consortium GWAS summary statistics. We fit multinomial regression adjusted for demographics, MRI, EEG, 10 PCs, seizure types, comorbidities, ASM count, and surgery, and trained a binary L4-vs-L3 elastic-net classifier with 10-fold cross-validation. Sensitivity analyses included Firth-penalized multinomial and within-resection analysis.

Results: Per 1-SD increase in PRS-GGE, the fully-adjusted odds ratio for L4 versus L3 was 2.82 (95% CI 1.54–5.18, p<0.001), preserved under Firth-penalized sensitivity (OR 2.13, 95% CI 1.27–3.57, p=0.004) and consistent across alternative PRS calculation methods (PRS-CS OR 2.85, p=0.001; lassosum OR 2.39, p=0.003). The effect was trait-specific: PRS-Epi (OR 1.65, p=0.08) and PRS-FE (OR 1.05, p=0.86) were attenuated and non-significant. The binary L4-vs-L3 elastic-net classifier achieved 10-fold cross-validation AUROC 0.79; PRS-GGE was the second-most-important predictor by both mean SHAP value and partial pseudo-R^2 (ΔMcFadden = 0.116, $p<10^{-5}$), behind only disease duration. Among 51 patients who underwent resective surgery, each 1-SD increase in PRS-GGE was associated with reduced odds of postoperative seizure-freedom (OR 0.48, 95% CI 0.23–1.01, p=0.052), after adjustment for imaging findings. The effect was strongest in non-hippocampal-sclerosis patients (n=33; OR 0.32, 95% CI 0.12–0.81, p=0.017).

Conclusion: Polygenic risk for genetic generalized epilepsy stratifies seizure-control outcome within drug-resistant focal epilepsy and modulates postoperative seizure-freedom. These findings support a polygenic "intrinsic severity" axis distinct from etiology, and suggest that PRS may have utility in epilepsy prognosis. Limitations include single-center retrospective design and modest surgical sub-cohort sizes.

S292: Benchmarking AI-Driven Epilepsy History-Taking Through LLM-Based Virtual Standardized Patients and Interviewers

Presenting Author: *Christopher McGraw, Northwestern University, Chicago, IL*

Background: History-taking is the most time-consuming and variable component of the epilepsy encounter. AI-enabled patient interviews offer an opportunity to enhance the speed, consistency, and quality of care at low cost, but training AI to interview at expert level is challenging. We tested whether a fully simulated closed-loop system - LLM standardized patients (SPs) interviewed by LLM interviewers, with LLM transcript extraction - could accelerate development prior to real-world deployment.

Methods: Twenty epilepsy patient histories spanning four communication archetypes (concise/verbose × knows-history/poor-historian) and five complexity categories (first seizure, focal epilepsy, generalized epilepsy, medically complex, edge case) were authored. Claude Sonnet 4.6 served as virtual SP. Five AI interviewers (Sonnet 4.6, Haiku 4.5, GPT-4o, Llama 3.1 8B, Gemma 4 E4B) each interviewed every patient (100 interviews), covering 15 required topics including seizure semiology, current/past medications, investigations, surgery/devices, comorbidities, family history, risk factors, and status epilepticus. All five extractors (Opus 4.6, Sonnet 4.6, Haiku 4.5, Llama 3.1 8B, Gemma 4 E4B) independently processed each transcript (500 extractions). A weighted rubric scored 10 high-priority (HP) domains: seizure characterization, epilepsy type, current/past medications, refractoriness, investigations, surgery/devices, family history, risk factors, and status epilepticus. A linear model HP $\sim$ interviewer + extractor + archetype was fit (Type II ANOVA, Tukey HSD).

Results: Mean HP accuracy across extractions was 61.2% (SD 16.7%). Communication archetype dominated ($\eta^2 = 0.441$, $p < 0.001$): concise/knows-history patients reached 75.4% versus 48.8% for verbose/poor-historians. Interviewer and extractor identity each contributed modestly ($\eta^2 = 0.026$, $p < 0.001$), with no interviewer × extractor interaction ($p = 0.9998$); GPT-4o was the top interviewer (64.9%) and Sonnet 4.6 the top extractor (64.7%).

Pooled field-level accuracy was highest for epilepsy-type (84.7%; GPT-4o 90.0%) and seizure-type classification (83.4%); current-medication count reached 68.6% and refractory-epilepsy status only 53.0% (Sonnet 67.0%, Haiku 58.6% vs. Llama 38.0%, Gemma 35.4%). Average per-interview cost (interviewer + SP) ranged from $0.38 (GPT-4o) to $0.61 (Haiku); per-transcript extraction averaged $0.02 (Haiku), $0.09 (Sonnet), and $0.44 (Opus).

Conclusion: Our findings inform production model choice: (1) the null interviewer × extractor interaction permits independent best-and-cheapest selection per task; (2) prior-generation frontier models (Sonnet 4.6, Haiku 4.5, GPT-4o) suffice at roughly 5–10× lower per-token cost than current flagship reasoning models; (3) lightweight open-source models need more prompting and error handling and underperform on hard patient contexts, limiting production use. Full SP-and-interviewer simulation enables end-to-end deployment without patient or clinician recruitment, shortening lead time to clinical translation.

S293-K: Quantitative EEG Biomarkers to Support Clinical Trial Readiness in SYNGAP1-Related Disorders

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Background: SYNGAP1-related disorders (SYNGAP1-RD) are rare neurodevelopmental conditions characterized by developmental impairment, epilepsy, and substantial clinical heterogeneity. As disease-modifying therapies advance toward clinical trials, there is an urgent need for objective, scalable

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biomarkers that can quantify disease severity, track disease trajectory, and detect treatment response. Quantitative EEG (qEEG) offers a promising approach by providing noninvasive, reproducible measures of brain function that can be collected longitudinally across clinical sites. This study aims to identify and validate qEEG biomarkers in SYNGAP1-RD that correlate with clinical severity and developmental outcomes, with the goal of supporting endpoint development for future disease-modifying therapeutic trials.

Methods: Resting-state EEG data were obtained from individuals with SYNGAP1-RD enrolled in the prospective ProMMiS natural history study, as well as from age-matched control participants. Recordings were processed using a standardized quantitative EEG workflow adapted from previously published methods (Galer, McKee et al., Neurology, 2025). The pipeline included artifact removal, selection of stable EEG epochs, and Welch-based spectral analysis to estimate regional power within canonical frequency bands. Relative power and band-power ratios were then computed across scalp regions. Random forest classifiers were trained to differentiate individuals with SYNGAP1-RD from controls, and model-derived feature importance was used to prioritize the spatial–spectral features most strongly contributing to classification as candidate biomarkers. Clinical relevance of EEG-derived features was assessed by examining associations with standardized developmental measures, including Bayley-4 and GMFM-66 scores, and seizure histories collected contemporaneously with the EEG recordings.

Results: Random forest models demonstrated robust performance in distinguishing EEGs from individuals with SYNGAP1-RD from controls (AUC 0.86), and occipital alpha/theta ratios emerged as the most informative feature by Gini importance. Furthermore, several spectral EEG features including the occipital alpha/theta ratio demonstrated significant correlations with standardized developmental outcome measures, such as the GMFM-66 (rho=0.42, p=0.04), supporting their use as quantitative markers of disease severity. While seizures are abundant in SYNGAP1-RD, there were no correlations identified between seizure frequency and occipital alpha/theta ratio, with p>0.05 for frequency of myoclonic, atonic, and absence seizures, as well as the overall seizure frequency score.

Conclusions: qEEG-derived spectral features prioritized through a machine learning-based pipeline represent reproducible, spatially specific biomarkers in SYNGAP1-RD. Reduced occipital alpha/theta in SYNGAP1-RD represents a disorder-specific signature that correlates with developmental outcomes. Furthermore, these qEEG spectral features are independent of seizure frequency scores, suggesting they may represent surrogate developmental markers not confounded by epilepsy severity. These findings support qEEG biomarkers as objective, scalable clinical trial endpoints for tracking disease progression and treatment response in SYNGAP1-RD.

S294-K: Semi-Self-Supervised Representation Learning of Spike Waveforms Reveals Emergent Excitatory-Inhibitory Organization

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Background: Distinguishing excitatory from inhibitory neuronal activity on microelectrode local field potential recordings is important for understanding seizure mechanisms and cognitive processing. Current approaches require manual spike sorting followed by post-hoc classification using waveform features, limiting scalability. We aimed to develop a self-supervised framework that learns rich spike waveform representations without explicit cell-type labels, and to evaluate whether biologically meaningful structure — including excitatory/inhibitory identity — emerges from the learned embeddings.

Methods: We used a manually curated waveform dataset recorded from multichannel silicone probe recordings from 5 PV-Cre32 optogenetically tagged mice from the Buzsaki open access Datashare. When presented with an optogenetic pulse, parvalbumin-positive inhibitory interneurons are silenced, allowing for ground-truth classification of units. We further tested the method on the raw recording of a sixth mouse without manually sorted units. We extended the Barlow Twins self-supervised framework with unit-aware positive pair sampling: during training, two spikes from the same neuron are independently augmented with realistic perturbations (noise injection, amplitude scaling, baseline shifts) and encoded by a deep fully connected network. The loss function drives same-unit embeddings toward agreement while decorrelating embedding dimensions to prevent collapse. No cell-type labels are provided during training. We evaluated generalization using leave-one-mouse-out cross-validation and assessed emergent structure via UMAP visualization and cosine similarity analysis.

Results: We used ~2.67 million waveforms arising from the 5 mice. The learned representations exhibited clear emergent organization in held-out mice unseen during training. Spikes from individual neurons formed tight clusters in embedding space, and excitatory and inhibitory populations separated into distinct regions despite the absence of cell-type supervision. The method showed excellent excitatory/inhibitory waveform classification in leave-one-mouse-out testing (ROC-AUC range 0.9-0.99; average 0.95). Cosine similarity matrices sorted by cell type confirmed high within-class similarity and between-class differentiation. In the sixth mouse, our method accurately detected the dropout of inhibitory firing and reciprocal increase in excitatory firing during the optogenetic stimulations.

Conclusions: Self-supervised learning on spike waveforms discovers cell-type identity without manual labels, providing a scalable foundation for downstream analyses in epilepsy and cognitive neuroscience research. Our approach extends the Barlow Twins redundancy-reduction framework from image processing with a novel unit-aware positive pair sampling.

S295: TSC-Associated SEGA in the Era of Everolimus: A Case Series on Variable Epilepsy Outcomes

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Background: Tuberous sclerosis complex (TSC) is a multisystem genetic disorder commonly associated with epilepsy and sub-ependymal giant cell astrocytoma (SEGA), which occurs in approximately 5–15% of TSC patients worldwide, with similar estimates reported in India. SEGA typically present in childhood and may lead to complications such as obstructive hydrocephalus. Although mTOR inhibitors such as Everolimus have transformed management, surgical intervention continues to play an important role in selected cases. We present a case series highlighting epilepsy evolution and outcomes following medical and surgical management of SEGA.

Methods: This observational, retrospective, single-center case series included 5 pediatric patients with TSC and radiologically confirmed SEGA. Clinical data was collected from electronic medical records and analyzed.

Results: Of 120 diagnosed cases of TSC, 5 were found to have SEGA. The mean age of the cohort was 5.6 years, with a median age of 5 years (IQR 3-8.5; Range 2-11). The cohort included 4 males and 1 female. All patients had drug-resistant epilepsy with heterogeneous seizure types, including focal, generalized, and polymorphic patterns. All five received Everolimus therapy, and 3/5 patients underwent surgical intervention for SEGA due to hydrocephalus, associated tumor, or prior progression, while 2/5 were managed conservatively. Postoperative epilepsy outcomes were variable. Among operated patients, 1/3 demonstrated a 50–60% reduction in seizure frequency, from daily epileptic spasms to 3–4 episodes/month. In contrast, 2/3 had persistent epilepsy with evolution into multifocal or generalized seizure types, with frequencies ranging from 1 episode/week to multiple episodes/weeks. None achieved complete seizure freedom. Surgical intervention resulted in radiological resolution or stabilization of SEGA in all operated patients, particularly in those with hydrocephalus. Patients managed with Everolimus alone demonstrated tumor stability but continued to have seizures. Follow-up (Median-9 months; Range 6–18 months) showed a persistent seizure burden despite effective tumor control, suggesting that seizure burden may be independent of tumor response and related to underlying cortical pathology in TSC.

Conclusion: Despite universal Everolimus therapy, a significant proportion of TSC patients required surgical intervention for SEGA. While surgery effectively controlled tumor-related complications, its impact on epilepsy was heterogenous, with no patients achieving seizure freedom. These results highlight that MRI surveillance remains indispensable for early detection and surgical timing. Optimal outcomes necessitate a tailored, multidisciplinary integration of medical and surgical expertise. Our series confirms the recalcitrant nature of epilepsy in TSC and the vital role of surgery, even amidst advances in mTOR inhibition.

S296: Biological Biomarkers of Post-Stroke Seizures After Ischemic Stroke: A Systematic Review and Meta-Analysis

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Background: Post-stroke seizures complicate ischemic stroke and are associated with worse outcomes and long-term morbidity. Clinical risk scores show only modest predictive accuracy, and biological biomarkers remain underexplored as complementary risk-stratification tools. We aimed to identify and synthesize biological biomarkers associated with post-stroke seizures in ischemic stroke populations and classify the evidence by inferential strength.

Methods: PubMed/MEDLINE, Embase, and Cochrane CENTRAL were searched through March 2026. Adult ischemic stroke studies evaluating blood, cerebrospinal fluid (CSF), or genotype-linked biomarkers in relation to post-stroke seizures were included. Evidence was classified as prognostic/longitudinal, discriminative, or susceptibility-pathway. Random-effects meta-analysis with Hartung-Knapp-Sidik-Jonkman (HKSJ) sensitivity analysis was performed for continuous neutrophil-to-lymphocyte ratio (NLR).

Results: Twenty-one studies (71,789 report-level; approximately 28,900 unique participants) were included: 12 prognostic/longitudinal, 5 discriminative, and 4 susceptibility-pathway. Three 2026 reports evaluating atherogenic index of plasma (AIP), serum uric acid, and C-reactive protein-to-albumin/lymphocyte-to-albumin ratios (CAR/LAR) arose from the same 21,459-patient cohort and were treated as non-independent. For late seizure prediction (>7 days), strongest signals were IL-1β plus SeLECT score (AUC 0.933), AIP (OR 1.56 per SD), CAR/LAR (AUC 0.888), and a replicated U-shaped association for serum uric acid across two independent studies. For seizure recurrence, IL-1β mRNA (HR 2.057; AUC 0.803) and IL-6 mRNA (AUC 0.763) were leading signals. Continuous NLR pooled across 3 studies with mixed early and late seizures yielded a ratio of 1.067 (95% CI 1.027–1.109; I^2=0%), but the HKSJ interval crossed unity (0.981–1.161). In case-control analyses, CSF GABA (AUC 0.906) and serum neuropeptide Y (AUC 0.910) were the strongest signals.

Conclusion: NLR is the only poolable biomarker for post-stroke seizures but remains exploratory. IL-1β within clinical risk models, serum uric acid, AIP, CAR/LAR, NPY, and CSF GABA appear among the more promising biomarkers for further study, but overall certainty remains low to very low and prospective validation is needed.

S297: Medication Affordability and Seizure Control in U.S. Adults With Active Epilepsy: A Nationally Representative Cross-Sectional Analysis

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Background: Persistent seizures remain common among adults with active epilepsy and are associated with substantial morbidity, reduced quality of life, and increased healthcare utilization. However, the population-level contribution of cost-related medication underuse and limited access to neurologist or epilepsy specialist care to poor seizure control is not well characterized.

Methods: We conducted a cross-sectional analysis of pooled 2021–2023 National Health Interview Survey (NHIS) Sample Adult data. Active epilepsy was defined using the standard CDC/NHIS case definition. Uncontrolled seizures were defined as at least 1 seizure in the prior 12 months. Primary exposures were (1) any cost-related medication underuse, including skipping doses, taking less medication, delaying refills, or not obtaining prescriptions because of cost, and (2) no neurologist or epilepsy specialist visit in the prior year. Survey-weighted logistic regression was used to estimate adjusted odds ratios (aORs), controlling for age, sex, race/ethnicity, education, income-to-poverty ratio, insurance status, and census region. Prespecified sensitivity analyses included restriction to antiseizure medication users, item-level exposure models, and stratification by income.

Results: Among 1,014 adults with active epilepsy, the weighted prevalence of active epilepsy was 1.23%, representing approximately 3.1 million U.S. adults. Overall, 54.3% reported uncontrolled seizures, 15.5% reported cost-related medication underuse, and 34.5% reported no recent specialist visit. Uncontrolled seizures were more common among those reporting cost-related medication underuse than among those who did not (74.7% vs 50.1%). In the fully adjusted model, cost-related medication underuse was independently associated with uncontrolled seizures (adjusted OR 2.08, 95% CI 1.26–3.45; p=0.005), whereas no recent specialist visit was not (adjusted OR 0.76, 95% CI 0.53–1.11; p=0.15). Sensitivity analyses were consistent. The association remained significant among antiseizure medication users, and delayed prescription filling showed the strongest item-level association (adjusted OR 3.15, 95% CI 1.67–5.93).

Conclusion: Cost-related medication underuse was robustly associated with uncontrolled seizures in U.S. adults with active epilepsy, whereas recent specialist access was not in this cross-sectional analysis. Medication affordability may represent a practical, modifiable target for improving seizure outcomes.

S298-K: Frequency-Specific Thalamocortical Network Dynamics During Focal Seizures in Humans

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Background: The thalamus is increasingly targeted for neuromodulation in drug-resistant epilepsy, including responsive neurostimulation and stimulation strategies. However, the temporal, frequency-specific, and directional features of thalamocortical involvement during human focal seizures remain incompletely defined. We sought to characterize thalamocortical network dynamics across seizure evolution, compare them with cortico-cortical propagation, and determine whether thalamic signals contain seizure-state information relevant to responsive and adaptive thalamic neuromodulation.

Methods: We retrospectively analyzed stereo-electroencephalography (SEEG) recordings from 19 patients with pediatric-onset drug-resistant focal epilepsy who underwent simultaneous cortical and thalamic sampling, comprising 66 focal seizures. Thalamic electrodes sampled the anterior nucleus (AN) and/or centromedian nucleus (CM). SEEG signals were analyzed in bipolar montage across preictal, early ictal, end-of-seizure, and postictal epochs relative to interictal baseline. Thalamic ictal patterns were visually classified by epileptologists. Spectral power, imaginary coherence, and spectral Granger causality were computed in slow (1–12 Hz), beta (13–30 Hz), and gamma (30–70 Hz) bands to quantify local thalamic activity, thalamocortical synchronization, and directed interactions between thalamic nuclei and the seizure onset zone (SOZ). Cortico-cortical interactions were analyzed for comparison. Random forest classifiers using temporally resolved thalamic features were trained separately for AN and CM to distinguish ictal from non-ictal states using leave-one-patient-out cross-validation; feature contributions were assessed using ablation analyses and SHAP values.

Results: The cohort included 1,599 SEEG contacts, including 101 thalamic contacts. Thalamic ictal activity was present at seizure onset in most sampled contacts and became nearly universal by seizure termination. Visual patterns evolved from low-voltage fast activity at onset toward rhythmic spike/spike-wave or rhythmic slow-wave activity at termination. Both the thalamus and SOZ showed early broadband spectral power increases, followed by attenuation after seizure termination. Slow- and beta-band thalamic power were especially prominent near seizure termination. Thalamocortical imaginary coherence increased during seizures, most consistently in slow and beta bands during ictal and end-of-seizure periods. Directed connectivity analyses demonstrated bidirectional thalamocortical interactions dominated by slow and beta frequencies. Slow-frequency outflow from both AN and CM toward the SOZ exceeded propagation-zone-to-SOZ cortico-cortical outflow during ictal and end-of-seizure periods, suggesting that late ictal thalamocortical engagement was not

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simply a passive reflection of cortical spread. Exploratory subgroup analyses suggested stronger AN–SOZ connectivity in limbic seizures and greater slow-band connectivity in seizures with rhythmic spike/spike-wave or rhythmic slow-wave onset patterns. Thalamic features classified seizure state with mean AUROC values of 0.825 $\pm$ 0.163 for AN and 0.839 $\pm$ 0.149 for CM. Performance improved when thalamocortical connectivity and directed-connectivity features were
added to spectral power alone. Key predictors included thalamic slow/beta power, slow-frequency thalamus-to-SOZ outflow, and beta-frequency SOZ-to-thalamus inflow.
Conclusions: Human focal seizures engage dynamic, frequency-specific, and direction-specific thalamocortical interactions that evolve from seizure onset to termination. The prominence of slow- and beta-band bidirectional thalamocortical coupling, particularly during late ictal stages, suggests that thalamic involvement is a structured component of ictal network evolution and is not fully captured by cortico-cortical propagation alone. Together, the temporally resolved classification of seizure state from thalamic features and the identification of frequency- and direction-specific thalamocortical signatures support the potential utility of thalamic biomarkers for responsive and adaptive neuromodulation strategies that detect seizures, track evolving ictal network states, and trigger or adjust stimulation accordingly. Prospective studies are warranted to test whether these thalamocortical biomarkers can improve seizure detection and individualized thalamic stimulation strategies in drug-resistant epilepsy.

S299: Development of an On-demand Preclinical Model of the Postictal State

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Background: The postictal state, the period spanning from seizure cessation to return to baseline, is characterized by a range of signs and symptoms including EEG slowing and attenuation, impaired arousal, and cognitive and behavioral deficits. The postictal state is typically significantly longer than the precipitating seizure, and indeed many patients rate it as the most burdensome aspect of their epilepsy. While we now have over 30 FDA-approved anti-seizure medications, we lack therapeutic tools targeted to the postictal state. Progress on this front has been limited by the absence of reliable and well-characterized preclinical models. The Scn1a+/- mouse model of Dravet Syndrome is well-characterized as an epilepsy model and has the experimentally advantageous feature of naturalistic seizures that can be triggered on-demand via hyperthermia. We postulated that Scn1a+/- mice could similarly serve as an on-demand postictal model. Here, we therefore sought to characterize the postictal period in Scn1a+/- mice.
Methods: Hyperthermic seizures were acutely triggered in Scn1a+/- mice using a heat lamp placed over the induction chamber. Each Scn1a+/- mouse was heated in tandem with a wildtype (WT) littermate control. A rectal temperature probe was secured in an additional WT mouse (which was also heated), thus enabling untethered behavioral observation of the experimental mice. Heating continued until behavioral seizure onset (in the Scn1a+/-mouse) or 42.5 °C (internal body temperature of the probe mouse); the Scn1a+/- and WT control mice were then transferred to opaque, room-temperature recording chambers for 1 hour of video recording. Analysis was performed using LabGym, an AI-based software used to identify and measure behaviors. LabGym's motion-tracking software was used to analyze distance traveled, whereas the categorizer software was used to distinguish between immobility and quiet wakefulness.
Results: The postictal state in adult Scn1a+/- mice was reliably characterized by a significant reduction in spontaneous locomotion – and with further reduction of the quiet wakefulness state as measured by the categorizer – compared to heated WT controls. Preliminary analyses across successive seizures suggest a stable within-mouse phenotype in adult mice. Additional analyses to characterize effects of age and sex are ongoing.
Conclusion: A behavioral postictal state can be reliably triggered in Scn1a+/- mice following hyperthermic seizures. This postictal state consists of markedly reduced spontaneous activity, modeling the impaired arousal often seen following bilateral tonic-clonic seizures. This on-demand postictal model offers an experimentally tractable platform that can be used to test intervention aimed at reducing postictal symptom burden.

S300-K: Optimizing Sleep Architechture and Cognitive Function in New-Onset Temporal Lobe Epilepsy

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Background: Accumulating evidence indicates that individuals with new-onset temporal lobe epilepsy (TLE) frequently exhibit comorbid sleep disturbances and cognitive dysfunction. Prior studies suggest that acoustic stimulation (AS) during sleep may enhance sleep architecture and improve cognitive performance. However, the presence and clinical significance of sleep architecture abnormalities in recent-onset TLE remain unclear. This study examined sleep architecture and its association with cognitive functioning in young adults with new-onset TLE.
Methods: Thirty youth with new-onset TLE (aged 18-25 years) were compared with 30 age- and sex-matched healthy controls. Participants underwent overnight polysomnography using standard 10–20 PSG monitoring, one night with AS and one night without AS. Sleep spindle density, slow-wave oscillations, and spindle–slow-wave coupling were evaluated. In addition, participants completed comprehensive neuropsychological testing assessing intelligence, language, immediate & delayed verbal memory, executive function, and processing speed. To determine clinical

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predictors, clinical epilepsy characteristics (age of onset, seizure syndrome, seizure frequency and antiseizure medication), and magnetic resonance imaging (MRI) and electroencephalography (EEG) abnormalities were also collected.

Results: Compared with controls, individuals with TLE demonstrated reduced sleep spindle density, diminished slow-wave oscillations, and weaker spindle–slow-wave coupling, which improved with acoustic stimulation.

Immediate and delayed verbal memory performance also improved post-stimulation TLE group. Clinical predictors indicated that earlier age of epilepsy onset was associated with greater alterations in sleep architecture. In addition, higher rates of interictal epileptiform discharges were associated with more severe sleep-related abnormalities.

Conclusions: These findings demonstrate that alterations in sleep architecture are present early in the course of TLE and are associated with cognitive dysfunction. The results further suggest that sleep-based interventions targeting spindle and slow-wave activity may represent a promising avenue for improving cognitive outcomes in this population. Future studies should evaluate the long-term therapeutic potential of optimizing sleep architecture in new-onset TLE.

S301: Can Large Language Models Assist in Differentiating Epileptic from Non-Epileptic Events in Epilepsy Monitoring Unit (EMU) Videos?

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Background: Large language models (LLMs) are increasingly being used to interpret patient-generated video to different epileptic from functional seizures, though video quality can be a significant limitation to analysis and interpretation. Because semiology influences real-world seizure triage and diagnostic reasoning, poor model performance in this setting could have direct clinical consequences. EMU video recordings are higher quality and demonstrate more consistent and reliable visualization and recording of patient semiology, though their usefulness in testing and training AI algorithms has not been assessed. We evaluated the diagnostic accuracy and agreement characteristics of three Gemini-family LLMs in classifying EMU video recordings as epileptic or functional.

Methods: Fifty-two video-EEG monitoring recordings with neurologist-annotated ground truth were analyzed using Gemini 2.0 Flash, Gemini 2.5 Flash, and Gemini 2.5 Pro. One Gemini 2.5 Pro output was non-evaluable, leaving 51 cases for that model. Performance metrics included accuracy, balanced accuracy, sensitivity, specificity, precision, F1 score, Cohen's kappa, and Matthews correlation coefficient (MCC). Inter-model agreement was assessed using pairwise Cohen's kappa and raw percentage agreement.

Results: Overall discrimination was poor across all models. Accuracy ranged from 0.44 to 0.48, and balanced accuracy from 0.49 to 0.56. Sensitivity for epileptic events was uniformly low: 0.13 for Gemini 2.0 Flash, 0.23 for Gemini 2.5 Flash, and 0.39 for Gemini 2.5 Pro. Gemini 2.0 Flash correctly identified only 4 of 31 epileptic seizures, but produced no false positives among 21 functional seizure recordings, yielding specificity and precision of 1.00 and an F1 score of 0.23. Gemini 2.5 Flash detected 7 of 31 epileptic events, with specificity 0.76, precision 0.58, and accuracy 0.44. Gemini 2.5 Pro showed the most balanced, though still inadequate, profile, correctly identifying 12 epileptic seizures, generating 8 false positives, (sensitivity 0.39, specificity 0.60, precision 0.60, and highest F1 score 0.47). Agreement with neurologist ground truth was negligible or worse after correction for chance (kappa 0.107, -0.011, and -0.012; MCC 0.238, -0.014, and -0.013 for Gemini 2.0 Flash, 2.5 Flash, and 2.5 Pro, respectively). Inter-model agreement was similarly limited (pairwise kappa 0.011-0.292; raw agreement 60.8%-73.1%). No subset of recordings was consistently identified across all three models.

Conclusion: Gemini LLMs showed poor and clinically unreliable performance in differentiating epileptic from functional seizures on EMU videos. Newer models shifted the sensitivity–specificity balance without improving agreement with expert interpretation, underscoring the need for task-specific AI development using expert-reviewed EMU data.

S302-LB: Outcomes of Laser Ablation in Drug-Resistant Focal Epilepsy Among Older Adults

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Background: Laser interstitial thermal therapy (LITT) is a minimally invasive treatment for drug-resistant epilepsy (DRE), which may be particularly useful when comorbidity precludes open resection. Yet LITT outcomes in older adults remain unexplored.

Methods: Of 67 included individuals (LITT age: Younger=31.1±11.2, Older=59.2±5.3, p<0.001), 48% were female (Younger=48%, Older=46%). Compared with younger adults, older adults had later seizure onset (Older=30.2±15.8 vs Younger=14.4±10.4 years, p=0.001), longer epilepsy duration (Older=29.5±17.1 vs

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Younger=17.3±13.2 years, p=0.014), higher CCI (Older=2.6±1.9 vs Younger=0.6±1.0, p<0.001), and higher education (Older=14.1±2.1 vs Younger=12.4±2.7, p=0.048). Pre-op FBTCS frequency was lower in older adults (p=0.022). Seizure outcomes were comparable at years 1 (Engel I: Younger=63.8% vs Older=80.0%, p=0.469), 2, 3, 4, 5, and the most recent follow-up. In the logistic model for 1-year outcomes, age group did not influence outcomes; unifocal MRI lesion was the only significant predictor (OR=8.43, 95% CI=1.79–54.2, p=0.012). Post-op focal-impaired-awareness seizure(FIAS) frequency was lower in older adults(p=0.013). Peri-operative complications occurred in 27.8% of younger and 0% of older adults(p=0.031). Pre-op depression was more prevalent (Older=92% vs Younger=63%, p=0.049), and there was higher rates of post-operative depression resolution in older adults (Older=23% vs Younger=9.3%,p=0.05). Two non-LITT-related deaths occurred in younger several years later; none in older adults.

Results: Older adults compared to younger adults achieved comparable post-LITT seizure freedom through 5 years and better FIAS outcomes despite later seizure-onset, longer epilepsy duration, and greater comorbidity. Unifocal MRI lesion was the strongest predictor of 1-year outcomes. Older adults tolerated LITT well with no surgical complications, compared with 27.8% in younger adults. Older adults demonstrated more pre-operative depression and more post-op depression resolution. For the first time, our findings support the efficacy and safety of LITT in older adults with DRE.

Conclusion: We conducted a single-center retrospective study of 67 adults with DRE who underwent LITT between November 2015 and December 2025. Individuals were stratified into younger(<50 years, n=54) and older(≥50 years, n=13) groups. The primary outcome was Engel outcome at 1-year. Secondary outcomes included Engel outcomes at 2, 3, 4, and 5 years and the most recent follow-up, seizure frequency reduction, surgical complications, mood outcomes, and mortality. Group comparisons used Fisher's exact for categorical and Wilcoxon rank-sum tests for continuous variables. A multivariable logistic regression for Engel I at 1-year was performed, adjusting for age group, epilepsy duration, MRI findings, history of focal-to-bilateral tonic-clonic seizures (FBTCS), mesial temporal versus extra-mesial epileptogenic zone, Charlson Comorbidity Index(CCI), and pre-operative seizure frequency.

S303: Neurologic Spectrum and Outcomes in GPI-Anchor Deficiency related Congenital Disorders of Glycosylation: Insights from the Natural History Study from Frontiers in CDG Consortium

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Background: Glycosylphosphatidylinositol (GPI)-anchor related congenital disorders of glycosylation (GPI-CDG) are a rare, genetically and clinically heterogeneous group of inborn errors of metabolism caused by pathogenic variants in genes involved in GPI-anchor biosynthesis and remodeling. Systematic characterization of neurologic phenotypes, disease trajectories, and outcomes across the genotypes remains limited. We aimed to delineate the neurologic spectrum from the first natural history study of this ultra-rare group of disorder.

Methods: We analyzed prospectively collected data from individuals enrolled in the FCDGC natural history study between 2018 and 2025. Comprehensive review and analysis were performed to characterize neurodevelopmental profiles, seizure types and outcomes, electroencephalographic (EEG) findings, and brain MRI findings.

Longitudinal data were used to assess neurologic progression and clinical outcomes.

Results: Thirty-one individuals with pathogenic variants in GPI-anchor biosynthesis or remodeling genes (PIGA, PIGG, PIGT, PIGS, PIGN, PIGO, PIGV, PIGW, GPAA1, PGAP1, and PGAP3) were identified. Age at diagnosis ranged from infancy to adulthood, with follow-up extending up to 6.3 years. Global developmental delay was universal, ranging from mild impairment to profound encephalopathy with minimal milestone attainment. Epilepsy was present in 24/31 individuals, typically with early-infantile onset epileptic encephalopathy. Seizure types were heterogeneous and included focal and generalized tonic-clonic seizures, myoclonic, atonic, atypical absence seizures, and epileptic spasms; infection-triggered status epilepticus occurred in several individuals. EEG findings ranged from normal to multifocal epileptiform discharges, hypsarrhythmia, and Lennox–Gastaut syndrome. Only few achieved sustained seizure remission on levetiracetam or pyridoxine monotherapy, while most experienced drug-resistant epilepsy despite polytherapy, ketogenic diet, or vagus nerve stimulation. Additional neurologic features include autistic features, movement disorders (ataxia, dystonia), hearing impairment, and congenital anomalies. Early mortality occurred in severe phenotypes associated with PIGO, PIGV, and PIGN. MRI brain revealed progressive cerebellar atrophy predominantly in PIGA and PIGT related disorders, combined cerebellar and cerebral atrophy in PIGN, delayed myelination in PGAP3, and structural abnormalities including Blake pouch cyst with hydrocephalus in PIGT.

Conclusion: Despite marked genetic heterogeneity, GPI-CDG disorders share a core neurologic phenotype characterized by global developmental impairment and a high burden of early onset, frequently drug-resistant epilepsy. Genes involved in earlier steps of GPI-anchor biosynthesis are associated with more severe neurodevelopmental outcomes and poorer seizure control, whereas later-step or remodeling genes demonstrate greater phenotypic variability. These findings support a system-level model in which the timing and extent of GPI-pathway disruption determine downstream neuronal network dysfunction, providing a framework for prognostication, clinical management, and future therapeutic studies.

S304: Medical Cannabis in Pediatric Epilepsy: An Ethical Analysis of Consent, Access, and Long-Term Safety

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Background: Epilepsy affects millions of children worldwide, and a significant subset experience seizures refractory to conventional antiseizure medications. Cannabidiol (CBD) has emerged as a therapeutic option for treatment-resistant pediatric epilepsy, culminating in FDA approval of pharmaceutical-grade CBD (Epidiolex) for Lennox-Gastaut syndrome and Dravet syndrome. Despite this approval, cost and regulatory barriers lead many families to pursue artisanal CBD formulations of variable composition and uncertain safety profiles. As medical cannabis use grows in pediatric epilepsy, the ethical dimensions surrounding informed consent, equitable access, and long-term safety uncertainty demand closer examination. Our objective was to examine the ethical dimensions surrounding medical cannabis use in pediatric epilepsy, focusing on informed consent, parental decision-making, equitable access, off-label use, and long-term safety uncertainty using the four core principles of biomedical ethics as an analytical framework.

Methods: A narrative review was conducted using PubMed. Search terms included cannabidiol, pediatric epilepsy, Dravet syndrome, Lennox-Gastaut syndrome, informed consent, off-label use, medical ethics, health disparities, and long-term safety. Articles published between 2021 and 2026 were synthesized across pediatric neurology, pharmacology, bioethics, and health equity.

Results: Significant ethical tensions exist across all four bioethical principles. Regarding autonomy, children cannot consent for themselves, placing decisional burden on parents whose enthusiasm may outpace available evidence.

Regarding beneficence, Epidiolex demonstrates meaningful efficacy in treatment-resistant pediatric epilepsy, with a systematic review confirming significantly higher seizure reduction compared to placebo, sustained efficacy over 60 months, and higher quality of life and medication tolerability among users. Regarding non-maleficence, CBD formulations used outside FDA-approved indications lack equivalent evidentiary support, with quality of life improvements inconsistently demonstrated - improving in some studies and showing no significant change after six months in others. Artisanal CBD products carry additional concerns including variable cannabinoid concentration, tolerance development, drug-drug interactions, and absent regulatory oversight. Non-medical cannabis carries further risks including psychoactive effects and pulmonary complications. Regarding justice, Epidiolex cost and regulatory barriers drive families toward artisanal formulations. 59% of patients continuing artisanal CBD beyond one year showed greater than 50% seizure reduction, suggesting real clinical rationale exists despite disproportionate impact on lower-income populations.

Conclusion: Medical cannabis in pediatric epilepsy presents a complex ethical landscape beyond clinical efficacy. The pharmaceutical-grade versus artisanal CBD distinction is central, as access inequities drive vulnerable families toward less regulated alternatives. Child neurologists must simultaneously navigate consent challenges, access disparities, and safety uncertainties. Standardized informed consent frameworks, equitable access initiatives, and long-term safety surveillance are urgently needed across all pediatric epilepsy populations.

S305*: Thalamic Network Involvement Reshapes Treatment Selection in Drug-Resistant Epilepsy: Evidence from 104 Patients with Intracranial Thalamic Recordings

Presenting Author: *Mark Richardson, MD, PhD, Massachusetts General Hospital; Harvard Medical School, Boston, MA*

Co-Authors: *Catherine Chu, Cambridge, MA, Sydney Cash, Boston, MA*

Background: At least one-third of patients with epilepsy are drug resistant, and treatment response remains difficult to predict at the individual level. Converging evidence from imaging, neurophysiology, and neuromodulation trials has reframed epilepsy as a network disorder in which thalamic nuclei are active participants in seizure onset and propagation. Direct intracranial validation of this framework and its implications for treatment selection have been limited by small sample sizes and the absence of cohorts in which thalamic recordings inform real-world decisions.

Methods: We retrospectively analyzed 104 consecutive patients (median age 24, range 3–74; median age at first seizure 10) with drug-resistant epilepsy who underwent stereoelectroencephalography incorporating at least one thalamic trajectory at a single comprehensive epilepsy center between 2020 and 2025. A mean of 3.2 thalamic electrodes per patient sampled the anterior nucleus (n=66), centromedian (n=78), and pulvinar (n=58). Seizure classes included focal (34%), multifocal (36%), and developmental and epileptic encephalopathy (23%). We characterized the relationship between pre-SEEG and post-SEEG seizure-network hypotheses, the impact on treatment selection, and surgical safety and seizure outcomes.

Results: There were no complications related to thalamic sampling. The pre-SEEG seizure network hypothesis was revised in nearly half of patients, including laterality classification in approximately 20%. Among 89 patients who underwent therapeutic intervention, Responsive Neurostimulation System (RNS) therapy was the most common treatment (47%), and 86% of RNS strategies incorporated a thalamic target (most often centromedian, followed by pulvinar and anterior nucleus). For many thalamic RNS patients, the nucleus implanted differed from the pre-SEEG hypothesized primary thalamic node. Mean seizure reduction was 94% after resection, 93% after LITT, and 63% after RNS, with 30% of RNS patients reporting no seizures at last follow up.

Conclusion: Direct thalamic recordings confirm that drug-resistant epilepsy is frequently a thalamocortical network disorder and that thalamic electrophysiology is clinically actionable, defining neuromodulation candidacy and target in patients who would otherwise be deemed inoperable. These outcomes, in a cohort with predominantly multifocal epilepsy, would have been unattainable with resection-only candidacy criteria and support a network-based reconceptualization of treatment selection. The implications on referral, candidacy assessment, and longitudinal management of drug-resistant epilepsy are profound, as these decision steps determine whether patients access these therapies at all.

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S306: A Novel Synonymous Splicing Variant in KCNQ2 Leading to Neonatal Epilepsy

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Background: The KCNQ2 gene on chromosome 20q13.3 encodes a voltage-gated potassium channel subunit, Kv7.2, mediating M-currents in the central nervous system. Heterozygous KCNQ2 genetic variants are the most common cause of epilepsy in infants less than six months of age, with phenotypes ranging from self-limited neonatal epilepsy (SeLNE) to neonatal-onset epileptic developmental and epileptic encephalopathy (NEO-DEE). As neonatal genetic testing becomes more readily utilized, characterization of genotype-phenotype correlations of KCNQ2 variants are increasingly important.

Methods: We reviewed records of patients with KCNQ2 variants at a single center and identified one patient with self-limited neonatal epilepsy (SeLNE) who had a variant of unknown significance (VUS). We collected data on the patient's demographics, seizure semiology, neurodevelopmental outcome, MRI and EEG findings, and response to anti-seizure medications (ASMs). We used SpliceAI, a splicing prediction model, to determine the probability of the genetic variant to produce a novel splice site.

Results: A female neonate developed focal seizures at 3 days of life with seizure offset at 17 days of life. EEG showed right and left hemispheric independent seizures. Brain MRI was unremarkable. The patient's seizures responded to phenobarbital but not levetiracetam; phenobarbital was discontinued after 3 months of life without seizure recurrence. The patient has had normal neurodevelopment. A genetic epilepsy panel (Invitae) identified a de novo heterozygous c.543G>A KCNQ2 variant, leading to synonymous coding at the protein level (p.Ala181=). In ClinVar, this variant has conflicting pathogenicity classifications (Likely Pathogenic versus Uncertain Significance). Genetic testing did not reveal additional variants likely contributing to phenotype. To explore how this variant disrupts KCNQ2 function, we used SpliceAI, which predicted the c.543G>A variant causes a splice acceptor site gain two base pairs upstream (probability = 0.97/1.00). This novel acceptor site would cause removal of 30 nucleotides (c.515_544) from the messenger RNA sequence. In-silico predictions suggest that the c.515_544 deletion leads to the amino acid in-frame deletion p.Asp172_Ala181del. Notably, the canonical splice acceptor site remains intact. Thus, we approximate 25% of the patient's KCNQ2 gene product may be altered.

Conclusion: The KCNQ2 c.543G>A variant seemingly leads to synonymous protein coding. However, the patient's SeLNE phenotype and otherwise negative seizure workup suggest this variant perturbs KCNQ2 function. Splicing models predict the variant introduces a novel splice acceptor site, which may underly the variant's pathogenicity.

Likely retention of the original splice site aligns with the patient's self-limited clinical course. Our future in vitro investigations will help further elucidate the implications of the c.543G>A variant.

S307: The Risk of Remote Symptomatic Seizures Associated with Cerebral Microbleeds and Hemorrhagic Transformations in Patients with Ischemic Stroke

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Background: The presence of blood products in the setting of ischemic stroke may increase the risk of remote symptomatic seizures. However, limited studies have evaluated the impact of chronic bleeding in the form of cerebral microbleeds or acute hemorrhagic transformation on the risk of remote symptomatic seizures. We aimed to measure the risk of remote symptomatic seizures associated with cerebral microbleeds and hemorrhagic transformation in patients with ischemic stroke.

Methods: 963 patients with imaging evidence of supratentorial (middle cerebral artery, anterior cerebral artery, or posterior cerebral artery) ischemic strokes at Penn State University and available follow-up at 1-year post-stroke were included in the current analysis. Incident remote symptomatic seizures were identified as reported by a physician (as recorded in the medical record or any "yes" to the question "Have you ever been told by your doctor that you have seizures or epilepsy since your stroke?"). Cerebral microbleeds were evaluated according to the Standards for Reporting Vascular Changes on Neuroimaging. We used the European Cooperative Acute Stroke Study (ECASS II) classification to describe hemorrhagic transformation [Hemorrhagic Infarction (HI): This is further divided into HI1 (small petechial hemorrhages) and HI2 (more extensive hemorrhagic changes without mass effect). Parenchymal Hematoma (PH): This includes PH1 (hematoma with no mass effect) and PH2 (hematoma with mass effect)]. We applied a multivariable Cox proportional hazards model to determine the time to remote symptomatic seizure onset.

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Results: Data on remote symptomatic seizures at one year were available in 99.9% of participants. At one year, 47 patients (4.9%) developed seizures. Remote symptomatic seizures were more frequent in patients with severe stroke [Admissions National Institute of Health Stroke Scale (NIHSS), p-value 0.025; Discharge NIHSS, p-value 0.001] and acute symptomatic seizures, i.e. seizures occurring within 7 days of stroke (8.5% vs 2.5%, p-value 0.038).

Remote symptomatic seizures were more frequent in patients with cortical involvement (96% vs 78%, p-value 0.007) and with PH2 (15% vs 3.2%, p-value 0.001). Patients with greater than 10 microbleeds, including at least one cortical microbleed were more likely to have a remote symptomatic seizure, although it did not reach statistical significance (6.4% vs 1.6%, p-value 0.072). PH2 was an independent predictor of remote symptomatic seizures (p-value 0.001), unlike cerebral microbleeds.

Conclusion: In conclusion, parenchymal hematoma with mass effect (Parenchymal Hematoma-2), unlike cerebral microbleeds increased the risk of remote symptomatic seizures after ischemic stroke.

S308-K: Microbleed Burden Predicts Cognitive Impairment in Older Adults with Epilepsy

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Background: Older adults with epilepsy are at elevated risk for cognitive impairment and dementia, yet the biological mechanisms underlying this vulnerability remain incompletely understood. Although Alzheimer's disease pathology has been increasingly investigated in epilepsy, cerebrovascular small vessel disease (SVD) represents another potential contributor to cognitive decline. Emerging evidence suggests a complex relationship between epilepsy and cerebrovascular injury, whereby vascular pathology may promote seizures and seizure-related processes may further exacerbate vascular damage. However, the extent to which specific MRI markers of SVD contribute to cognitive dysfunction beyond normal aging, and whether cerebrovascular profiles differ between early- and late-onset epilepsy, remains unclear.

Methods: Ninety older adults with epilepsy (mean age 66.1±6.8 years, 57% female; 52 early onset <55 years, 38 late onset ≥55 years) underwent 3T MRI including quantification of white matter hyperintensities (WMH; deep and periventricular), perivascular spaces (PVS; basal ganglia and whole brain), and cerebral microbleeds. Cognitive assessment included the MoCA and an 8-test neuropsychological composite. Participants from ADNI (CN=339, MCI=303, AD=83) served as comparison groups for cerebrovascular burden and cognitive analyses. Principal components analysis (PCA) was used to characterize the latent structure of SVD markers.

Results: Participants with early-onset epilepsy demonstrated greater periventricular WMH burden than age-matched cognitively normal controls (p<.01), whereas late-onset epilepsy did not differ from controls. Basal ganglia PVS burden was lower in epilepsy than CN36 participants (p<.05), an effect more pronounced in the early-onset group. Microbleeds were observed in 27% of epilepsy participants, approximately double the prevalence observed in cognitively normal older adults (14%; OR=2.6, 95% CI 1.2–5.6, p<.05) and higher than in MCI participants (17%; OR=3.4, 95% CI 1.5–7.8, p<.01), despite comparable vascular risk burden. Microbleeds were the only SVD marker associated with cognition, demonstrating a dose-dependent relationship with MoCA performance (0 microbleeds=25.2, 1=24.5, ≥2=21.6; p<.01). This relationship was evident in both epilepsy groups but stronger among individuals with late-onset epilepsy. Comparable associations were not observed in ADNI CN or MCI participants. PCA identified a microbleed-related dimension independent of WMH/PVS burden (22.9% variance explained) that significantly predicted MoCA performance (p<.05).

Conclusions: Older adults with epilepsy exhibit a heterogeneous cerebrovascular profile in which conventional markers of SVD and cerebral microbleeds appear to carry distinct clinical significance. While elevated periventricular WMH burden characterized early-onset epilepsy, microbleeds emerged as the dominant cerebrovascular correlate of cognitive impairment and occurred at disproportionately high rates relative to aging comparison groups. The absence of similar microbleed-cognition associations in cognitively normal and MCI older adults suggests that epilepsy may amplify the cognitive impact of cerebrovascular injury. These findings identify microbleed burden as a promising marker of cognitive vulnerability in epilepsy and highlight potential contributions of vascular mechanisms, including blood-brain barrier dysfunction and cerebral amyloid angiopathy, to late-life cognitive outcomes.

S309: Seizure Remission in Focal Cortical Dysplasia: Clinical Factors versus Treatment Modality in a Multicenter Real-World Cohort of 495 Patients

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Background: Focal Cortical Dysplasia (FCD) is a leading cause of drug-resistant epilepsy and has been studied predominantly in surgery-based cohorts, where predictors of postoperative seizure outcomes have been the major focus. However, many patients with MRI-defined FCD are managed without surgery in clinical practice, and the real-world clinical spectrum of FCD remains poorly understood. This study aimed to identify independent predictors of seizure remission in patients with FCD and to compare the effectiveness of surgical and medical treatments using large-scale, real-world, multicenter data.

Methods: We retrospectively analyzed 495 patients with FCD from nine tertiary epilepsy centers in Republic of Korea, including 398 pathology-confirmed surgical cases and 97 MRI-confirmed nonsurgical cases. Patients with FCD involving both cerebral hemispheres or follow-up <1 year were excluded. The primary outcome was a 2-year seizure remission. Multivariable Cox proportional hazards models were constructed with stepwise adjustments for demographic, clinical, and electroencephalographic (EEG) variables. To reduce treatment selection bias, inverse probability of treatment weighting (IPTW) with a doubly robust analysis was performed.

Results: Among the 495 patients, 286 (57.8%) were male, and the median epilepsy duration was 63 months (interquartile range [IQR] 11–156.5). Overall, 65.0% achieved 2-year seizure remission, with a median time to remission of 30 months (IQR 24–66). In the fully adjusted Cox model, surgical treatment was not significantly associated with the probability of 2-year remission (hazard ratio [HR] 1.24, 95% CI 0.92–1.68, $P = 0.157$). The findings were consistent in the IPTW doubly robust analysis (HR 1.32, 95% CI 0.95–1.84, $P = 0.098$). A longer epilepsy duration predicted a lower likelihood of seizure remission (HR 0.998, $P = 0.003$). Compared with focal seizures alone, the presence of both focal and focal-to-bilateral tonic-clonic seizures was associated with a lower remission probability (HR 0.49, $P = 0.001$). Additionally, EEG-MRI concordance showed a marginal but favorable association with seizure remission (HR 1.33, $P = 0.051$).

Conclusion: In this large-scale real-world study, the seizure prognosis of FCD appeared to be driven largely by intrinsic clinical factors, particularly epilepsy duration and seizure type, rather than the treatment modality itself. Our findings suggest that in patients with FCD who are not clear surgical candidates, optimized medical therapy may achieve seizure control comparable to that of surgery. These results support a tailored approach prioritizing early intervention and precise seizure phenotyping rather than a uniform surgery-first strategy for FCD.

S310-K: Profiling and Engineering the Ion Channel Transcriptome

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Background: In the human brain, a large repertoire of ion channels regulates the excitability of neurons, circuits, and networks, generating complex human cognition and behavior. There are over 200 genes encoding various ligand- and voltage-gated ion channels as well as auxiliary proteins. This vast repertoire is further amplified by alternative splicing, which generates up to hundreds of isoforms for each gene. During brain development, many ion channels undergo changes in splicing that critically regulate neuronal function. Dysregulated splicing of ion channels is implicated in disorders ranging from epilepsy to neurodegenerative diseases. While previous studies have highlighted the roles of individual ion channel splicing events in brain development, homeostasis, and disease, there has never been a systematic study of the alternative splicing of ion channels. Two major barriers have impeded a systematic study of ion channel isoforms. First, most ion channels are encoded by large, multi-exon genes with complex alternative splicing. Second, ion channels are orders of magnitude lower in abundance compared to housekeeping genes. One recent study showed that these barriers can be overcome by combining two technologies: 1) long-read RNA-sequencing, which generates full-length transcripts over 5-10 kb in length, and 2) transcript capture, which can enrich for lowly expressed transcripts by up to several hundred-fold. This approach has been validated in studies of alternative splicing in cancer, as well as for several brain-enriched genes, but it has not been applied to study ion channels. As such, the repertoire of ion channel isoforms in the brain is likely vastly underappreciated. My own research showed that SCN1A, a gene encoding a subunit of the voltage-gated sodium channel, utilizes alternative poison exon splicing during human brain development to regulate transcript abundance. Furthermore, aberrant splicing of these poison exons occurs in certain individuals with Dravet syndrome, and RNA therapeutics can rescue protein production, neuronal excitability, and disease phenotypes.

Here, I follow the example of SCN1A to develop a systematic approach to study the alternative splicing of ion channels (Aim 1), with the hypothesis that there are numerous unidentified isoforms of ion channels which are differentially regulated during human brain development.

Additionally, I develop a system to evaluate the functional impact of alternative splicing, using the human BK channel as a proof of concept, to demonstrate that developmentally regulated isoforms of this gene differentially impact the excitability of human stem cell-derived neurons (Aim 2).

Methods: In Aim 1, I combine transcript capture and long-read sequencing to systematically identify the isoforms of 226 voltage- and ligand-gated ion channel genes in the cerebral cortex of the neonate and young adult. Using existing and new bioinformatic tools, I will 1) generate an expanded list of ion channel isoforms with annotations of predicted protein-coding capacity, 2) estimate their relative abundance for each gene, and 3) identify isoforms that are differentially expressed between the brains of neonates and young adults.

The result will be the most comprehensive resource of ion channel isoforms to-date, providing the basis for additional

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studies to evaluate the functional impact of ion channel splicing. In Aim 2, using a splice modulation toolkit, I will interrogate the functional impact of alternative splicing in the BK channel (encoded by KCNMA1) in human stem cell-derived neurons, comparing the conditions of total knockdown, single exon-switching, and isoform-switching. Patch-clamp electrophysiology will be used as the primary readout to study the consequences of splice modulation on action potential kinetics, afterhyperpolarization, and firing frequency. The results will provide an isoform-specific level of understanding of KCNMA1 function and identify novel RNA therapeutic targets for BK channelopathies.

Results: In a pilot experiment, I combine transcript capture and long-read RNA-sequencing to study 42 epilepsy-associated ion channel genes in two samples of human cerebral cortex from neurotypical individuals at two developmental timepoints, neonate (1 month old) and adult (age 27). I demonstrate that this approach achieves an average of 70-fold enrichment for the 42 targeted ion channels, leading to a 50-60% on-target rate. These results demonstrate that this approach is highly effective for increasing the depth of coverage for ion channel genes. Taking KCNMA1 as an example, I show distinct patterns of developmental regulation of two functionally important, alternatively spliced cassette exons in this gene. Adopting an existing splice-modulation toolkit, I demonstrate the feasibility of splice-switching exons at endogenous loci in a heterologous cell line.

Conclusions: Here, I demonstrate proof-of-concept for combining transcript capture and long-read RNA-sequencing to achieve deep coverage of the ion channel transcriptome in the human brain. Next, I will use this approach to generate an atlas of developmentally regulated transcript isoforms for the approximately 226 human ion channel genes. I will also create a readily accessible web application to enable easy visualization. Additionally, I will generate a splice modulation toolkit in stem cell-derived neurons to study the functional impact of alternative splicing events in ion channels, including the human BK channel. Taken together, the skills and resources developed in this project serve as a platform for a multi-modal investigation of the role of alternative splicing in disease contexts. My future aims are to 1) identify pathologic splicing patterns in epilepsy using disease models and surgically resected human brain tissue, and 2) use splice modulation to discover RNA-targeting therapeutics for epilepsy and other disorders of network excitability.

S311: Cenobamate and Epilepsy Surgery

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Background: Cenobamate is a relatively new antiseizure drug that has shown particularly good results in clinical trials and may reduce the need for epilepsy surgery.

Methods: Thirty-five adults with drug-resistant epilepsy (18 female, mean age, SD. 34.7 +/- 9.2) were evaluated with neuroimaging and ictal video-EEG monitoring. Eleven had had unsuccessful surgery. Cenobamate was titrated to the maximum tolerated dose. Patients who had a persistent 50% or greater decline in seizure frequency throughout follow-up (mean 18.5 +/- 14 months) after reaching their maximum tolerated dose were considered to have responded.

Results: Nineteen patients responded to cenobamate, of whom three were seizure-free (including one with previous surgery). The mean maximum tolerated dose in responders was 254 milligrams per day compared with 200 milligrams per day in non-responders ($P = 0.20$). The mean maximum tolerated dose was 221 milligrams per day in patients taking other sodium channels agents (carbamazepine, lamotrigine, lacosamide) compared to 232 milligrams per day in patients not on another sodium channel agent ($p = 0.8$). Only one patient was on cenobamate alone.

Sixteen patients had surgery, including one of the seizure-free patients, who decided to have surgery for mesial temporal sclerosis. At most recent follow-up nine were in Engel category 1, two in 2, three in 3, and two in 4. Two patients had responsive neurostimulation and one vagal nerve stimulation; neither was seizure free. Seven patients were not considered surgical candidates, and nine either declined or were still considering surgery.

Conclusion: Cenobamate in combination therapy led to seizure freedom in 8-9% of our patients, comparable to results reported in previous studies of revised anti-seizure medication treatment in patients being considered for surgery. Thirty percent of our patients had had previous unsuccessful surgery, perhaps suggesting a particularly severe seizure disorder.

S312*: Efficacy of Open-Loop versus Closed-Loop Stimulation in a Rat Model of Infantile Epileptic Spasms Syndrome

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Background: Infantile Epileptic Spasms Syndrome (IESS) is a severe developmental epileptic encephalopathy (DEE) characterized by clusters of spasms, unique electroencephalogram (EEG), and neurodevelopmental regression. Electrographically, ictal recordings demonstrate electrodecrement, whereas interictal EEG exhibits hypsarrhythmia, the hallmark pattern of high-amplitude, disorganized sharp-waves with asynchronous, multifocal spikes. Despite their status as first-line therapies, adrenocorticotropic hormone (ACTH) and vigabatrin fail to achieve electroclinical resolution in 50-60% of patients and are associated with adverse effects, including immunosuppression and irreversible visual field deficits. Prognosis remains poor, with an increased risk of premature mortality and progression to other DEEs, including Lennox-Gastaut Syndrome. Although IESS arises from diverse

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etiologies, evidence suggests a shared dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, underscoring hypothalamic nuclei as promising targets for circuit-based intervention.

Methods: To investigate this potential, we used our translational model of IESS that combines prenatal betamethasone exposure with postnatal (P) induction of spasms using N-methyl-D-aspartate (NMDA) at P12, P13, and P15. This model recapitulates key behavioral and electrographic features of human semiology, enabling the assessment of spasm burden and EEG activity. To assess the contribution of the paraventricular nucleus of the hypothalamus (PVH) in spasms, stereotaxic cannulas were implanted at P13, followed by microinfusions at P15 with saline, GABAA receptor antagonist bicuculline, or GABAA receptor agonist muscimol. To examine the anti-spasm effects of low-frequency stimulation (LFS; 10 Hz), cortical EEG electrodes and a stimulation electrode were implanted at P10. Stimulation current thresholds were determined at P12 in 50 μA increments (50-400 μA) based on the emergence of an EEG afterdischarge. Open-loop LFS (3 s ON/60 s OFF; 20 minutes) was delivered following cessation of spasms at P12, while closed-loop LFS was triggered in response to detected spasms at P13 during the 60 min. observation period. Primary outcomes included spasm burden and EEG normalization at P15.

Results: PVH microinfusions of bicuculline reduced spasm frequency at P15, whereas muscimol did not alter spasm frequency but increased spasm severity by prolonging their duration. In stimulation experiments, controls demonstrated persistent spasm burden and abnormal EEG activity across P12-P15. Both open-loop and closed-loop LFS significantly reduced spasm burden at P15 while preserving NMDA responsiveness. These effects were accompanied by normalization of EEG activity relative to P12 and controls. Open-loop stimulation achieved comparable efficacy with lower total energy delivered, suggesting enhanced efficiency.

Conclusion: These findings identify the PVH as a functionally relevant node in spasm control and support neuromodulation as a promising therapeutic strategy for IESS.

S313: Bilateral Mesial Temporal Lobe Epilepsy in a Patient with Gaucher Type III Disease

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Background: Gaucher Disease (GD) is an autosomal recessive lysosomal storage disorder characterized by accumulation of glucocerebrosidase. Patients with Gaucher Disease Type III (GD3) can develop generalized tonic-clonic (GTC) and myoclonic epilepsy which may be due to accumulation of a toxic glycolipid known as glucosylsphingosine. We describe herein the first case of genetically confirmed GD3 with a novel epileptic phenotype of bilateral mesial temporal lobe epilepsy, confirmed by stereo EEG recording. The patient was diagnosed with GD3 at the age of 2 and at 16 years of age, developed clustering seizures with clinical manifestation of episodic drooling and confusion lasting 1-5 minutes. He was placed on an ASM regimen of Oxcarbazepine 600 mg BID, Onfi 10 mg BID, Perampanel 4 mg daily on which the patient continued to have monthly disabling seizures. He is now pending surgical intervention.

Methods: Our patient underwent whole-genome-sequencing, epilepsy monitoring unit admission with both scalp and stereo EEG recordings. Structural MRI, functional MRI, SPECT, FDG-PET, MEG, and Wada tests were also performed.

Results: Whole-genome-sequencing (WGS) was performed and revealed that the patient had Type 3 Gaucher Disease GBA p.Leu483Pro variant. MRI brain was non-lesional and showed nonspecific bilateral white matter changes. Scalp EEG showed occasional interictal bilateral temporal sharp waves, and continuous slow in the right temporal region. Ictally, multiple seizures were captured from the left and right temporal lobes. Left temporal seizures were electrographic with the exception of one tachycardic seizure. Right temporal clinical seizure semiology were classified as apneic → dialeptic → chapeau de gendarme → bilateral asymmetric arm tonic → sialorrheic → left versive → left head clonic. MEG interictals clustered in the right mid-temporal region with extension into the temporal operculum, posterior insula, and medial/basal regions. Ictal MEG was non-localizing. Ictal SPECT was equivocal. FDG-PET showed hypometabolism in the bilateral anterior temporal, temporal operculum, and insular lobes R > L. Stereo EEG recorded 11 habitual seizures from the right hippocampus and 34 electrographic seizures from the left hippocampus which were diagnostic of bilateral independent mesial temporal lobe epilepsy.

Conclusion: Herein, we report the first case of GD3 with drug-resistant bilateral mesial temporal lobe epilepsy. The diagnosis of GD3 was confirmed by WGS which found GBA p.Leu483Pro mutation. MRI brain was non-lesional and stereo EEG confirmed bilateral independent mesial temporal lobe seizures. We provide detailed clinical features of this case and expand the phenotypic spectrum of epilepsies associated with GD3 to include bilateral mesial temporal lobe epilepsy.

S314: Educational Gaps in Long-Term Video-EEG Monitoring: Convergent Perspectives from Patients and Multidisciplinary Clinical Staff

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Background: Long-term video-EEG (LT-VEEG) is essential for seizure characterization and presurgical epilepsy evaluation but remains underutilized, in part due to patient knowledge

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gaps around the testing process. In a prior single-center cross-sectional study, we recruited adult patients undergoing inpatient LT-VEEG (July–December 2024) to assess pre- and post-LT-VEEG knowledge. Of the 23 respondents who completed the post-testing survey (52% response rate), 54% reported a change in their understanding of LT-VEEG from baseline, and 73% believed educational materials would help prepare future patients, preferring short videos (58%), pamphlets (23%), or other formats. Six qualitative themes emerged from patient responses: Preparation and Information, Personal Comfort and Entertainment, Accommodations, Communication, Testing Experience and Tolerance, and Privacy and Mobility. In the present study, we sought to identify additional educational gaps from the perspectives of multidisciplinary clinical staff involved in administering LT-VEEG.

Methods: This cross-sectional qualitative study was conducted between December 2025 and February 2026. Nurse leaders and EEG technologist supervisors were presented with findings from our prior study and asked to collect structured feedback from their respective teams regarding patient educational needs. Responses were compiled and organized into qualitative themes, which were then compared across professional groups and against the six patient-generated themes from the original study.

Results: Nursing staff identified the following themes: Safety and Mobility, Patient Education/Procedures, Bathroom and Privacy, Prohibited Items, Length of Stay, What to Bring, and Visitors. EEG technologists identified: Safety and Mobility, Patient Education/Procedures, Hygiene/Personal Care, What to Wear, What to Bring, and Entertainment. Five of the six original patient-generated themes had concrete overlap with feedback from both professional groups; one theme originated exclusively from patient responses. Privacy and Mobility and Personal Comfort and Entertainment were the most consistently represented themes across all three groups, while Communication--identified by patients but not clinical staff--was the only theme without cross-group representation.

Conclusion: Patients and multidisciplinary clinical staff administering LT-VEEG independently identified a largely overlapping set of high-priority educational gaps. This convergence across stakeholder groups provides a validated framework for developing targeted patient educational materials. Addressing these gaps through accessible formats such as short videos and pamphlets may improve patient preparedness, enhance patient satisfaction, and ultimately support greater utilization of LT-VEEG testing.

S316-LB: Sex-Specific Differences in Seizure-Associated Cognitive Decline in Older Adults: A Longitudinal Multicenter Study

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Background: Seizures are associated with accelerated cognitive decline, with a 2-to-4-fold increase in dementia incidence. Biological sex modifies both epilepsy and dementia risk. However, whether sex modifies the relationship between seizures and cognitive decline remains unclear. We investigated sex-specific differences in seizure-associated cognitive decline in older adults with normal cognition and mild cognitive impairment (MCI).

Methods: We included 13,766 participants who were cognitively normal (women=9,031[65.6%]; median age: 71 years) and 11,413 who had MCI at enrollment (women=5,628 [49.3%]; median age: 73 years). In the cognitively normal cohort, active seizures conferred a 2.4-fold increased risk of cognitive decline in women (adjusted hazard ratio[aHR] =2.42, 95% CI:1.65,3.55,p<0.001) and 1.8-fold increased risk in males(aHR=1.8, 95%CI=1.17,2.78,p=0.02) compared to no-seizure controls. In MCI, active seizures conferred a 1.5-fold higher risk of dementia in women (aHR=1.49, 95%CI=1.03,2.17) and 1.7-fold higher risk in men (aHR=1.66, 95%CI:1.21,2.29,p=0.008). In cognitively normal individuals, chronic-active seizures conferred a 2.3-fold increased risk of decline in women (aHR=2.34, 95%CI:1.43-3.83,p=0.003) but not in men. In contrast, new-onset active seizures were associated with substantially higher risk of decline in both sexes, with larger effect estimates in men. Notably, in the cognitively normal cohort, new-onset active seizures conferred a 3.7-fold increased risk of decline in men (aHR=3.7, 95%CI:2.18,6.28,p<0.001) compared to a 2.5-fold risk in women (aHR=2.5,95% CI:1.38,4.55,p=0.008). Similarly, in MCI, new-onset active seizures conferred a 3.14-fold higher risk of dementia in men (aHR=3.14,95%CI:2.02,4.88,p<0.001) and 2.28-fold higher risk in women (aHR=2.28,95%CI:1.32,3.95,p=0.011).

Results: Seizure-associated cognitive decline in older adults demonstrates important sex-specific patterns that vary by seizure-onset timing. Chronic epilepsy confers greater cognitive vulnerability in women, whereas late-onset seizures signal particularly high risk for decline in men. These findings highlight that biological sex may differentially influence seizure-associated cognitive decline with implications for risk stratification and clinical monitoring of older adults with epilepsy.

Conclusion: This longitudinal, multi-center study included participants from 39 Alzheimer's Disease Research Centers across the US, who were enrolled between 9/2005 and 12/2021. Participants with normal cognition /or MCI, and at least 2 visits, were included. Cognitive decline (primary outcome) was assessed using the Clinical Dementia Rating (CDR-Global) from 1) Normal-to-Impaired (CDR-global> 0.5) or 2) MCI-to-Dementia (CDR-global > 1). Unstratified and sex-stratified effects of active seizures (preceding 12-months), remote seizures (prior seizures, none recently), and no seizures on cognition were assessed using Cox models, including seizure-by-sex interaction terms and adjusting for age, race, education, hypertension, and diabetes. Sensitivity analyses examined chronic(pre-enrollment) and new-onset active seizures(developed during follow-up) separately.

S317-K: Parvalbumin-positive Interneuron Density and Intrinsic Property Alterations in a Mouse Model of Pcdh19 Clustering Epilepsy

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Background: Protocadherin-19 (PCDH19)-clustering epilepsy (PCE) is a severe developmental and epileptic encephalopathy (DEE) and one of the most common monogenic epilepsies. It is characterized by cognitive impairment and intractable seizure clusters with onset in the first few years of life. PCDH19 is an X-linked gene that encodes a transmembrane cell adhesion molecule critical for cell-cell interactions during brain development. PCE affects females and rare mosaic males, while hemizygous males expressing only mutant PCDH19 do not develop epilepsy. A leading hypothesis to explain this phenomenon is that it occurs due to cellular interference associated with random X-inactivation (or mosaic mutations) in which cells expressing only wild type and those expressing only mutant PCDH19 fail to interact properly during brain development. This is demonstrated in our mouse model in which we see a striking pattern in which the Pcdh19+ and null neurons (after random X-inactivation) segregate from one another in the cortex, hippocampal CA1 region, and in interneuron progenitors in the ganglionic eminences. PCE mice show a lower seizure-threshold and more severe seizures when exposed to hyperthermia.

Given the key role of inhibitory interneurons in many genetic epilepsies, we sought to examine parvalbumin (PV) interneuron distribution and intrinsic properties based on regional Pcdh19 expression.

Methods: Female Pcdh19+/-; PV-cre mice were crossed with X-GFP; tdTomato cre-reporter males. Female offspring expressed GFP on approximately half of their neurons, while males do not express GFP. All PV-cre x tdTomato offspring expressed tdTomato on PV-positive interneurons. Patch clamp electrophysiology was performed on acute slices in the cortex at P25-32. Histological studies were performed on fixed brain sections at P45-90.

Results: PV-interneuron density was decreased in the CA1 region of the hippocampus in PCE mice compared to WT controls. When examining the cortex, there was no difference in overall cell density between groups. However, PV-density was significantly lower in the GFP-/Pcdh19- regions compared to GFP+/Pcdh19+ regions of the cortex. Current clamp electrophysiology revealed hypoexcitability of both the PV and non-PV neurons in the knockout males when compared to wild-type. In PCE females, PV+ neurons within the GFP+ regions displayed similar firing patterns to WT mice. However, in the GFP- regions, there was a leftward shift in the firing pattern of the PV+ interneurons, with early depolarization block that was not observed in the GFP+ regions.

Conclusions: PV-interneuron density is decreased in the hippocampus and Pcdh19- regions of the cortex of PCE mice. Intrinsic properties of PV-interneurons are altered in the Pcdh19- regions of the cortex such that they fire more with physiologic current input, but reach early depolarization block with high current input – a phenomenon observed in other DEE mouse models. This pattern was not observed in the knockout mouse, suggesting that it is not simply due to cell genotype and may instead be related to transcriptional changes in cellular properties that are altered in the mosaic state. This suggests that seizures in PCE may be driven by abnormal PV-tone in the mutant regions of a Pcdh19-mosaic brain. Further examination of circuit dynamics will provide further insight to the underlying mechanisms of PCE.

S318: Diagnostic Accuracy of Multi-modal Deep Learning Models for Epileptogenic Zone Localization in Drug-Resistant Focal Epilepsy: A Systematic Review and Descriptive Analysis

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Background: In recent years, artificial intelligence (AI) and machine learning (ML) approaches have been increasingly applied to epilepsy research for the automated detection and localization of epileptogenic regions. However, despite growing interest and rapid methodological advancements, the clinical translation of AI-based models in epilepsy remains limited. Variability in study design, datasets, validation strategies, and outcome measures poses significant challenges in assessing their true clinical utility. Therefore, we conducted a comprehensive systematic review to evaluate the effectiveness of deep learning (DL) techniques as promising tools for localizing the epileptogenic zone (EZ) and improving surgical outcomes in patients with drug-resistant epilepsy.

Methods: A comprehensive literature search was performed across PubMed, Scopus, Google Scholar, Cochrane Library, and Embase databases up to March 31, 2026. Eligible studies included those that applied deep learning models for epileptogenic focus localization, utilized multimodal data (e.g., EEG, MRI, PET, DTI) for EZ localization, and reported diagnostic accuracy or post-surgical outcomes. Extracted metrics included sensitivity, specificity, area under the curve (AUC), localization error, and seizure outcomes.

Results: A total of 7 studies comprising 208 patients were included. All studies were retrospective and single-center, with no external validation. Sample sizes ranged from 15 to 52 patients. Most studies utilized multimodal data, combining intracranial EEG with structural and functional imaging (MRI, DTI, PET), while one study used scalp EEG alone. Diagnostic performance was consistently high, with AUC values ranging from 0.84 to 0.90, sensitivity from 79.6% to 97.3%, and specificity from 79.7% to 86%. Localization accuracy was strong, with Dice similarity coefficients up to

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96% and localization error ranging from 0.38 mm to 12 mm. Post-surgical seizure freedom (Engel Class I) ranged from 63% to 100% in all studies except one, which did not report outcomes.

However, substantial heterogeneity in study design, input modalities, outcome definitions, and reporting metrics limited direct comparison across studies.

Conclusion: This meta-analysis demonstrates that multimodal deep learning approaches substantially enhance the accuracy of epileptogenic zone localization and prediction of surgical outcomes in drug-resistant focal epilepsy.

Across the included studies, these models achieved high localization precision and consistently favorable post-surgical seizure freedom rates, underscoring their potential to support clinical decision-making and improve patient selection for epilepsy surgery. However, despite these promising results, the current evidence base remains limited by small sample sizes and retrospective single-center designs. Future large-scale, prospective, multicenter studies are essential to confirm generalizability, standardize methodologies, and facilitate the safe translation of these AI-driven tools into routine clinical practice.

GLOBAL NEUROLOGY

S320: Educational Interventions to Address Neurophobia in Medical Training: A Scoping Review

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Background: Neurophobia refers to the fear of neural sciences and clinical neurology resulting from students' inability to apply their knowledge of basic sciences to clinical scenarios. It is commonly seen in residents and practitioners, leading to avoidance of neurological problems, over-referrals and inadequacy in patient care. Several interventions have been proposed but there is limited evidence regarding their implementation and effects. This scoping review aims to explore educational interventions aimed at addressing neurophobia in medical training.

Methods: We searched MEDLINE from inception to April 2026 using keyword terms related to neurophobia, and limited our search to English-language studies. Eligible studies included cohort, case-control, QI studies and randomised trials. After identification, specific data variables were extracted from each article under review. Data were extracted based on group variables (e.g., study characteristics, interventions, outcomes, limitations).

Results: Of 143 identified studies, 15 met inclusion criteria and were narratively synthesised due to heterogeneity. Most interventions are single center and use a pre-post study design which includes primarily active-learning approaches, including e-learning, gamification, and case-based methods. Only two studies used validated neurophobia screening tools (NeuroQ and Schlon) while other studies used self-made Likert scales. Most studies reported improvement in knowledge and confidence outcomes relative to their pre-intervention scores. While short-term retention is assessed immediately post-intervention, long-term retention measures were rarely assessed.

Learner satisfaction was consistently high, with participants reporting improved engagement and perceived learning. Major limitations include small sample size and subjective outcome measures.

Conclusion: The current literature is heterogeneous and limited by a lack of standardized evaluation methods. While short-term improvements are commonly reported, long-term retention is rarely assessed, and studies are constrained by small sample sizes, limited generalisability, and subjective outcomes. Interventions are largely focused on neuroanatomy, with limited evaluation in other areas. More rigorous and standardized approaches are needed to better address neurophobia in medical training.

S321: Early CSF and Serum Biomarker Dynamics Are Associated with Functional Recovery in Tuberculous Meningitis: Insights from the ALTER Trial

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Background: Better tools are needed to predict disease outcomes and guide risk stratification and treatment decisions in tuberculous meningitis (TBM).

Methods: Using data from the Adjunctive Linezolid for the Treatment of Tuberculous Meningitis (ALTER) study, we applied binary logistic regression models to predict favorable clinical outcomes at week 4, 12, and 24, defined as a modified Rankin scale (mRS) score <3. A total of 13 cerebrospinal fluid (CSF) and 26 serum laboratory variables obtained at screening, entry, and week 2 were considered for inclusion based on clinical relevance. To assess whether early biomarker dynamics improve prediction relative to values at individual timepoints, we developed models incorporating log-transformed changes in laboratory values between screening and week 2.

Models were evaluated using leave-one-out cross-validation (LOOCV), with area under the receiver operating characteristic curve (AUC) and classification accuracy as key metrics.

Results: A three-feature model using screening CSF WBC count, serum absolute lymphocyte (ALC), and serum neutrophil count (ANC) predicted week 24 mRS with moderate discrimination (AUC 0.740). Higher CSF WBC count and serum ALC were associated with favorable outcomes, whereas

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higher serum ANC was associated with worse outcomes. We next modeled functional change, defined as change in mRS between weeks 4–12 and weeks 4–24. Three screening CSF features emerged as top predictors: color/turbidity, CSF WBC count, and protein. In the week 4–12 model (AUC 0.702), less clear (more turbid) CSF, higher CSF WBC count, and higher protein predicted improvement (decrease in mRS). In the week 4–24 model (AUC 0.736), higher CSF WBC count and protein predicted improvement, whereas less clear (more turbid) CSF predicted worse outcomes. Decreases in CSF WBC count and protein between screening and week 2 were also associated with improvement between weeks 4–24. To assess whether early biomarker dynamics added predictive value, we modeled log-transformed changes in CSF parameters from screening to week 2. A two-feature model using CSF WBC count and protein changes demonstrated moderate discrimination for improvement between weeks 4–24 (AUC 0.673). A 50% decrease in CSF WBC count was associated with a 1.31-fold increase in the odds of improvement, while a 50% decrease in CSF protein was associated with a 1.55-fold increase.

Conclusion: Early CSF and serum profiles provide modest prognostic value for clinical outcomes in TBM. Reductions in CSF pleocytosis and protein over the first two weeks were associated with subsequent functional recovery, suggesting that dynamic inflammatory changes may offer complementary prognostic insight. Validation in larger cohorts is needed.

S322: Socioeconomic and Regional Disparities of Neurocognitive Disorder and Multimorbidity Among Peruvian Younger and Older Adults

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Background: Age-related neurocognitive disorders (NCDs) are an increasing public health concern in low- and middle-income countries (LMICs), where life course structural and socioeconomic exposures may contribute to brain health disparities, yet population-based evidence across age groups in Latin America remains limited. This study examines the prevalence of NCD, cardiometabolic risk, and depression by education, socioeconomic status, and region of origin in an urban-marginalized sample in Lima, Peru, and evaluates associations between these vulnerability indices and health outcomes.

Methods: Data from 1,099 adults (two groups: ages 30–59 and ≥60) participating in a population-based, door-to-door study in Lima, Peru were analyzed. Participants completed in-home assessments of cognition, functional status, depressive symptoms (PHQ-9), and cardiometabolic conditions. NCD classification was based on age-appropriate cognitive and functional assessments. Prevalence of NCD, depression, and cardiometabolic conditions was examined across SES quintiles, education levels, and geographic region of origin. Socioeconomic inequalities were quantified using the Slope Index of Inequality (SII), which estimates absolute (percentage-point) differences in outcomes across ranked groups (0–1) using regression models.

Results: Among younger adults (ages 30-59), higher SES was associated with lower rates of NCD (SII = -0.32, p<.001), but higher rates of hypertension (SII = 0.14, p<.01) and overweight/obesity (SII = 0.14, p<.01). There was no significant association between SES and diabetes or depression in younger adults. Among older adults (ages ≥60), higher SES was associated with higher rates of NCD (SII = 0.30, p<.01) and hypertension (SII = 0.20, p<.05), but no association between SES and diabetes, overweight/obesity, and depression. Among both younger and older adults, higher educational attainment was associated with lower rates of NCD (younger: SII = -0.64, p<.001, older: SII = -0.46, p<.001) and depression (younger: SII = -0.28, p<.001; older: SII = -0.27, p<.01).

Only among younger adults, region of origin was associated with NCD (SII = -0.34, p<.001) with highest NCD prevalence among individuals originating from the Andes mountainous region (30.6%) and Jungle (28.9%), and lower NCD prevalence among those from the Coast other than Lima (15.1%) and Lima (10.8%). Region of origin was not associated with NCD prevalence or other comorbidities among the older adult group.

Conclusion: Findings highlight the role of life-course socioeconomic disadvantage in influencing cognitive vulnerability in an urban-marginalized sample of Lima, Peru. Results emphasize the need for early, integrated prevention strategies that ameliorate modifiable social and structural determinants of brain health, particularly among marginalized populations.

S323: Significant Decline in Stroke Mortality Emerging After the Early 2010s in the Dominican Republic, 2000–2018

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Background: Although age-standardized stroke mortality has declined globally, the absolute burden in Latin America and the Caribbean (LAC) remains substantial due to an aging population and prevalent modifiable cardiovascular risk factors (CVRF). Recent regional analyses suggest a deceleration in mortality but detailed country-level trend analyses for the Dominican Republic (DR) are lacking. We aimed to characterize age- and sex-stratified temporal trends in stroke mortality in the DR.

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Methods: We conducted a retrospective analysis of stroke mortality using World Health Organization (WHO) Mortality Database data (2000–2018). Stroke deaths were identified using ICD-10 codes I60–I69. Age-standardized death rates (ASDRs) per 100,000 population were calculated using the WHO World Standard Population. Temporal trends were analyzed using joinpoint regression to estimate annual percent change (APC) and average annual percent change (AAPC) with 95% confidence intervals (CI). Age-specific rates were stratified into predefined groups: 45, 45-64, 65-74, and ≥75. Sex-specific models and male-to-female rate ratios were computed. Analyses used de-identified, publicly available data; IRB approval was not required.

Results: Between 2000 and 2018, 51,630 stroke deaths were recorded in the Dominican Republic. The ASDR declined from 43.8 to 27.4 per 100,000, representing a 37.4% relative reduction (overall AAPC: −3.7% (95% CI, −4.6% to −2.8%)). Males had consistently higher mortality rates than females (RR 1.19 (95% CI, 1.17–1.21)).

Joinpoint analysis identified two distinct trend periods. In males, the APC was −0.9% (95% CI, −2.4% to 0.6%, nonsignificant (NS)) from 2000 to 2012, followed by −7.8% (95% CI, −10.9% to −4.6%) from 2012 to 2018. In females, the APC was −1.5% (95% CI, −3.0% to 0.1%, NS) from 2000 to 2011, followed by −9.8% (95% CI, −12.9% to −6.7%) from 2011 to 2018. The difference in sex-specific trends in the later period was not statistically significant ($p = 0.20$). Mortality demonstrated a pronounced age-dependent gradient, from 2.3 per 100,000 (95% CI, 2.22–2.38) among individuals <45 years to 609.7 (95% CI, 602.1–617.3) among individuals ≥75. Crude mortality declined less markedly than ASDR, reflecting the effect of population aging.

Conclusion: Stroke mortality in the DR declined substantially between 2000 and 2018, with an accelerated decline after the early 2010s following a period of nonsignificant change. While recent regional data showed deceleration in stroke mortality across LAC, these findings are consistent with improvements in CVRF control and healthcare delivery, though the ecological design precludes causal inference. The widening gap between crude and standardized rates underscores the need for sustained surveillance and age-targeted prevention strategies.

S324-K: Predictors of Caregiver Burden and Depression Among Zambian Caregivers of Older Adults with Neurologic Disease

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Background: With aging populations, long term care needs have dramatically increased in communal societies like Zambia and fall largely on family members as informal caregivers. While caregiver burden has been associated with greater depression in Western settings, little is known about the impact of these demands on caregiver outcomes in Zambia, particularly when providing care to older adults with neurologic disease. This study aimed to evaluate caregiver burden and depression and their predictors and investigate whether burden and depression differ among Zambian caregivers based on participant medical history.

Methods: The Zambian Cohort of Healthy Aging and Dementia is a population-based cross-sectional study of aging of adults ≥ 55 years and their informal caregivers. Patient and caregiver sociodemographic characteristics, caregiver burden, and depression were assessed. Participants underwent a complete medical history, physical examination, and neuropsychologic testing to assess neurologic diagnoses. Caregiver burden was assessed using the Zarit Burden Inventory (high burden score>20) and depression via the PHQ-9 (depression score >10). Multivariable logistic regression assessed associations between participant and caregiver characteristics, participant medical history, and caregiver burden and depression.

Results: To date, 277 participant (mean age 66 years, 75% female) and caregiver pairs have completed data collection. Participant medical history included HIV (21%), diabetes (11%), stroke (11%), and epilepsy (5.4%). 56% reported a history of hypertension, of whom 24% were in hypertensive emergency during study participation. 15% of participants had dementia.

Caregivers (mean age 34 years; 75% female, mean monthly income 80 USD) were most frequently the participant's child (58%) or grandchild (21%). 44% had additional family/friends to aid with caregiving tasks, but only 8% had paid help and 22% had given up or cut back on work due to caregiving. 54/277 (19%) caregivers reported ongoing caregiver burden. Burden was associated with household wealth, with 54% of those experiencing caregiver burden in the lowest household wealth quartile compared to 23% of those not experiencing burden ($p<0.01$). The availability of additional family members to aid with caregiving tasks did not decrease burden. After adjusting for caregiver sex, age, household wealth, and the presence of other caregivers, caring for a participant with dementia (OR 3.63 [95% CI 1.69-7.84]) or hypertension (OR 2.16 [95%CI 1.12-4.27]) was associated with greater burden.

Participant history of HIV, stroke, epilepsy, or diabetes did not significantly impact burden. 38/277 (14%) caregivers met criteria for moderate to severe depression, which was associated with increased caregiver burden (OR 3.88 [95%CI 1.75-8.56]). There were no other significant predictors of depression.

Conclusions: Informal caregiving is associated with significant burden among caregivers in Zambia, which in turn, leads to greater likelihood of depression. Health outcomes of informal caregivers have been largely overlooked in this setting and improving formal care for conditions like hypertension and dementia may indirectly improve caregiver wellbeing in addition to patient outcomes.

S325: Pediatric Neurological Care in Sub-Saharan Africa: Current Status and Future Directions

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Background: Although the study of childhood neurological conditions dates back centuries, pediatric neurology has evolved significantly since its recognition as a subspecialty in the mid-20th century. However, the field remains underdeveloped in sub-Saharan Africa (SSA) despite the rising prevalence of neurological disorders, including epilepsy, cerebral palsy, cerebral malaria, autism spectrum disorder, and pediatric brain tumors.

Methods: A literature search was conducted using specific MeSH terms in databases such as PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library. The inclusion criteria permitted various study designs, including observational studies, case-control studies, cohort studies, randomized controlled trials, systematic reviews, and meta-analyses. Of the initial 12,837 articles screened, 5,037 were examined after 7,800 duplicates were excluded. Ultimately, 118 studies were considered for the main results of this study.

Results: This study summarized epidemiological trends and barriers to pediatric neurological healthcare in SSA regions. For example, studies in SSA regions report a higher annual incidence of epilepsy, estimated at 81.7 per 100,000 people (95% confidence interval [CI]: 28.0–239.5). This figure significantly surpasses the incidence rate in more developed regions, estimated at around 45.0 per 100,000 people (95% CI: 30.3–66.7). Regarding other pediatric neurological cases besides epilepsy, most studies reported country-specific data. In Nigeria, for instance, several surveys have found ADHD prevalence rates between 7.6% and 8.7%. Studies from Kenya and Sudan have also reported rates of 6.3% and 9.4%, respectively. While in other countries in SSA, there are no comprehensive regional prevalence estimates for ADHD. Furthermore, the case fatality ratio for bacterial meningitis in SSA is estimated at around 31%, which is more than twice the global average of 14%. These conditions account for a significant proportion of pediatric morbidity and mortality in the region. However, limited epidemiological data, underdiagnosis, and health system constraints continue to obscure their true impact. Although countries such as South Africa have made strides in diagnosis and care, progress remains uneven across the region.

Conclusion: Despite these efforts, the burden of pediatric neurological conditions in SSA remains substantial. We recommend the further implementation of task-shifting strategies to empower general practitioners and community health workers, the expansion of local pediatric neurology training programs, and the strengthening of collaborative efforts with clinical services and epidemiological research.

S326: Building a Brain in Cambodia: From Concept to Validation of a Novel, Structured Clay-Based Neuroanatomy Teaching Tool in a Low-Resource Global Context

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Background: Neuroanatomy is frequently cited as one of the most challenging subjects in medical education, contributing to "neurophobia" due to the difficulty of grasping complex three-dimensional spatial relationships of neural structures. In low-resource settings, this challenge is amplified by the prohibitive cost of advanced 3D tools such as virtual reality platforms or extensive cadaver laboratories, leading to reliance on two-dimensional diagrams and didactic lectures that poorly support spatial reasoning. To address this gap, we evaluated Build-a-Brain, a cost-effective, hands-on clay-modeling curriculum designed to enhance anatomical knowledge, spatial understanding, and learner satisfaction among medical students in Cambodia.

Methods: We conducted a mixed-methods study involving 41 Year-5 medical students at the University of Health Sciences in Cambodia. The intervention replaced passive learning with an interactive, "bottom-up" active-creation curriculum that utilized low-cost air-dry clay kits (total cost 137.94 USD). Instruction was delivered sequentially through PowerPoint presentations, real-time camera demonstrations, and standard anatomical models; as each neuroanatomical segment was introduced, collaborative student groups immediately translated 2D content into 3D space by building upward from the brainstem to the cerebral cortex. Anatomical labeling, functional mapping (e.g., pinning cranial nerve origins), and clinical correlations were integrated concurrently during the physical construction of each structure. Outcomes were assessed using a 15-item, multi-station practical examination across three modalities (clay models, plastic models, and cadaveric slices), capstone group presentations evaluated by a joint Cambodian–American neurology panel, and a structured post-activity feedback survey.

Results: Despite receiving only 12 hours of Build-a-Brain workshop instruction, students demonstrated strong anatomical mastery, with a mean practical examination score of 77.4% (11.61/15) and a median of 80%. Retrospectively, 56.1% of students estimated they would have scored 0–50% on the same exam without the intervention, indicating substantial perceived and actual knowledge gains. The activity received a mean satisfaction rating of 4.71/5; 92.7% of participants agreed that the 3D clay-based approach was more effective than traditional lectures or two-dimensional diagrams, and 85.4% reported increased confidence in identifying major neuroanatomical structures.

Conclusion: Low-cost clay modeling thus represents a highly effective and engaging pedagogical tool for teaching neuroanatomy in resource-limited settings. By transforming students into active creators, this kinesthetic methodology bridges the gap between two-dimensional representations and three-dimensional spatial reality and appears to mitigate elements of neurophobia. The Build-a-Brain curriculum offers a scalable, affordable model for democratizing access to high-

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yield neuroanatomy education and may ultimately support improved clinical localization skills in global neurology training.

S327: Diagnosis of Multiple Sclerosis Before MRI: Clinical Approaches from the Pre-Imaging Era

Presenting Author: *Shaweta Khosa, MBBS, Olive View-UCLA Medical Center, Sylmar, CA*

Co-Authors: *Robert Freundlich, MD, Olive View-UCLA Medical Center, Sylmar, CA*

Background: Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammation, demyelination, gliosis, and neuronal loss in central nervous system. Early diagnosis is crucial to facilitate initiation of therapy to prevent long-term disability. Dissemination in space (DIS) and dissemination in time (DIT) are two key criteria for accurately diagnosing MS. Before introduction of magnetic resonance imaging (MRI), diagnosis of MS relied primarily on clinical expertise, careful longitudinal follow-up, and use of evolving paraclinical investigations. In absence of direct visualization, neurologists were challenged to identify a disease defined by its temporal and spatial heterogeneity, often leading to significant diagnostic uncertainty. This literature study aimed to examine evolution of MS diagnosis prior to MRI, with a focus on clinical reasoning, and to highlight lessons applicable to contemporary practice.

Methods: Information was gathered through literature review using PubMed, ClinicalKey, OVID and primary texts. A narrative historical literature review was conducted, tracing development of MS diagnosis from Jean-Martin Charcot's initial characterization in 1868 through late 20th century. Emphasis was placed on emergence of concept of dissemination in time and space, role of serial neurological examinations, and integration of adjunctive tools including cerebrospinal fluid (CSF) analysis and evoked potentials. Evolution of diagnostic frameworks, including Schumacher (1965) and Poser (1983) criteria, was also examined.

Results: Early descriptions of MS show establishment of initial clinical framework including Charcot's triad of nystagmus, intention tremor, and scanning speech. However, diagnosis relied heavily on recognizing recurrent, anatomically distinct neurological deficits over time. Serial examinations were essential, often requiring prolonged follow-up to establish diagnostic confidence. The introduction of CSF analysis, particularly oligoclonal bands, and evoked potentials improved diagnostic sensitivity by identifying subclinical disease.

Despite these advances, misdiagnosis remained common, with conditions such as neurosyphilis, vitamin B12 deficiency, and intracranial neoplasms frequently misidentified as MS judgment. Overall, these difficulties show that older diagnostic tests had clear limitations, and careful clinical judgment by experienced physicians has always been essential in diagnosing demyelinating diseases.

Conclusion: Diagnosis of MS in pre-MRI era highlights a period in which diagnostic uncertainty was an inherent component of neurological practice. While MRI has significantly improved diagnostic accuracy, modern clinicians continue to encounter atypical presentations and cases where imaging alone may be insufficient. Revisiting this history emphasizes that core principles of MS diagnosis-careful clinical evaluation, longitudinal assessment, and pattern recognition-remain essential. In an era of rapidly advancing diagnostics and artificial intelligence, these lessons underscore that technology enhances, but does not replace clinical reasoning.

S328: Hippocampus and Amygdaloid Nuclei - The Brain Structures Most Resistant to Volume Decrease in Physiological Aging: MR Volumetric Study

Presenting Author: *Dusko Kozic, - Novi Sad, Serbia*

Background: The differentiation between physiological aging and initial or subclinical forms of dementia is a rather demanding task. The main goal of this study was to determine which brain structures are most prominently prone to aging.

Methods: The study group was composed of 40 healthy patients who were, based on age, divided in two groups, younger with average age 26,75 +/-2,47 SD and older group which averaged 68,5 +/-5,26 SD years. All patients were scanned with an MR scanner and volumes of their brain structures were calculated by voxel based morphometry.

Results: In the group of older patients compared with younger group, there was statistically significant decrease of total cerebral volume ($p<0.001$), total grey matter volume ($p< 0.0001$), total white matter volume ($p<0.024$), average thalamic volume ($p<0.0001$), average putamen volume ($p<0.0001$) and average caudate volume ($p<0.004$), while the average volumes of lateral ventricles presented statistically significant increase ($p< 0.002$). There was no significant decrease of hippocampal ($p=0.438$) and amygdala ($p=0.373$) volumes between two groups.

Conclusion: Hippocampi and amygdala seem to be the most resistant to volume loss in healthy brain aging compared to other brain structures.

S329: Integrating Neurodivergent Panel-Based Education and Innovative Reflection in a Neuroscience Medical Student Curriculum

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Background: There is growing recognition of gaps in medical training related to caring for individuals with neurodivergent conditions. U.S. medical student surveys report that only 36% felt their programs adequately prepared them to provide care for patients with disabilities, while 97.6% agreed that additional instruction in disability-related competencies is necessary. Despite this need, limited literature examines the impact of panel-based educational formats for neurodivergent populations in U.S. medical education. Additionally, there are limited studies that explore innovation-based activities within neurodivergence-focused

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medical school curricula. This study evaluates whether a didactic session, panel, and innovation-focused reflection assignment for pre-clinical medical students improves perspectives and innovative approaches in caring for these populations.

Methods: The intervention was incorporated into the first-year neuroscience block at the Carle Illinois College of Medicine, an engineering-focused medical school. The session began with a didactic lecture led by a developmental pediatrician and a local autism program, followed by large and small-group panel discussions comprised of neurodivergent adults and family members of neurodivergent children. Students submitted a reflective assignment describing key takeaways and a proposed innovation following the session. Pre- and post-session anonymous surveys assessed student confidence, knowledge, and attitudes toward neurodivergent populations using 12 Likert-scale items (1–5), with preliminary analysis comparing pre- and post-intervention median scores. Student reflections were analyzed to identify and categorize the innovations proposed.

Results: Descriptive statistical analysis showed a shift in median responses from "neither agree nor disagree" (pre-intervention) to "somewhat agree" (post-intervention) across all survey items (n=57). There was increased student favorability towards motivations in developing innovations for neurodivergent populations, rising from 66.1% (pre-intervention) to 87.7% (post-intervention) for "somewhat agree" or "strongly agree" categories.

Preliminary qualitative thematic analysis of the reflection assignments revealed proposed innovations related to sensory accommodations, early communication of patient preferences, screening tools, and communication aids for patient–provider interactions. These solutions focused on creating or modifying mobile applications, electronic health record displays, physical tools, and clinic spatial arrangements.

Conclusion: Students demonstrated improved confidence, knowledge, and perceptions of neurodivergence following this curricular intervention, adding to the limited body of U.S.-based studies. Exposure facilitated the development of innovative ideas to improve clinical care and quality of life for neurodivergent populations. These gains may contribute to preparedness for caring for neurodivergent patients as future physicians and support development of innovation-based approaches in clinical training. Further analysis will inform future iterations of the curriculum.

S330: Mortality Trends in Traumatic Brain Injury Complicated by Sepsis in the United States: A Population-Based Analysis, 1999-2024

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Background: Traumatic brain injury (TBI) and sepsis are avoidable yet lethal. Their coexistence amplifies mortality through immune dysregulation, prolonged hospitalization, and multi-organ failure. This study maps U.S. mortality disparities across age, sex, race, and geography in TBI-related deaths complicated by sepsis from 1999 to 2024, exposing critical research gaps.

Methods: We conducted a retrospective CDC WONDER analysis (1999–2024) using ICD-10, followed by S06 (TBI) and A40-A41 (Sepsis). Age-adjusted mortality rates (AAMR) were stratified by sex, race, census region, and urbanization. Joinpoint regression calculated Annual Percent Change (APC) and Average Annual Percent Change (AAPC) with $p<0.05$.

Results: From 1999-2024, 5578 deaths were reported. Among adults aged 75–84 years, mortality demonstrated an early non-significant decline from 1999–2012 (APC: -1.71,95%CI:-4.1 to 0.7; p=0.156635) followed by a significant increase from 2012–2024 (APC: 4.5714, 95% CI: 2.1128 to 7.0892; $p = 0.000811$). Males exhibited higher mortality than females (9.80 vs. 4.70) in 2024. Sex-specific trends showed no significant overall change among females although mortality increased significantly from 2001–2024 (APC: 4.6203*, 95%CI:3.02 to 6.25; $p = 0.000005$) after a non-significant decline from 1999–2001(APC-41.2641,95% CI:-69.6 to 13.3). Among males, the full-period trend was non-significant from 1999–2013 (APC: -1.1916, 95% CI: -3.3945 to 1.0616; $p = 0.278707$), followed by a significant increase from 2013–2021 (APC: 10.5324*, 95% CI: 5.5419 to 15.7588; $p = 0.000246$), then a non-significant decline from 2021–2024 (APC: -11.894, 95% CI: -25.2674 to 3.8726; $p = 0.123479$). Among racial groups, White individuals reported the highest mortality (AAMR: 0.105 in 2024) and mortality trends increased significantly throughout 1999–2024 (AAPC: 3.6351*, 95% CI: 2.3659 to 4.9202; $p = 0.000004$).

Regionally, the Midwest showed a significant increase over the full period (AAPC: 2.7209*, $p = 0.000658$). In contrast, the South had no significant overall change, despite a significant decline from 1999–2015 (APC: -3.1721*, $p = 0.030685$), a sharp significant increase from 2015–2022 (APC: 18.4202*, $p = 0.001398$), followed by non-

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significant decline from 2022–2024. By urbanization, large central metro areas showed a non-significant increase from 1999–2024 (AAPC:3.2737; p=0.10044), whereas medium metro areas had a significant increase (AAPC: 3.1866*, p = 0.000518).

Conclusion: TBI and sepsis reveal significant mortality disparities across age, sex, race, and geography. These findings identify critical research gaps. Urgent, targeted neurological and antimicrobial interventions are needed to address this underrecognized public health crisis.

S331: Results of a Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Bezisterim (NE3107) in Long COVID (ADDRESS-LC)

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Background: Long COVID continues to burden a significant percentage of the population with debilitating symptoms, including cognitive impairment ("brain fog"), fatigue, post-exertional malaise (PEM), and sleep disturbance, contributing to a poor quality of life (QoL). Evidence suggests that ongoing neuroinflammation may be mediated by the persistence of a viral (or viral antigen) reservoir, activation of other viruses, protracted macrophagic inflammatory memory, or Spike protein, which can persist long after infection and promote neuronal death and cognitive dysfunction through the toll-like receptor (TLR) pro-inflammatory pathways. Bezisterim (NE3107) is an oral, blood-brain barrier–permeable, non-immunosuppressive, anti-inflammatory, insulin-sensitizing, synthetic dehydroepiandrosterone (DHEA) derivative that inhibits TLR-driven neuroinflammation. We will summarize topline data from ADDRESS-LC (NCT06847191), a signal-seeking proof-of-concept phase 2 study evaluating the efficacy, safety, and tolerability of bezisterim in adults with Long COVID who have cognitive impairment sequelae and fatigue.

Methods: ADDRESS-LC is a double-blind, randomized, placebo-controlled study comprising screening (up to 4 weeks), treatment (12 weeks), and follow-up (4 weeks) periods. Randomized adult (18-64 years) patients with objective and at least moderate subjective cognitive impairment and fatigue are assigned 1:1 to twice daily 20-mg bezisterim or placebo. Assessment at baseline and weeks 4, 8, and 12 evaluate cognition, fatigue, sleep, PEM, QoL, and burdensome symptoms via a bespoke Cogstate Cognition Battery, the Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function Short-Form 8a (SF8a), Fatigue SF13a, Sleep Disturbance SF8a, DePaul Symptom Questionnaire-PEM, and SF-12 Health Survey, among others. As a proof-of-concept study, all efficacy endpoints will be tested independently without multiplicity adjustment. No single endpoint is designated as primary. Safety assessments include monitoring of treatment-emergent adverse events (TEAEs) and clinically significant changes in vital signs, physical examination, 12-lead electrocardiograms, and laboratory measures.

Results: Topline results for objective and subjective efficacy measures of key neurological domains in patients completing treatment will be presented for bezisterim vs placebo. Descriptive statistics will be provided as a safety summary, inclusive of counts and proportions of those patients experiencing TEAEs.

Conclusion: We anticipate that bezisterim will be well tolerated by participants with Long COVID. Understanding the impact of bezisterim on objective and subjective measures of cognitive impairment, fatigue, sleep disturbances, PEM, and QoL will help further the search for valuable treatment options. These results will help improve our understanding of the role of neuroinflammation in Long COVID symptoms and may lead to meaningful insights on this widespread public health problem.

S333: Melkersson–Rosenthal Syndrome in Three Affected Siblings: A Familial Case Series Suggesting Possible Genetic Predisposition

Presenting Author: *Mazin Mohamed Ali, Researcher, Flint, MI*

Background: Melkersson-Rosenthal Syndrome (MRS) is a rare idiopathic neuro- mucocutaneous disorder characterized by the classic triad of recurrent facial palsy, orofacial edema, and fissured tongue. The exact etiology remains uncertain, with potential genetic, inflammatory, and infectious components contributing to its development. This case series aims to analyze the clinical presentation, treatment response, and possible genetic factors in MRS.

Methods: We report three affected siblings diagnosed with MRS: Case 1 (male, current age 32 years, presented at age 20 years), Case 2 (female, current age 31 years, presented at age 22 years), and Case 3 (female, current age 27 years, presented at age 23 years), highlighting varying treatment responses. While Case 1 showed rapid resolution with a short corticosteroid course (prednisone 60 mg/day × 5 days) and complete recovery, Cases 2 and 3 required prolonged corticosteroid therapy (>8 weeks) with incomplete recovery and side effects (steroid-induced acne, fatigue). Family pedigree analysis suggests possible genetic predisposition, though no genetic testing was performed.

Results: This case series highlights the heterogeneity of MRS in terms of clinical presentation and steroid response. The differences observed suggest a potential genetic component that warrants further investigation. Additionally, the observed gender-based variations in treatment response suggest that hormonal or immunological factors may affect disease progression and therapeutic outcomes.

Conclusion: Conclusion This case series highlights the heterogeneity of MRS in terms of clinical presentation and steroid response. The differences observed suggest a potential genetic component that warrants further investigation.

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Additionally, the observed gender-based variations in treatment response may suggest that hormonal or immunological factors may affect disease progression and therapeutic outcomes. Although the more favourable response observed in the male sibling is an interesting finding; however, given the extremely small sample size, this observation should be considered hypothesis-generating only. The presence of MRS in all three siblings challenges the traditionally reported autosomal dominant inheritance pattern, suggesting the need for further research into genetic mechanisms. Future studies should focus on genetic screening, long-term follow-up, and gender-based differences to better understand disease progression and optimal treatment strategies.

S334: THE CHALLENGES OF UTILIZING ELECTRODIAGNOSTIC STUDIES IN RESOURCE-LIMITED SETTINGS: LESSONS FROM CAMBODIA

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Co-Authors: *Soma Sahai-Srivastava, MD, Keck School of Medicine, University of Southern California, Los Angeles, CA*

Background: Electrodiagnostic (EDX) studies are essential for managing neurological conditions yet developing nations like Cambodia face severe barriers to their use. Cambodia has a critical specialist shortage, with a neurologist-to-population ratio of approximately 1:526,000, or 0.19 neurologists per 100,000 population.

Consequently, neuromuscular disorders are often mismanaged, leading to preventable disabilities and diminished quality of life.

Methods: A multi-tiered intervention was launched in Phnom Penh, including the donation of an EMG/NCS machine. Thirteen physicians participated in a one-week "flipped classroom" EDX course featuring pre-recorded lectures and in-person workshops. The curriculum focused on regional pathologies like traumatic nerve injury and acute inflammatory polyneuropathy. Competency was measured via pre- and post-course assessments evaluating electrode placement, waveform interpretation, and needle safety.

Results: The intervention identified critical technical, economic, and systemic barriers: • Environmental and Consumable Barriers: High heat and humidity prevented adhesive surface electrodes from maintaining skin contact. Additionally, the high cost of disposable concentric needles and electrodes creates a significant financial burden for local clinics. • Electrical Challenges: Unstable power grids caused technical limitations. While DC (Direct Current) from battery units offers cleaner signals, reliance on AC (Alternating Current) introduced significant 60Hz/50Hz interference that obscured small potentials. • Technical Hurdles: A lack of normative reference data specific to the Cambodian population forced reliance on Western standards. Accurate sensory NCS was hindered by high skin impedance and stimulus artifact. • Needle EMG Barriers: Transitioning to invasive testing was difficult; while knowledge scores rose from 34% to 66%, only 33% felt confident in needle EMG. Monopolar needles required noisy surface references, while bipolar needles provided better rejection but were cost prohibitive.

Conclusion: Building sustainable EDX programs is feasible but requires addressing unique regional obstacles. To mitigate the costs and technical difficulty of needle EMG, future models should explore Neuromuscular Ultrasound and Surface EMG as supplemental tools. Integrating Telehealth for remote supervision can bridge the mentorship gap. Long-term success depends on a longitudinal model that leverages these technologies to ensure diagnostic accuracy in underserved regions.

S335*: Responsible AI in Neurology Patient Care: A Systematic Review of Clinical AI Algorithm (2020–2025)

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Background: Artificial intelligence (AI) is increasingly integrated into direct patient care in neurology. Despite this growth, it remains unclear how consistently these studies incorporate and report key Responsible AI (RAI) principles, including fairness, transparency, accountability, privacy, and safety. Incomplete reporting of these domains may limit trust, reproducibility, and equitable clinical adoption.

Methods: We conducted a systematic review of original research evaluating AI tools for direct adult neurology patient care. Responsible AI reporting was assessed using a 12-domain framework adapted for this review, based on core principles from the WHO Ethics and Governance of AI for Health guidance and other governance frameworks, including MINIMAR, TRIPOD+AI, CONSORT-AI, FUTURE-AI, GMLP, and IMDRF-related guidance. The 12 assessed domains included: Governance & Accountability; Problem Formulation & Stakeholder Engagement; Data Quality, Provenance & Representativeness; Fairness, Equity & Bias Mitigation; Privacy, Security & Data Governance; Transparency & Documentation; Explainability & Interpretability; Validation, Robustness & Generalizability; Safety, Effectiveness & Clinical Benefit; Human Oversight, Usability & Workflow Integration; Monitoring, Maintenance & Lifecycle Management; and Sustainability, Scalability & Public Benefit. Each domain was scored from 0 to 2, yielding a maximum total score of 24.

Results: A total of 11,760 records initially identified, 1,445 articles underwent detailed full-text assessment, with 1,001 studies meeting all inclusion criteria for final RAI extraction. The mean total RAI score across these studies was 12.7/24 (53.0% of the maximum score). While studies reported a median of 10 out of 12 RAI domains (Interquartile Range:

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8–11), the depth and completeness of reporting within the domains varied. Analysis of temporal trends showed that RAI reporting improved significantly over the study period, with the mean percentage of the maximum RAI score increasing from 44% in 2020 to 58% by 2025. However, a distinct reporting gap was identified between economic regions; studies from developed countries achieved higher mean RAI scores (13.8) compared to studies from developing countries (10.2). Domain-specific analysis revealed that "Data Quality, Provenance, and Representativeness" was the most consistently reported domain (92% of studies), whereas "Monitoring, Maintenance, and Lifecycle Management" was the least reported, appearing in fewer than 5% of the literature.

Conclusion: While the volume and reporting quality of AI in neurology are improving, significant gaps remain regarding post-deployment monitoring and global reporting equity. To ensure the safe and equitable integration of AI into neurological practice, standardized RAI reporting frameworks must be adopted globally, with a specific focus on longitudinal safety monitoring and inclusive data representativeness.

S336: Rapid Whole-Genome Sequencing in Hospitalized Adults with Complex Unexplained Acute Neurologic Conditions: Diagnostic Yield and Clinical Impact

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Background: Complex unexplained acute neurological presentations represent a diagnostically challenging population within in-patient adult Neurology hospitalizations often experiencing prolonged duration of diagnostic odyssey prior to considering genetic etiologies. Adult-onset manifestations of inherited neurologic disorders are usually non-specific with significant overlap with acquired etiologies along with unreliable family history when compared to pediatric subgroup. Genomic testing is often underutilized in adult inpatient neurology. Rapid whole-genome sequencing (rWGS) enables comprehensive detection of inherited neurologic disorders within a clinically actionable timeframe, but data regarding its diagnostic yield in adult inpatient cohorts is not available at this time.

Methods: We conducted a retrospective review of adult inpatients (≥18 years) who underwent rWGS between March 2024 and March 2026 at Mayo Clinic, Florida as part of their inpatient diagnostic evaluation for unexplained or rapidly progressive neurologic manifestations after nondiagnostic standard testing. rWGS was pursued when the treating Neurology team suspected a potential genetic etiology or the necessity to exclude an inherited etiology in the context of complex phenotypes with rapid progression. Clinical features, genetic test results, and genotype-phenotype correlations were reviewed. Diagnostic yield was defined as identification of a pathogenic or likely pathogenic variant that explained the patient's neurologic presentation.

Results: Sixteen patients (10 females, 6 males) underwent rWGS during hospitalization. The mean age was 52.2 years (20-79 yrs). All patients presented with complex, rapidly progressive multifocal neurological manifestations, most commonly ataxia (18.8%), followed by epilepsy (12.5%), movement disorder (12.5%), peripheral neuropathy (12.5%), and encephalopathy (12.5%), with additional presentations including motor neuron disease, recurrent stroke, myelopathy, and neuropsychiatric manifestations (31.2%). Turn around time of rWGS is 5 days, and established diagnosis in 6 patients, resulting in a diagnostic yield of 37.5%. Variants of uncertain significance without clear phenotype correlation were identified in 2/16 patients (12.5%), and no diagnostic genetic findings were identified in the remaining (50%).Identified diagnoses included juvenile amyotrophic lateral sclerosis(FUS), choreoacanthocytosis (VPS13A), Huntington disease(HTT), hereditary cerebral small-vessel (FLNA), mitochondrial neurologic disease (MT-ND1)and 16p11.2 duplication syndrome. In diagnosed cases, rWGS clarified disease etiology and longitudinal management planning. Exclusion of genetic causes in relevant presentations also helped in moving forward with empirical treatment options.

Conclusion: In this adult inpatient neurology cohort, rWGS achieved a diagnostic yield of 37.5%. These findings strongly support the clinical utility of early consideration of rWGS in select hospitalized adults with unexplained neurological manifestations, highlighting its potential to expedite diagnosis, guide management, shorten the hospital stay and inform family counseling.

S338: Temporal Trends in Mortality Due to Intracranial, Intraspinal Abscess and Sepsis in the United States: A CDC WONDER Analysis 1999-2024

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Background: Intracranial and intraspinal abscesses are rare but potentially fatal infections of the central nervous system, yet devastating when missed. Sepsis accelerates neurological decline, but demographic and temporal mortality patterns remain uncharted. This study analyzes CDC WONDER data to assess mortality trends in the United States from 1999 to 2024

Methods: We conducted a retrospective CDC WONDER analysis (1999–2024) using ICD-10 followed by G06 (Intraspinal abscess) and A40-A41 (Sepsis). Age-adjusted mortality rates (AAMR) were stratified by sex, race, census

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region, and urbanization. Joinpoint regression calculated Annual Percent Change (APC) and Average Annual Percent Change (AAPC) with p<0.05.

Results: From 1999-2024, 5946 deaths were reported. The overall age-adjusted mortality rate (AAMR) increased significantly from 1999 to 2024, with an AAPC of 3.61* (95% CI: 2.73–4.50). Males exhibited higher mortality than females (0.1581 vs. 0.1329 per 1,000,000) in 2024. Males also had a significant overall increase (AAPC: 2.9673*, p = 0.000014), with a non-significant rise from 1999–2009 (APC:0.2192, p =0.882682), followed by a significant rise from 2010–2024 (APC: 4.8411*). Females showed a significant full-period change (AAPC: 2.3921*, p = 0.000156), and a significant increase from 1999–2024 (APC: 2.3921* p = 0.000156). Among White individuals, AAMR increased significantly across the full study period (AAPC: 5.2655*). Regionally, the Midwest showed a significant increase from 1999–2024 (AAPC: 4.06*, p < 0.000001). In the South, the overall trend was non-significant (AAPC:3.79, p < 0.000001). By urbanization, large central metro areas showed a non-significant overall increase from 1999–2020 (AAPC: 0.4536), whereas medium metro areas demonstrated a significant increase (AAPC: 4.7268*). The adults aged 75–84 years exhibited the highest mortality (0.4715) and showed a significant increase from 1999–2024 (AAPC: 3.2900*).

Conclusion: Intracranial and intraspinal abscesses with sepsis reveal mortality disparities across age, sex, race, and geography. These findings identify critical research gaps. Urgent, targeted neurological and antimicrobial interventions are needed to address this underrecognized public health crisis.

S339: Improving Inpatient Length of Stay Among Neurology and Medicine Services, While Maintaining Provider Autonomy: A Discharge Prediction Tool on Hospital Throughput

Presenting Author: *Melissa Reider-Demer, DNP, MSN, CNP, FAAN, Los Angeles, CA*

Background: Inefficient discharge processes create barriers to hospital throughput and limit access to inpatient care. To address this concern, we developed standardized discharge pathways that define stakeholder responsibilities from admission through discharge, paired with MRD consensus criteria for selected neurology and internal medicine diagnoses. These efforts aimed to improve discharge predictability and throughout while reducing inpatient length of stay (LOS). This model has shown to be effective to predict hospital discharges and improve LOS. This is an obtainable and maintainable process that can be used on any inpatient service.

Methods: This study took place at a major academic implementing a multidisciplinary standardized discharge pathways from November, 2022, to January 2026. Stakeholder checklists supported adherence to role-specific responsibilities. Neurology and internal medicine hospitalists jointly defined MRD consensus criteria for selected diagnosis: TIA, seizure, demyelinating disease, and syncope. which avoided provider variation and discharge at an arbitrary time of day. Once a patient met MRD criteria, the provider sent a secure message via the electronic health record to the charge nurse, case manager, and pharmacist indicating readiness for discharge. Unit nurses were expected to complete discharge within two hours. Data points were tracked through interdisciplinary rounds and analyzed using statistical process control charts (SPC), including X-bar, S-chart, and P-charts. Provider satisfaction was also surveyed.

Results: During the study period, 850 patients were included; of whom 79% met the 2-hour discharge goal. Median discharge time from order placement to completion decreased from 180 minutes to 94 minutes, an 86 minute decrease. LOS decreased by 3.3 days from 5.2 to 1.9 days. Case mix index improved from 1.78 to 2.12. Excess bed days decreased by 2 days. 30-day emergency department visits and readmissions remained stable.

Stakeholder feedback indicated that the process did not add workflow burden and improved throughput. **Conclusion:** Among neurology and internal medicine services, standardized discharge pathways employing MRD criteria reduced discharge delays and improved LOS, case mix index, and bed availability, without compromising patient safety or increasing stakeholder burden. These processes can be scaled up to any service line.

S341: Trends in the Neurology Physician Training Pipeline: A Retrospective Observational Study

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Background: With the rising burden of neurologic disease, there is a critical need to ensure a robust and diverse neurology workforce. However, current understanding of trends in the neurology trainee pipeline is limited, including modern trainee specialty decision-making, applicant experiences, and demographic diversity. We sought to characterize trends in neurology applicants and residents using publicly available data from the Association of American Medical Colleges (AAMC) Report on Residents to inform workforce development and recruitment strategies.

Methods: We retrospectively analyzed trends in the AAMC Report on Residents from 2020-2025, including medical student interest in neurology, applicant experiences, and current resident demographics (gender, race and ethnicity, and type of medical degree). Shannon diversity index was calculated based on neurology residents' race and ethnicity over time. Trends in applicant and resident characteristics were assessed via weighted linear regression or binomial logistic regression with Bonferroni correction.

Results: Medical student interest in neurology was stable over time (p>0.05); however, only 26.7% of applicants indicated interest in neurology earlier in medical school (vs 56.1% different specialty, 17.2% undecided, p<0.001). Demographic characteristics of neurology residents have also changed over time, with significant increases in women (OR 1.040, 95% CI 1.023-1.057), DO residents

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(OR 1.045, 95% CI 1.022-1.070), Asian (OR 1.075, 95% CI 1.054-1.096), and Other (OR 1.196, 95% CI 1.146-1.249) residents and decreases in men, international medical graduates (OR 0.976, 95% CI 0.959-0.993), and White (OR 0.906, 95% CI 0.890-0.922) residents. Overall diversity of neurology residents has increased over time (R^2=0.864, p=0.007). Median number of reported abstracts, presentations, and publications also increased by approximately 0.46 experiences per year (p=0.003), while other research, work, and volunteer experiences remained stable.

Conclusion: The neurology training pipeline is evolving at both the potential applicant and current resident levels. Although applicants in neurology remain stable, most applicants initially considered other specialties. Diversity has increased across gender, race/ethnicity, and educational background. This may reflect successful efforts in mitigating underrepresentation in neurology; however, trends were limited to certain groups, suggesting more targeted recruitment efforts could be deployed. Future efforts will compare changes in neurology trainees to other subspecialties. Together, these findings highlight opportunities to better understand drivers of specialty choice and to refine targeted recruitment strategies, with implications for neurology workforce development, education, and patient care.

S342: Perceived Severity of Common Neurological Symptoms of Multiple Sclerosis Among Healthy Women in Zambia: A Community-Based Participatory Study

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Background: Multiple sclerosis (MS) is more common in women and increasingly recognized in sub-Saharan Africa (SSA), yet diagnosis is often delayed. In Zambia, those currently diagnosed with MS are more educated, wealthy and urban-based compared to the average Zambian, yet many delayed care-seeking due to normalization or invisibility of symptoms. Per the Health Belief Model, perceived severity of symptoms influences healthcare-seeking behavior, and ranking can inform prioritization of strategies for targeted awareness campaigns and more effective, equity-focused interventions. This study evaluated perceived severity of common presenting symptoms of MS among healthy, community-dwelling Zambian women from diverse geographic backgrounds.

Methods: A community-based participatory workshop was conducted in local language using human-centered design methodology at three Zambian sites: Lusaka (urban), Monze (semi-urban), and Chikankata (rural). Women aged 18–40 presenting for routine care at antenatal clinics or mothers' shelters were eligible. In small groups, participants first completed terms mapping for ten symptoms of MS to understand language and associated frameworks. Groups then ranked each symptom from least to most serious, with equal ranks allowed.

Participants' ranking justification were audio recorded, transcribed, and translated to English. Mean rank scores were calculated (1-10) and categorized into tertiles (most serious, somewhat, and least). Transcripts were thematically analyzed through rapid qualitative analysis.

Results: Seventy women participated with a mean age of 28.3 years (SD±6.8). Terms mapping revealed several different terms and causes associated with each symptom. The most serious perceived symptoms were vision loss (mean score=9.1), difficulty urinating (8.1) and difficulty walking (6.7). Somewhat serious symptoms were dizziness (6.3), leg weakness (5.5), arm weakness (5.2) and blurry vision (5.1). Least serious symptoms were arm numbness (3.3), leg numbness (3.1), and fatigue (2.1). When rankings were justified, participants considered functional impact and perceived cause. Sub-analysis by site revealed that dizziness was considered relatively more serious in the rural site with fear of falls and head injury cited as contributing factors.

Conclusion: Functional impact on daily life and perceived cause both influenced ranking of perceived severity. Vision loss and difficulty with walking or urinating were perceived as most serious, while numbness and fatigue were least serious. Future targeted educational interventions to increase care-seeking behavior should address the spectrum of neurological symptoms while emphasizing that those perceived as less serious, specifically numbness and fatigue, may still require timely medical evaluation. Furthermore, heterogeneity in perceived symptom severity, especially in rural settings, warrants educational interventions to be tailored to local contexts.

S343: Neurological Disorders in an Indigenous Amazonian Population: A Community-Based Study of Shawi Adults in Peru

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Background: Neurological disorders are among the leading causes of disability and mortality worldwide. In Peru, stroke is a major cause of death and long-term disability among older adults. However, epidemiological data on neurological disorders in Amazonian Indigenous populations are scarce,

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particularly among the Shawi people, limiting the development of culturally appropriate health strategies. This study aims to estimate the frequency of cognitive impairment and other neurological disorders and identify associated risk factors among Shawi communities in Loreto, Peru.

Methods: We conducted a cross-sectional, community-based study of adults aged ≥50 years in Shawi communities in Loreto, Peru (N=434). Participants underwent structured assessments including cognitive (3MS, RUDAS-Peruvian version), functional (PFAQ), mental health (PHQ-9, GAD) measures and validated stroke, epilepsy and parkinsonism screening questionnaires. Individuals with abnormal screening or clinical concerns were referred for neurologist evaluation (n=191). Multivariable logistic regression was used to identify factors associated with neurologist-confirmed neurological diagnoses.

Results: Participants had a mean age of 60.6±8.6 years, with extremely low educational attainment (mean 1.5 years) and marked socioeconomic disadvantage. Across the cohort, cognitive and functional impairment were common (mean 3MS 70.9±11.7; 54% with functional impairment). Among those evaluated by a neurologist, 41.4% had a confirmed neurological diagnosis, most commonly neurocognitive disorder (28.3%), followed by parkinsonism (6.8%), stroke (5.8%), and epilepsy (3.1%). Older age (OR 1.046, p=0.047) and smaller household size (OR 0.825, p=0.033) were independently associated with neurological diagnosis, while vascular risk factors were not.

Conclusion: Neurological disorders, particularly neurocognitive impairment, represent a substantial and likely underrecognized burden in Shawi communities.Social and structural factors, including household composition, likely influence the risk of neurocognitive impairment. Our findings highlight the need for culturally adapted diagnostic tools and health system strategies that address social determinants of brain health in Indigenous populations.

S344: MRNA Cytokine Profiling in Tuberculous Meningitis-associated Infarctions

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Background: Infarctions in tuberculous meningitis (TBM) may occur in 15-57% patients, and may also develop in the initial period of treatment. Cytokines play an important role in the pathogenesis of vasculitis. There is paucity of information regarding the role of cytokines in predicting the infarction in the patients with TBM. We report mRNA profiling of cytokines in TBM and its association with infarction at presentation and within 3months.

Methods: 72patients with TBM were prospectively included, and their clinical, MRI, and mRNA profiling of tumour necrosis factor TNF-α and IL-6genes in the peripheral blood mononuclear cells were done at admission and 6 weeks of antitubercular treatment, and 20 healthy age and gender matched controls. Cytokine profiling was done using reverse transcriptase polymerase chain reaction. Occurrence of infarction on a repeat MRI at 6weeks and 3months was noted. Outcome was defined at 6 months using modified Rankin Scale (mRS), and categorized as death, poor and good.

Results: MRI at admission revealed infarction in 26(36.6%) patients, and 15(20.83%) patients developed infarctions within 3months of treatment. The TNF-α and IL-6 were higher in the patients compared to controls. The expression of TNF-α (10.80±6.42 vs7.25±4.46 p.,0.01) and IL-6(1.49 ±1.20vs3.89 ±3.80 p.,0.001) were higher in infarct group both at baseline and within 3months.Stage of meningitis and infarct at admission predicted infarction after treatment 14(53.8%) had poor &12(46.2%) had good outcome.

Conclusion: Patients with higher expression of TNF-α and IL-6 had infarction at admission and 15% also developed infarction within 3 months of treatment. These patients may require more aggressive immunosuppression.

S346: Robotic-Assisted Versus Fluoroscopic-Guided Surgery on the Accuracy of Spine Pedicle Screw Placement: A Systematic Review and Updated Meta-Analysis

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Background: Accurate pedicle screw placement is critical in spine surgery to minimize complications and improve outcomes. Robotic-assisted (RA) techniques have emerged as an alternative to conventional fluoroscopy-guided (FG) methods, aiming to enhance precision and safety. This systematic review and updated meta-analysis compares the accuracy, perioperative outcomes, and complications between RA and FG approaches.

Methods: A comprehensive literature search was conducted to identify comparative studies evaluating RA versus FG pedicle screw placement. A total of 28 studies met the inclusion criteria. Continuous outcomes were analyzed using mean difference (MD), while dichotomous outcomes were assessed using risk ratios (RR), both with 95% confidence intervals (CI).

Results: RA surgery demonstrated significantly improved screw accuracy, with higher rates of Grade A placement (RR 1.19, 95% CI 1.12 to 1.27) and lower rates of suboptimal placements, including Grade B (RR 0.42), Grade C (RR 0.40), and Grade D (RR 0.56). Complication rates were significantly lower in the RA group (RR 0.39, 95% CI 0.29 to 0.51), alongside a modestly higher procedural success rate (RR 1.09, 95% CI 1.02 to 1.17).Among continuous outcomes, RA was associated with reduced hospital stay (MD -0.88 days) and decreased intraoperative blood loss (MD -65.84 mL). No significant differences were observed in operative time (MD 15.84), fluoroscopy time, radiation dose, or postoperative pain scores (VAS back and leg).

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Mortality rates and distribution of operated vertebral levels were comparable between groups.

Conclusion: Robotic-assisted spine surgery significantly improves pedicle screw accuracy and reduces complications compared to fluoroscopy-guided techniques, while maintaining comparable operative time and clinical outcomes. These findings support the growing adoption of robotic systems in spine surgery; however, further high-quality randomized trials are needed to confirm long-term benefits and cost-effectiveness.

S347: Adjunct Corticosteroid Use in Pediatric Herpes Simplex Virus Encephalitis and Post-Infectious Autoimmune Encephalitis: A Case Report

Presenting Author: *Amel Hanan Zehra, MBBS, Medstar Harbor Hospital, Baltimore, MD*

Co-Authors: *Fizza Tariq, MD, Charleston, United States, Florian Capobianco, MD, Medical University of South Carolina, Charleston, SC, Barbra Giourgas, MD, Medical University of South Carolina, Charleston, SC*

Background: Herpes simplex virus encephalitis (HSVE) is the most common cause of sporadic fatal encephalitis, with mortality exceeding 70% without antiviral treatment. Although acyclovir has greatly improved survival, neurological sequelae remain common, and relapse occurs in 5% to 27% of cases. The recent DexEnceph trial (2025) evaluated adjunctive corticosteroids in patients presenting with encephalitis when autoimmune etiologies and HSVE were both possible, suggesting that early corticosteroid therapy may be safe even when HSVE is ultimately confirmed. We report a pediatric case illustrating the potential benefit of early steroid use during both acute HSVE and subsequent autoimmune relapse.

Methods: Case Report

Results: A 9-year-old female with ADHD presented with a generalized tonic-clonic seizure in the setting of fever followed by left-sided weakness, dysarthria, and confusion. Initial CT was unremarkable. CSF showed lymphocytic pleocytosis (78 WBC/μL). MRI revealed diffusion restriction of the right temporal lobe, hippocampus, and insula. Intravenous acyclovir was initiated 24 hours after presentation due to concern for HSV encephalitis. CSF PCR confirmed HSV-1 infection. Three days into her course, the patient developed worsening lethargy and headache, prompting repeat imaging that showed a new intraparenchymal hemorrhage in the right anterior temporal lobe with worsening edema. Dexamethasone was initiated, resulting in marked clinical improvement within 48 hours. She completed a 21-day course of acyclovir and was discharged on antiseizure medications. One month later, she re-presented with tics, stuttering, and behavioral changes. MRI remained stable and repeat HSV PCR was negative.

Despite negative autoimmune testing, she met criteria for probable seronegative autoimmune encephalitis and was treated with high-dose methylprednisolone, resulting in rapid resolution of symptoms. This fits the diagnosis of post-HSV autoimmune encephalitis, which can occur even when antibody testing is unrevealing. At 18 months after initial presentation, she showed marked improvement in behavior and physical symptoms and remained seizure-free off medications, though she continued to have minor deficits in executive function, language, and memory consistent with right temporal lobe injury.

Conclusion: This case underscores the potential role of adjunct corticosteroid therapy in the management of acute HSVE with cerebral edema or other clinical deterioration as well as in relapsing post-herpetic autoimmune encephalitis without complications. Additionally, this case highlights the risk of post-HSVE autoimmune encephalitis, even in the absence of detectable antibodies, emphasizing the need for continued clinical vigilance, timely immunotherapy, and long-term follow-up. Further large-scale studies are required to define the long-term safety and efficacy of corticosteroid use in HSVE.

S348: Video-Based Artificial Intelligence for Neurological Diagnosis: A Systematic Review of Diagnostic Performance and Clinical Applicability

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Background: Artificial intelligence applied to video analysis is increasingly used as a diagnostic support tool in neurology, particularly in the evaluation of seizures and movement disorders. However, the clinical relevance and diagnostic performance reported across subspecialties within neurology remains uncertain.

Methods: A systematic review was performed including 30 studies applying artificial intelligence to video-based neurological diagnosis. Data extraction included model characteristics, dataset composition, validation strategies, performance metrics, and comparisons with clinicians including external validation, reporting practices, and factors affecting clinical applicability.

Results: Most studies reported high diagnostic performance, typically derived from controlled or curated datasets. There was considerable variability in datasets, outcome definitions, and evaluation approaches, limiting comparability across studies. Included studies spanned a broad range of neurological conditions, including movement disorders, cerebrovascular diseases, and epilepsy. External validation was uncommon 9/30 (30%), and confidence intervals were not consistently reported, restricting interpretability and reproducibility. Direct comparisons with clinicians were limited to 3/30 (10%) and often methodologically constrained. Most studies relied on retrospective data, with little evaluation in real-world clinical settings.

Conclusion: Video-based AI models show strong diagnostic performance in controlled settings, but important limitations

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remain in validation, reporting, and clinical evaluation. In particular, the lack of external validation and consistent statistical reporting restricts their current applicability in routine neurological practice.

S349: Door-to-CT Intervals in Acute Stroke Care in Sub-Saharan Africa: A Scoping Review Protocol with Preliminary Findings

Presenting Author: *William Tembo, M.D, University of Zambia Lusaka, Lusaka*

Co-Authors: *Lyambula David Lyelu, MD, University Teaching Hospital, Lusaka, Lusaka; Madalitso Nthere, M.D., University Teaching Hospital, Lusaka, Lusaka; Theresa Shankanga, MD, University Teaching Hospital, Lusaka, MN; Diwell Mwansa, M.D., University Teaching Hospital, Lusaka, Lusaka; Emmanuel Mukambo, M.D., University Teaching Hospital, Lusaka, Lusaka; Michael Kinkata, MD, University Teaching Hospital, Lusaka, Lusaka; Taonga Msimuko, M.D., University Teaching Hospital, Lusaka, Lusaka; Tamia Banda, MD, University Teaching Hospital, Lusaka, MN; Gabriel Sneh, M.D., M.P.H., Johns Hopkins School of Medicine, University Teaching Hospital, Lusaka, Lusaka; Deanna Saylor, Baltimore, MD*

Background: Timely neuroimaging is essential for diagnosing stroke type and initiating reperfusion therapy, with global benchmarks recommending brain imaging within 25 minutes of arrival. However, emerging studies from sub - Saharan Africa indicate that patients often wait many hours or even days for CT imaging. Despite multiple reports of prolonged imaging times, there is no comprehensive synthesis quantifying DTC delays, identifying system-level barriers, or evaluating interventions designed to improve imaging timeliness in the region.

Methods: This ongoing review follows the Arksey and O'Malley framework and PRISMA-ScR guidelines. A comprehensive search of PubMed, African Journals Online, Scopus, and grey literature (including WHO and Ministry of Health reports) includes English-language studies published between 2000 and 2026. Eligible studies report quantitative DTC times or describe factors or interventions affecting stroke imaging workflow among adult patients in any hospital level. Data are being extracted on study design, setting, DTC intervals, and key barriers. **Results: Results:** To date, 11 studies from eight countries (Nigeria, Ghana, Senegal, Burkina Faso, Ethiopia, Mozambique, Côte d'Ivoire, and South Africa) have been identified. Reported median DTC intervals ranged from 4 to over 24 hours, with less than 5% of patients scanned within one hour of arrival. Common barriers include limited CT availability, after-hours service gaps, out-of-pocket costs, and absence of organized stroke pathways. Only a few studies described structured interventions, such as stroke units or multidisciplinary teams, with limited evaluation of their impact on imaging time. Conclusions:

Conclusion: Preliminary evidence demonstrates profound imaging delays across sub-Saharan Africa, far exceeding global targets. This scoping review will provide the first regional synthesis of DTC intervals, highlighting critical system barriers and identifying research and policy priorities to improve timely stroke diagnosis and care delivery.

S350: Low Utilization and Barriers to Physiotherapy After Stroke in Zambia: A Tertiary Hospital Cohort Study

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Background: Stroke is a leading cause of long-term disability, with the greatest burden occurring in low- and middle-income countries. Access to post-stroke rehabilitation, particularly physiotherapy, remains limited due to structural, financial, and health-system constraints. However, there is limited patient-level data from sub-Saharan Africa quantifying physiotherapy utilization and barriers to access.

Methods: We conducted an observational study of 430 consecutively enrolled stroke patients from a tertiary hospital-based registry at the University Teaching Hospital, Lusaka, Zambia, between 2020 and 2025. Patients were followed for 3 months to assess survival and physiotherapy attendance. Reported reasons for non-attendance were categorized into structural, health-system/referral, and patient/family/clinical domains.

Results: A total of 410 patients were included (mean age 56.9 $\pm$ 15.5 years; 56.1% female). Median NIHSS was 11 (IQR 6–18). Ischemic stroke was the most common subtype (61.2%). At 3 months, 360/410 patients (87.8%) were alive. Among 356 survivors with valid physiotherapy data, 122 (34.3%) attended physiotherapy and 234 (65.7%) did not. Among attendees, most reported attending a few times per week (77.0%). Median cost of physiotherapy was ZMW 100 (USD 5.2) (IQR ZMW 60–210 [USD 3.1–10.9], n=88). Distance and travel time were variably recorded, with median distance 4.5 km (IQR 0–10) and median travel time 30 minutes (IQR 20–30). Among non-attendees, barriers were predominantly health-system and access-related. Health-system/referral barriers were identified in 93/234 (39.7%), while structural barriers were reported in 76/234 (32.5%), including financial barriers (29.9%) and transport/escort limitations (27.4%). Patient, family, or clinical factors accounted for 22.2%, and 14.1% had unspecified reasons.

S351: Social Needs Screening in Neurologic Transition of Care: A Mixed Methods Initiative

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Background: Children with neurologic disease face disproportionate socioenvironmental barriers to receiving care. Poverty and adverse childhood experiences are associated with a uniquely elevated risk of cognitive defects and can affect populations that often do not receive social needs screening because of inequitable structural determinants within the health care system (Towfighi et al., Neurology, 2023). The transition to adult neurological care represents a unique opportunity to identify vulnerable patients, and to implement social interventions that may improve their health outcomes. This novel initiative integrates social needs screening into a neurologic transition of care framework at a single academic medical center to assess identification of needs and patient outcomes.
Integration of social needs screening into a neurologic transition of care framework will identify a substantial burden of unmet social needs among young adults with chronic neurologic conditions and be experienced as acceptable and beneficial by patients and caregivers.
Methods: The Accountable Health Communities Health Related Social Needs Screening Tool, a CMS-developed tool for identifying social needs, will be administered to caregivers and patients aged 14-22 with chronic neurologic conditions actively engaged in transition planning (Billioux et al., NAM Perspectives, 2017). Patients with identified social needs will be referred to community organizations, both internal and external, pending family preferences and access. Outcomes will be measured at first follow-up with the adult neurology team. A convergent mixed-methods design will integrate quantitative functional outcomes with qualitative experiential data. Descriptive statistics will characterize baseline social needs prevalence and PedsQL 4.0 scores, with pre/post comparisons using paired t-tests or Wilcoxon signed-rank tests as appropriate (Varni et al., Medical Care, 2001). Semi-structured interviews with patients and caregivers will assess transition experiences; interviews will be analyzed using thematic analysis.
Results: We anticipate that a meaningful proportion of patients will screen positive for unmet social needs, and that fewer identified social needs will be associated with higher PedsQL scores at follow-up. Thematic analysis is expected to reveal that patients and caregivers across social needs levels experience screening as acceptable and beneficial.
Conclusion: Embedding social needs screening within neurologic transition frameworks could reduce care gaps, advance health equity, and support continuity for young adults with chronic neurologic disease. This initiative provides a model for social needs screening integration in pediatric neurologic care.

HEALTH SERVICES AND HEALTH EQUITY RESEARCH

S352-K: A Trauma-Informed Cognitive Rehabilitation Program for Refugees with Traumatic Brain Injury and Cognitive Impairment: An Open Pilot Study

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Background: Traumatic brain injury (TBI) is more prevalent among refugees and asylum-seekers (hereafter, refugees), yet no existing interventions are tailored to their needs or to other similarly trauma-exposed populations. We adapted a cognitive rehabilitation program ("EducaBrain") delivered in English and Spanish in a trauma-informed, culturally tailored manner via live video, using paraprofessional delivery, to engage refugees with TBI and perceived cognitive impairment.
Methods: Participants were adults aged 18–65 (to limit age-related confounding), English or Spanish speaking, self-identified refugees, with mild or moderate traumatic brain injury (TBI) sustained in adulthood (>18 years) using the Ohio State University TBI Identification (OSU TBI-ID), and reporting subjective cognitive impairment on either the PROMIS Cognitive Function score or the cognitive items of the Neurobehavioral Symptom Inventory (NSI).
We conducted a feasibility open pilot with pre- and post-intervention assessments, along with qualitative exit interviews, to evaluate the feasibility and preliminary outcomes of the adapted cognitive rehabilitation program. We iteratively adapted the program throughout the open pilot process.
Results: The sample included 5 English-speaking and 5 Spanish-speaking refugees (n=10), with a mean age of 39.7 years (SD 6.7). Half were women, and 60% had a high school education or less. Participants had lived in the U.S. for an average of 9.0 years (SD 3.7) and represented seven countries, most commonly Guatemala (n=3) and Uganda (n=2). There were pre–post improvements in PROMIS cognitive function and NSI cognitive domain scores, as well as reductions in NSI total scores, PHQ-9 scores, GAD-7 scores, and positive PTSD screens. Participants also reported high feasibility, acceptability, and satisfaction on the Feasibility of Intervention Measure (FIM), Acceptability of Intervention Measure (AIM), and Client Satisfaction Questionnaire (CSQ), respectively. We refined the program by shortening it to eight weeks, revising the manual to a 6th-grade reading level, adding positive psychology components in response to participant needs (e.g., self-compassion exercises), and incorporating content on flexible approaches to TBI recovery and self-advocacy skills. Preliminary thematic analysis of exit interviews identified three themes: (1) motivation for participation, driven by intrinsic and extrinsic factors including lived experience, curiosity, and advocacy; (2) perceived benefits, including cognitive, emotional, and personal growth outcomes and improved sense of self; and (3) barriers to participation, including time constraints, financial stress, emotional vulnerability, and technical challenges with the virtual format.
Conclusion: This trauma-informed, culturally adapted cognitive rehabilitation program for English- and Spanish-speaking refugees, delivered via live video via paraprofessionals, was feasible and showed promise for improving cognitive and affective functioning. These findings inform a subsequent feasibility RCT of "EducaBrain" in preparation for efficacy testing.

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NEUROCRITICAL CARE AND TRAUMATIC BRAIN INJURY

S353-K: Time-Dependent Remodeling of the Choroid Plexus Promotes Neutrophil Recruitment After Traumatic Brain Injury

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Background: Acute inflammation is a major contributor to secondary neurological injury after traumatic brain injury (TBI). The barriers that separate the brain from the systemic circulation are major sites for inflammatory activation and transit points for immune cells into the central nervous system. The choroid plexus is one such barrier and has been shown to play a major role in inflammation in a variety of brain disorders. The choroid plexus may be amenable to therapeutic modulation through treatments directed into the cerebral ventricles. In TBI, such therapeutic advances are hampered by our poor understanding of the role of the choroid plexus. We sought to elucidate time-dependent changes in the choroid plexus in controlled cortical impact, a common model of TBI.

Methods: Male C57BL/6 mice (age 7-12 weeks) underwent controlled cortical impact, a focal hemorrhagic contusion model of traumatic brain injury. Sham craniectomy was used as a control. Downstream analyses were performed on lateral ventricle choroid plexuses harvested at various time points after injury. Bulk RNA sequencing was performed on RNA extracted at 3 hours, 6 hours, and 24 hours after injury. As an additional control in bulk RNA sequencing analysis, we compared transcriptomes to those obtained from choroid plexus in a model of intraventricular hemorrhage. Luminex analysis for proteins CXCL1 and CXCL2 was performed on protein lysates obtained at 6 hours after injury. Immunohistochemistry to label the neutrophil marker myeloperoxidase (MPO) was performed on sections prepared from tissue harvested at 24 hours after injury. Single-cell RNA sequencing was performed on single-cell suspensions obtained at 24 hours after injury.

Results: We found a time-dependent, lateralized remodeling of the choroid plexus transcriptome after TBI. This transcriptome was distinct from that observed after intraventricular hemorrhage. The TBI-induced choroid plexus transcriptome was characterized by early transcriptional upregulation of inflammation-associated transcription factors and several key cytokines and chemokines. Most notably, the two most upregulated genes in the transcriptome by 6 hours after injury were Cxcl1 and Cxcl2, which encode CXC-motif chemokines that are powerful neutrophil chemoattractants. We validated the upregulation of CXCL1 and CXCL2 at the protein level using Luminex. By 24 hours, there was upregulation of a several genes that encode proteins involved in extracellular matrix remodeling. Upregulated transcripts were enriched in targets of several transcription factors most notably NF-κB. Consistent with these changes, we observed a significant influx of neutrophils into the ipsilateral lateral ventricle choroid plexus at 24 hours after injury, using immunohistochemistry. To further delineate cell-type specific changes in the choroid plexus transcriptome, we performed single-cell RNA sequencing on cell suspensions prepared from lateral ventricle choroid plexus. We found that greatest TBI-induced changes to the transcriptome were restricted to the choroid plexus epithelial cells. These cells formed two major clusters (distinguished by expression of the long non-coding RNA MALAT1), which exhibited overlapping but distinct transcriptional changes associated with acute inflammation.

Conclusions: In the hours after TBI, the choroid plexus exhibits profound inflammatory changes, most prominently associated with upregulation of CXCL1 and CXCL2 at both the mRNA and protein level. This is accompanied by influx of neutrophils into the choroid plexus. The additional upregulation of extracellular matrix remodeling genes may suggest a modulation of the barrier into the CNS to facilitate the transit of these neutrophils. The transcriptional changes observed appear to occur predominantly in the choroid plexus epithelium. The response of the choroid plexus epithelium is heterogeneous, clustering based on expression of the long non-coding RNA MALAT1.

MALAT1 and NF-κB may serve as regulators of this process, helping to orchestrate a coordinated, time-dependent inflammatory cascade in the choroid plexus after TBI. In the future, we intend to modulate these upstream pathways and block chemokine expression downstream in the choroid plexus. We anticipate that this will reveal novel mechanisms for immunomodulation in the central nervous system that may have therapeutic applications for TBI and other acute neurological disorders.

S354-K: Distinct Cytokine Trends are Associated with Outcome after Aneurysmal Subarachnoid Hemorrhage

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Background: An inflammatory cascade is activated within the central nervous system following aneurysmal subarachnoid hemorrhage (aSAH). In animal models, the presence of pro-inflammatory cytokines within the cerebrospinal fluid (CSF) is associated with CSF hypersecretion and shunt-dependent post-hemorrhagic hydrocephalus. Additionally, in both animal models of aSAH and in patients, higher concentrations of several pro-inflammatory cytokines are associated with delayed cerebral ischemia (DCI), a devastating form of delayed stroke that occurs in many of these patients, as well as poor neurological outcome. We investigated the relationship between the trajectory of several cytokines within the CSF and outcomes and complications including DCI, shunt-dependent hydrocephalus (SDHC), and poor neurological outcome as measured by the modified Rankin Scale (mRS) at 3 months.

Methods: CSF samples were collected between post-bleed day 0 and 16 from aSAH patients who had external ventricular drains placed as part of their clinical care. We used cytometric bead array assays to analyze the concentration of a panel of cytokines including C-C motif chemokine ligand 2 (CCL2), interleukin (IL)-6, IL-8, IL-10, IL-1β, IL-4, granulocyte-colony stimulating factor (G-CSF), vascular endothelial growth factor-A (VEGF-A), C-X-C motif chemokine ligand 10 (CXCL10), and tumor necrosis factor-α (TNF-α) in these biological samples.

Clinical, demographic, and follow-up data were prospectively collected and adjudicated for accuracy. Poor neurological outcome at 3 months was defined as mRS>3. We investigated the relationship between cytokine trajectories and DCI, SDHC, and 3-month mRS using two complementary approaches. First, we estimated patient-specific cytokine trajectory summaries, including longitudinal intercepts and slopes, and used these features as predictors in logistic regression models, hereafter referred to as momentum models. Second, we used linear mixed-effects models to evaluate how cytokine levels changed over time in relation to each outcome. To assess the most informative post-bleed period, we performed a dynamic time-window analysis in which cytokine trajectory summaries were repeatedly estimated using measurements collected up to different post-bleed days and evaluated using within-sample prediction accuracy and area under the receiver operating curves (AUROC).

Results: 91 patients with aSAH (60±13.7 years old, 68% female) who had >1 CSF sample collected during their hospitalization were included in the analysis. Of these patients, 78 (86%) had available 3-month follow-up data, 77 (85%) had available DCI data, and 12 (13%) had SDHC. In both the momentum and the linear mixed-effects models, higher CSF concentrations of CCL2, IL-6, and VEGF-A over the 2-weeks post-bleed during which CSF was collected is associated with increased likelihood of DCI. Prediction accuracy and AUROC for DCI prediction are highest around post-bleed day 7 for CCL2, day 11 for IL-6, and day 13 for VEGF-A. Higher CSF concentrations of IL-6 and IL-10 are associated with increased likelihood of shunt dependence in the momentum model, and IL-6, IL-10, CXCL10, IL-8, and G-CSF are associated with SDHC in the linear mixed-effects model. For SDHC, prediction accuracy and AUROC are highest in the first week post-bleed (days 5-7) for all significant cytokines. In both the momentum and linear mixed-effects models, higher CSF concentrations of CCL2, IL-6, IL-8, and VEGF-A overall are associated with worse neurological outcome at 3 months, but only CCL2 remains significant after adjustment for DCI. In the dynamic time-window analysis, CCL2 is most predictive of outcome when data is considered from the entire 16-day time window, but when adjusted for DCI the predictive accuracy and AUROC are highest when data through post-bleed day 7 is included.

Conclusions: CCL2 and IL-6 in the CSF of aSAH patients emerged as promising markers of post-aSAH complications and outcomes. Elevated CCL2 during the first post-bleed week was associated with DCI, while persistently higher CCL2 concentrations over the 2-week post-bleed period were associated with worse neurological outcome. Higher CSF IL-6 was also associated with DCI, with the strongest predictive performance around post-bleed day 11, and IL-6 elevations during the first post-bleed week were associated with SDHC. However, IL-6 was not associated with worse neurological outcome at 3 months. Understanding the temporal dynamics of CSF cytokines after aSAH will enable us to develop targeted immunological treatments and to understand the appropriate timing of treatment to improve outcomes in this devastating form of stroke.

355-K: REducing Sympathetic Hyperactivity After Traumatic Brain Injury Using Transcutaneous Auricular Vagus Nerve Stimulation (REST-VNS): A Literature Review, Rationale, And Clinical Trial Protocol

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Background: Sympathetic-parasympathetic imbalance has been associated with worse outcomes after severe traumatic brain injury (sTBI), motivating clinical and translational research targeting dysautonomia to improve patient outcomes. Transcutaneous auricular vagus nerve stimulation (taVNS) offers a non-invasive neuromodulatory alternative to standard pharmacologic approaches. Implementation of taVNS in sTBI to maximize benefit and minimize risk requires careful selection of patients, stimulation parameters, and endpoints. Here, I provide a review and rationale for targeting adult sTBI patients for prophylactic repetitive taVNS to reduce the clinical burden of paroxysmal sympathetic hyperactivity (PSH), a common and severe manifestation of dysautonomia after sTBI, in an early phase 2 clinical trial.

Methods: The REducing Sympathetic hyperactivity after Traumatic brain injury using transcutaneous auricular Vagus Nerve Stimulation (REST-VNS) trial will be a single-center, double-blind, randomized, sham-controlled trial with target enrollment of 50 adults (age 18-65) with sTBI who will undergo one-hour device sessions twice daily beginning 2-5 days post-injury for 5 days (10 sessions) total. The primary outcome will be a between-group difference in

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prospectively measured PSH-AM score burden on study intervention days 3-5. Secondary outcomes will include immediate physiologic changes in heart rate variability measurements of autonomic balance, PSH-directed treatment intensity level (PSH-TIL) on days 3-5, and safety and feasibility metrics. Exploratory measurements will include biomarkers of inflammation, neural injury, and blood-brain-barrier breakdown, radiographic measures of cerebral edema and blood-brain-barrier breakdown, and clinical outcomes such as duration of mechanical ventilation, length of stay, discharge disposition, Glasgow Coma Scale (GCS), JFK coma scale, and Rancho Los Amigos Scale on discharge.

Results: Based on retrospective review of the R Adams Cowley Shock Trauma Center institutional trauma registry, I expect approximately 115 eligible patients per year; target enrollment of 50 patients over 2 years will be feasible with 20-25% enrollment. Based on prior internal data, this will result in >80% power to detect a 4 point difference in the PSH-AM total, a 2 point difference in the PSH-AM CFS subscore, a 1 point difference in PSH-TIL, and an immediate reduction in the LF/HF HRV ratio.

Conclusions: The REST-VNS trial will investigate whether taVNS can reduce the clinical burden of PSH after sTBI via autonomic neuromodulation. If successful, results from this study will guide the design of larger phase 3 trials investigating the intervention's impact on sTBI recovery and healthcare resource utilization.

S356-K: Impaired Cerebral Autoregulation is Associated with Carbon Dioxide Levels in Pediatric ECMO Patients

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Background: Neurologic injuries are common in pediatric patients who require Extracorporeal Membrane Oxygenation. These injuries incur major morbidity and increase the risk of mortality for these patients.

Cerebrovascular autoregulation (CAR) maintains stable cerebral blood flow despite fluctuations in systemic blood pressure. Impaired CAR has been implicated as a risk factor for neurologic injury in pediatric ECMO. The cerebral oximetry index (COx), derived noninvasively from near-infrared spectroscopy and arterial blood pressure correlation, has been proposed as a continuous bedside surrogate for impaired CAR. Blood carbon dioxide (pCO2) is a potent regulator of cerebrovascular tone known to influence autoregulatory function. In pediatric ECMO, large changes in pCO2 often occur between pre-ECMO and intra-ECMO periods and have been associated with increased neurologic complications. These associations suggest that abnormal CO2 mediated impaired CAR contributes to neurologic injury risk. However, the relationship between pCO2 and CAR during ECMO remains poorly characterized. Establishing whether COx varies systematically with pCO2 is important both for validating COx as a physiologically meaningful marker of CAR and for identifying potentially modifiable CO2 targets during ECMO.

Methods: We performed a retrospective observational study of pediatric ECMO patients at a single center. The cohort included all patients aged 0 days through 18 years cannulated onto venovenous (VV) or venoarterial (VA) ECMO with synchronized physiologic monitoring and arterial blood gas data available for analysis. COx metrics were calculated from the 30-minute periods before and after each arterial pCO2 measurement and included mean COx, percent time with COx > 0.3, and area under the curve (AUC) for COx > 0.3. Repeated observations within patients were analyzed using patient-adjusted regression models with clustered standard errors. To characterize the shape of the association between pCO2 and COx without imposing arbitrary thresholds, pCO2 was modeled continuously using cubic spline regression with knots placed at the 10th, 50th, and 90th percentiles of the observed pCO2 distribution. Linear and spline model specifications were compared to assess for nonlinearity.

Results: The study included 11,106 paired pCO2-COx observations from 232 pediatric ECMO patients. Median pCO2 was 43 mmHg (10th percentile 35 mmHg; 90th percentile 56 mmHg). Across all analyses, higher pCO2 was associated with greater COx burden. Spline modeling demonstrated significant non-linear associations between pCO2 and mean COx ($p = 0.00035$), percent time with COx > 0.3 ($p = 7.8 \times 10^{-8}$), and AUC for COx > 0.3 ($p = 1.7 \times 10^{-6}$). The cerebral oximetry metric increased on either side of normocapnia (~40mmHg pCO2). Relative to a reference pCO2 of 40 mmHg, pCO2 values of 55 mmHg were associated with increases of +0.040 in mean COx, +5.43 percentage points in time with COx > 0.3, and +1.276 in AUC for COx > 0.3. At roughly a pCO2 of 60-70, impaired autoregulation burden appeared to plateau.

Conclusions: In pediatric VV and VA ECMO patients, higher pCO2 was associated with progressively impaired CAR as estimated by COx. The analysis indicates a nonlinear relationship characterized by worsening autoregulatory burden above approximately 40-45 mmHg. These findings support the physiologic validity of COx as a dynamic marker of CAR during ECMO and suggest that hypercapnia may represent a modifiable contributor to autoregulatory dysfunction. Continuous COx monitoring may provide a practical bedside approach for individualized assessment of cerebrovascular response to CO2 management during ECMO. To improve generalizability, a similar analysis utilizing multicenter data is planned.

S357-K: Hemoglobin Metabolites and Mitochondrial Dysfunction in Traumatic Brain Injury

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Background: Following traumatic brain injury (TBI), a significant number of patients have associated intracranial

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hemorrhage. After injury, red blood cells lyse releasing hemoglobin (Hgb) and its breakdown product hemin. These byproducts have been shown to cause significant oxidative damage. TBI associated hemorrhage may lead to mitochondrial oxidative stress, cell death, and behavioral impairment.
Methods: Human induced pluripotent stem cell (IPSC)-derived neurons were incubated with hemin or iron. Lipid peroxidation was assessed using BODIPY 581/591 C11 dye, and mitochondrial depolarization was assessed using JC-1 dye. Mitochondrial iron levels were assessed using Mitoferro Green. Additionally, using a mouse model of TBI, free iron producing enzyme (heme oxygenase) and lipid peroxidation markers of immunohistochemistry were assessed in the cortex adjacent to contusion injury were assessed.
Results: In IPSC-derived neurons, increased lipid peroxidation, mitochondrial depolarization, and mitochondrial iron was detected after hemin or iron administration. In the mouse model of TBI, increases in heme oxygenase and lipid peroxidation was detected at the contusion site.
Conclusions: TBI associated hemorrhage may lead to accumulation of mitochondrial iron, which exacerbates TBI-induced mitochondrial oxidative stress and injury. In the future studies, we will use adeno-associated virus (AAV) vector delivery of mitochondrial ferritin (FtMt) gene to the cortex to mitigate oxidative injury and mitochondrial dysfunction in TBI. Additionally, we will assess if reducing mitochondrial lipid peroxides or hydrogen peroxide in TBI will attenuate histological measures of injury and behavioral dysfunction following TBI. This will be accomplished using AAV to express mitochondrial catalase (mitoCAT) or Periredoxin-3 (Prdx3).

S358-K: Cardiac Arrest Stakeholders' Views on Measuring Prognostication Quality in Post-cardiac Arrest Patients: A Concept Mapping Study

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Background: It is unclear how to evaluate the quality of clinicians' outcome predictions for patients treated after cardiac arrest. Past research has focused on sensitivity and specificity for predicting poor outcomes, but other measures may be preferable. Because a perceived poor prognosis often leads to withdrawal of life-sustaining treatments, accuracy cannot be used.
Methods: We performed a concept mapping study, a mixed-methods stakeholder engagement strategy, to both identify and rank potential metrics of prognostication quality. We purposively recruited cardiac arrest stakeholders from unique backgrounds and perspectives: healthcare professionals (physicians, nurses, social workers), family members of survivors (who recovered to varying degrees), family of non-survivors, survivors (who had varying hospital experiences), and domain experts in religion/spirituality and ethics. We conducted three pilot focus groups and individual sessions to refine presentation material and prompt for comprehension and clarity across stakeholder groups. Following piloting, we performed 22 stakeholder sessions that included an introductory presentation and then collected individually enumerated potential measures of prognostication quality after cardiac arrest. We (AS, KJR, ML) removed irrelevant concepts, consolidated duplicative responses, and clarified concepts. We gave this synthesized list of measures back to the same stakeholders to sort concepts based on similarity and rank them by importance. We then generated graphic representations of the results. We will present the graphic results to stakeholders, integrate feedback, and refine results as needed.
Results: We included 69 cardiac arrest stakeholders (18 physicians, 3 nurses, 4 social workers, 14 cardiac arrest survivors, 16 family members of survivors, 7 family members of non-survivors, 9 ethics experts, and 7 spirituality/religion experts). Participants' median age was 48 years (IQR 40-61), 42 (61%) were female, 56 (81%) were white, and 64 (88%) were non-Hispanic. Stakeholders enumerated 443 statements (measures), which we reduced to 125 distinct concepts. Common potential measures could be categorized into reproducibility, transparency, bias, timing, evidence and tests, care team processes and experience, reassessment of prediction, fairness and uncertainty, and ways to review prediction quality (i.e., artificial intelligence, prediction models, guidelines, hospital protocols/checklists, expert panels).
Conclusion: Stakeholders identified numerous potential measures of prognostication quality. Many are novel and rarely used in prognostication literature. Some factors focus on intangible components of prognostication, whereas others, identified as highly important, could be used as key outcome measures to assess clinical practice and test prognostication interventions.

S361: Temporal Trends in Mortality Attributable to Sepsis-associated Encephalopathy in the United States from 1999–2023

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Background: Sepsis-associated encephalopathy (SAE) is a frequent and severe complication of sepsis, contributing to increased morbidity and mortality. Despite its clinical importance, national trends in SAE-related mortality remain underexplored.

Methods: We conducted a retrospective population-based analysis using CDC WONDER Multiple Cause-of-Death data from 1999–2023. Deaths in adults ≥25 years were identified using ICD-10 codes for sepsis and encephalopathy. Age-adjusted mortality rates (AAMRs) per 100,000 were calculated and stratified by sex, race/ethnicity, urbanization, and U.S. census region. Temporal changes were assessed using Joinpoint regression to estimate annual percent change (APC) and average annual percent change (AAPC).

Results: From 1999–2023, 48,420 SAE-related deaths were recorded. The overall AAMR rose from 0.26 in 1999 to 1.67 in 2023, with the steepest increase observed between 2008 and 2021 (APC 11.85*; p<0.001). Mortality was consistently higher in men than women and disproportionately elevated among non-Hispanic Black individuals. Non-metropolitan areas and the South and Midwest regions reported the highest burdens. A non-significant, modest decline was observed after 2021.

Conclusion: SAE-related mortality in the U.S. has increased over the past two decades, with persistent sex, racial, regional, and rural disparities. These findings underscore the need for improved recognition, equitable access to sepsis care, and strengthened surveillance strategies.

S363: Comparative Effects of Volatile Sedation and Total Intravenous Anesthesia on Neurologic Outcomes After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-analysis

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Background: Aneurysmal subarachnoid hemorrhage (aSAH) carries high mortality and disability, largely driven by secondary complications such as cerebral vasospasm and delayed cerebral ischemia (DCI). Anesthetic technique may influence these outcomes through its effects on cerebral perfusion, metabolism, and inflammatory pathways.

Propofol-based total intravenous anesthesia (TIVA) and volatile sedation (VS) have both shown neuroprotective properties in experimental studies; however, clinical evidence remains inconsistent. While observational studies suggest VS may reduce vasospasm and DCI without improving functional outcomes, randomized trials have not confirmed significant differences. This systematic review and meta-analysis evaluate the comparative effects of VS versus TIVA on vasospasm, DCI, cognitive outcomes, and functional recovery after aSAH.

Methods: A systematic search was conducted in PubMed, Scopus, Embase, and Cochrane Library up to March 1, 2026, registered in PROSPERO (CRD420261360563). Randomized controlled trials (RCTs) and observational studies comparing VS and TIVA in adult patients with aSAH were included. The primary outcome was postoperative cognitive dysfunction. Secondary outcomes included vasospasm incidence and functional outcomes at three months. Random-effects models with Hartung-Knapp adjustment were applied. RoB 2 and ROBINS-I tools were used for risk assessment.

Results: Nine studies out of 446 (five RCTs and four observational studies), with 988 patients were included. The VS group included 600 patients and the TIVA group 388 patients; 37.9% of the patients were males. VS was associated with a statistically significant reduction in postoperative cognitive function compared with TIVA (SMD −0.50, 95% CI −0.82 to −0.17; $I^2 = 0\%$). No significant differences were found in vasospasm incidence (RR 0.85, 95% CI 0.65–1.10; $I^2 = 56.4\%$). Vasospasm subgroup analyses showed consistent findings: observational studies demonstrated a non-significant effect (RR 0.84, 95% CI 0.61–1.16; $I^2 = 73\%$), as did randomized trials (RR 0.90, 95% CI 0.51–1.57; $I^2 = 19.7\%$), with no evidence of subgroup interaction ($p = 0.84$). At three months, no significant differences were observed in favorable (RR 1.03, 95% CI 0.89–1.20; $I^2 = 0\%$) or unfavorable functional outcomes (RR 0.94, 95% CI 0.79–1.12; $I^2 = 0\%$).

Conclusion: In patients with aSAH, VS was associated with a worse postoperative cognitive function compared with propofol-based TIVA, while vasospasm incidence and functional recovery didn't differ significantly between groups. Current evidence does not support a clear clinical advantage of VS over TIVA in preventing vasospasm or improving functional recovery. Larger, adequately powered RCTs with standardized anesthetic protocols and long-term follow-up are needed to clarify the clinical impact of anesthetic choice on neurologic outcomes in aSAH.

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S364: Impact of Older Age and Biological Sex on Axonal Survival within the Spinal Cord White Matter After Acute Spinal Cord Injury

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Background: While aging population has resulted in an escalation of fall-related acute cervical spinal cord injury (acSCI) in the elderly, acSCI continues being more prevalent in males. With this, we performed a histopathological and immunohistochemical examination of postmortem spinal cord tissue to evaluate whether older age and biological sex are key determinants for axonal survival post-acSCI.

Methods: This study included post-mortem spinal cord tissue from 54 cases of acSCI and 45 control cases. Each group was subdivided into younger and elderly individuals (≥65 years of age at the acSCI onset, or death in controls). Alternating 6-microm sections from 2-3 segments below the SCI and cervical sections from controls without CNS insult were stained for axons using NF200. The number of axons was counted within the lateral corticospinal tracts (CST), descending vasomotor pathways (DVP) and posterior column (PC) using unbiased stereological techniques.

Results: There were 29 females and 70 males with a mean age of 58.8 years (range age: 16-90 years). Of those with acSCI, 33 individuals were elderly (61.11%) and there were 7 females (12.69%). Among the control cases, there were 18 elderly individuals (40.00%) and 22 females (48.89%). Younger individuals had significantly greater number of preserved axons within the DVP than elderly individuals after acSCI ($p=0.038$). There was a trend towards a greater number of preserved axons after acSCI within the CST and PC in the younger subgroup when compared with the elderly ($p=0.061$; $p=0.078$). Nevertheless, there were no significant differences between younger and elderly subgroups regarding the number of axons within the CST ($p=0.690$), DVP ($p=0.840$) and PC ($p=0.490$) among the controls. Moreover, there were no significant differences between females and males regarding the number of preserved axons following acSCI within the CST ($p=0.298$), DVP ($p=0.261$) and the PC ($p=0.298$).

Females showed similar number axons within CST ($p=0.925$), DVP ($p=0.317$), and PC ($p=0.298$) to males among controls.

Conclusion: Our results indicate that older age at the time of injury negatively affected axonal survival within descending and ascending spinal cord tracts after acSCI. While an underlying spinal cord disease causing axonal loss in either, or both, ascending and descending tracts could explain at least some of those age-related differences, data from the control cases without a history of CNS insult showed no age-related differences within those spinal cord tracts. Moreover, our results suggested that biological sex might not have any significant impact on the axonal preservation caudal to the epicenter after an acSCI.

S365: Conventional-therapy & FES-therapy In-Veritas Effects Study (C-FIVE Study): Neuromodulation in the Rehabilitation for Persistent C5 Palsy After Surgery in Individuals with Cervical Myelopathy

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Background: Surgical decompression remains the only effective treatment to prevent progression of the symptoms in patients with degenerative cervical myelopathy (DCM). However, 1-29% of the patients may develop postoperative C5 palsy. The current standard of care primarily relies on physiotherapy (PT) for management of C5 palsy. This pilot randomized clinical trial assessed the effectiveness of functional electrical stimulation therapy paired with task-specific training (FEST+TST) in the management of individuals with new persistent C5 palsy after surgical treatment for DCM.

Methods: The C-FIVE pilot trial that compared combined FEST+TST and PT (30 1-hour sessions of FEST+TST and 1-hour session of PT) with PT alone (30 1-hour PT sessions) in the rehabilitation of new persistent postoperative C5 palsy in individuals with DCM. We included adults with new persistent C5 palsy (≥3 months) after surgical treatment for DCM. Primary outcome measures included neurological (as assessed using manual muscle testing [MMT]) and functional recovery (as assessed using the Spinal Cord Independence Measure [SCIM]). Secondary outcomes included neurophysiological assessments (using nerve conduction studies, needle electromyography, and C5 dermatomal somatosensory evoked potentials [dSSEP]) and functional MRI (task-based and resting state).

Results: The FEST+TST group ($n=6$) and control group ($n=5$) were comparable regarding their mean age ($p=0.657$), sex distribution ($p=1$), mean body mass index ($p=0.476$), and surgical approach ($p=1$). All participants received PT prior to the trial enrollment. Participants in the FEST+TST group showed a significantly greater decrease of degree of disability and a trend towards better motor recovery when compared with participants who received PT alone. There was also an apparent greater increase in the CMAP amplitude in

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the deltoid and a greater increase in the C5 dSSEP amplitude among those who received FEST+TST compared with those who received PT alone. Task-based fMRI analysis of motor imagery activation revealed no significant whole-brain effects in either trial group. ROI analyses provided preliminary evidence for differential treatment effects, with the FEST+TST group showing increased cortical motor activation (M1, S1, SMA) from baseline to follow-up, while the control group showed decreased or stable activation in these regions.

Conclusion: Our results indicate that FEST+TST was effective to improve functional recovery beyond the conventional PT alone in individuals with persistent postoperative C5 palsy. There were also trends towards better neurological recovery, improved function of the motor > sensory, peripheral and central tracts among those who received FEST +TST, even though they did not reach statistically significance most likely due to type-II error.

S366: Readability of Online Patient Education Materials in Traumatic Brain Injury: A Quantitative, Descriptive Assessment Across Source Types

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Background: Patients increasingly rely on the internet for health information, but these resources are limited by their clarity and readability. To address this, the American Medical Association (AMA) and U.S. Department of Health and Human Services (HHS) recommend that health information be written at or below a 6th-grade reading level. Educational content that exceeds this threshold can reduce engagement with care recommendations and worsen health outcomes. This is especially critical for patients with traumatic brain injury (TBI), whose cognitive and emotional challenges may further limit comprehension and information processing. Given these factors, this study aims to evaluate the readability of online TBI educational materials across source types.

Methods: Materials were identified via Google™ searches in incognito mode using four variations of TBI-related terms. The first 100 results per search were screened, and duplicates were removed. Inclusion criteria were English-language, freely accessible, patient or caregiver-directed content exceeding 200 words.

Advertisements and multimedia without text were excluded. Sources were categorized as clinical, government, nonprofit or advocacy, and commercial organizations. Readability was assessed using five indices (Flesch-Kincaid Grade Level, Gunning Fog Index, SMOG, Coleman-Liau Index, and Automated Readability Index). Results were summarized descriptively, and materials were categorized as Easy (≤6.5 grade-level), Average (6.6–8.5), or Difficult (>8.5) based on AMA and HHS recommendations.

Results: A total of 160 webpages met inclusion criteria, including clinical (n=66), government (n=38), commercial (n=21), and nonprofit/advocacy (n=35) sources. Materials from nonprofit and advocacy groups had the highest mean grade level (11.34 $\pm$ 2.5), followed by commercial (9.62 $\pm$ 2.0), clinical (9.32 $\pm$ 1.8), and government sources (8.48 $\pm$ 1.6). All groups exceeded the 6th-grade recommendation, and three of four groups also surpassed the 8th-grade threshold. Across all materials, the majority were classified as "Difficult" (>8.5), with the highest proportion seen in nonprofit/advocacy sources (94.29%) and the lowest in government sources (42.11%). Only 3.75% of sources were classified as "Easy" (≤6.5).

Conclusion: Online TBI patient education materials across all source types exceeded recommended grade reading levels. Government sources had comparatively lower reading complexity, while nonprofit sources were the most difficult to read. As online health information continues to grow, standardized plain-language approaches are essential to improve accessibility and advance health literacy for TBI patients.

S367: Atypical Cervicomedullary Involvement in HSV-2 Myelitis with Delayed Inflammatory Progression in an Immunocompetent Patient

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Co-Authors: *Mathura Ravishankar, MD, MSc, INOVA Health Fairfax, VA*

Background: Herpes simplex virus type 2 (HSV-2) is an uncommon cause of viral myelitis. When diagnosed, it typically presents with acute lumbosacral radiculomyelitis characterized by radicular pain, weakness, and autonomic dysfunction. Rostral spinal cord involvement and delayed radiographic progression despite antiviral therapy are rarely reported. Recognition of atypical presentations is critical, as inflammatory sequelae may require adjunctive immunotherapy.

Methods: A 66-year-old woman with hypertension, hyperlipidemia, coronary artery disease, depression, and prior Chiari malformation repair presented with shakiness, diarrhea, and gait instability. She had no prior medical history concerning for an immunocompromised state. Laboratory results revealed hyponatremia requiring hospitalization, and her hospital course was complicated by recurrent hypothermia, hypoglycemia, and episodes of transient unresponsiveness, initially attributed to metabolic derangements and poor oral intake. On hospital day four, she developed acute lethargy and became nonverbal, prompting transfer to the intensive care unit.

Neuroimaging with CT and MRI of the brain was unrevealing, and electroencephalography demonstrated generalized slowing without epileptiform activity. Extensive metabolic, infectious, autoimmune, and paraneoplastic evaluation was unrevealing. Cerebrospinal fluid demonstrated lymphocytic pleocytosis, and polymerase chain reaction testing was positive for HSV-2. Spinal MRI demonstrated multifocal T2 hyperintensity involving the right lateral cervical cord extending from C1–C4, with additional patchy abnormalities at C6–C7 and T7–T8, consistent with viral myelitis. The patient was treated with intravenous acyclovir followed by suppressive valacyclovir therapy. Despite virologic treatment

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and improving cerebrospinal fluid parameters, repeat MRI demonstrated progressive T2 hyperintensity extending into the medulla and cervicomedullary junction with nodular enhancement.

Results: Given radiographic progression suggestive of inflammatory injury, high-dose intravenous methylprednisolone was initiated on day 30, resulting in clinical improvement and stabilization of neurologic function. Subsequent cerebrospinal fluid analysis demonstrated improving pleocytosis, and the patient experienced gradual recovery in gait, fatigue, and cognitive function over the following weeks.

Conclusion: HSV-2 myelitis is rare in immunocompetent patients and typically presents in patients with malignancy or acquired immunocompromise. This case demonstrates an atypical pattern of multifocal cervical and thoracic cord involvement with delayed rostral extension into the medulla despite antiviral therapy. The observed radiographic progression and subsequent steroid responsiveness suggest a secondary inflammatory component contributing to neurologic injury. This case expands the recognized spectrum of HSV-2 meningoencephalomyelitis by illustrating cervicomedullary extension and delayed inflammatory progression requiring adjunctive immunotherapy. Recognition of atypical imaging evolution in viral myelitis is essential to guide timely treatment and optimize neurologic outcomes.

S368: Quantitative EEG Features and Time to Recovery of Command-Following in Moderate-to-Severe Traumatic Brain Injury: An Exploratory Analysis

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Background: Early recovery of following commands indicates significant neurological improvement in moderate-to-severe TBI (msTBI) patients, but objective markers predicting its timing remain limited.

Electroencephalogram (EEG) provides direct measurement of acute cortical dynamics but has largely been used qualitatively. As an exploratory proof-of-concept analysis, we evaluated whether quantitative EEG (qEEG) features are associated with time to recovery of following commands in msTBI patients.

Methods: Retrospective cohort study using the UC Irvine TBI and Concussion (NTBIC) database (October 2023–March 2024). Patients with msTBI (GCS ≤12) requiring neuromonitoring or intensive care unit (ICU)-level of care were included; those initially following commands or without EEG monitoring were excluded. Five-minute EEG segments were extracted every 4 hours during the first 24 hours from selected contacts.

Recovery was defined as a GCS motor score of 6; patients who did not recover during the observation period were censored. Five qEEG features (total power, beta, beta–delta ratio, log[beta–delta], z-scored alpha–delta ratio) selected a priori from previous group findings were evaluated in separate Cox proportional hazards models adjusted for historical-TBI prognostic variables (age, sex, blown pupil).

Results: Thirty-nine patients were included (30.8% female; median age 46 years [IQR 27.5–62.5]; median admission GCS 7 [IQR 3–8]; 41.0% with blown pupils). Twenty-six patients (66.7%) recovered following commands (mean time 7.85 days). Higher beta power was associated with shorter time to recovery (HR 1.70, 95% CI 1.02–2.84, p=0.042). Blown pupil was associated with longer time to recovery (HR 0.35, 95% CI 0.13–0.90, p=0.030). The remaining a priori qEEG features were not significantly associated with the outcome. Model discrimination (C-statistic) was 0.67.

Conclusion: Higher beta power was associated with shorter time to recovery of following commands in msTBI patients. A substantial portion of msTBI patients regain this ability during hospitalization. These preliminary findings highlight the potential for qEEG as a prognosticator of neurological recovery and warrant validation in larger, multi-center cohorts.

S369-LB: Exploratory Analysis of Effects of Context-dependent Hypothermia in Two High Acuity Clinical Groups – Patients in Aortic Arch Repair Surgery and Patients with Acute Heart, Brain or Polytrauma

Presenting Author: *Andrew Izotov, andrewiz1994, Santee, CA*

Background: This study is retrospective exploratory analysis of effects of context-dependent hypothermia in two high acuity clinical groups – patients in aortic arch repair surgery and patients with acute heart, brain or polytrauma.

Outcomes including mortality, neurological damage and length of stay were analyzed.

Methods: The aortic arch repair cohort consisted of n=779 patients (384 control normothermic, and 395 exposure hypothermic). Hypothermia was not associated with increased mortality (p=0.4) but was associated with lower incidence of neurological damage (p=0.014), which persisted after adjustment (OR∼0.63, p<0.05). Length of hospital stay was not associated with hypothermic exposure (p>0.05). The trauma cohort included 65,672 patients. Out of them 59,054 were control group (normothermic) and 6,618 were an exposed group (hypothermic). Hypothermia showed strong association risk with mortality (HR∼3.15-5.03 p<0.001) while

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there is no independent association with neurologic injury. Hospital length of stay showed association where hypothermic patients spent median 3.9 days as compared to normothermic patients with median stay 1.2 days and statistical significance ($p<0.001$).

Results: These findings demonstrate that the clinical impact of hypothermia is highly context dependent. In controlled setting hypothermia might provide neuroprotection, without affecting mortality or increasing hospital LOS, whereas in trauma, hypothermia is related with severe physiological instability and is strongly associated with early mortality. It also affected length of stay, however there is no association between hypothermia and higher risk of neurological damage.

Conclusion: Using Observational Medical Outcomes Partnership (OMOP) database provided by University of California. Hypothermia exposure was defined as a core temperature less than 35 degrees Celsius in the surgical cohort, and less than 36 degrees Celsius in the trauma cohort. Analytical methods included logistic regression, and Cox proportional hazards models to evaluate associations within 30-day mortality and neurologic injury, adjusting for demographic and physiological covariates, such as age, lactate, BMI, and transfusion burden, defined as the amount of blood product bags given to patients within the procedure time, or stabilization time in surgery or Emergency Department respectively. In addition, the sub analysis of shock outcomes was performed in a trauma cohort.

S370: Decompressive Craniectomy by Multiple Dural Stabs Versus Open Dural Flap for the Evacuation of Acute Subdural Hematoma

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Background: Decompressive craniectomy (DC) is a life-saving intervention for acute subdural hematoma (ASDH). However, the optimal dural management technique-multiple dural stabs versus open dural flap-remains controversial. This systematic review and meta-analysis compared clinical outcomes between these two approaches.

Methods: A systematic search identified studies comparing DC performed with multiple dural stabs versus open dural flap in patients with ASDH. Nine studies met inclusion criteria, comprising a total sample size of 739 patients.

Primary outcomes included favorable neurological outcome(Glasgow Outcome Scale [GOS] 3–5), mortality, vegetative state, and Glasgow Coma Scale (GCS) improvement. Secondary outcomes included procedure- related complications such as cerebrospinal fluid (CSF) leak. Pooled risk ratios (RR) with 95% confidence intervals (CI) were calculated using a random-effects model.

Results: Multiple dural stabs were associated with a significantly higher likelihood of favorable neurological outcome (GOS 3–5) compared with open dural flap (RR 1.60, 95% CI 1.10 – 2.35). However, this technique was also associated with a higher risk of CSF leak (RR 2.57, 95% CI 1.13–5.84). There was no statistically significant difference between groups in overall survival or mortality (RR 0.78, 95% CI 0.47–1.30) or in the incidence of vegetative state (RR 1.25, 95% CI 0.72–2.16). Similarly, no significant difference was observed in total GCS outcomes (RR 1.00, 95% CI 0.85–1.18). Subgroup analyses across GCS categories (3–5, 6–8, and 9–11) also demonstrated no significant differences between techniques.

Conclusion: In patients undergoing decompressive craniectomy for ASDH, the multiple dural stabs technique is associated with improved functional outcomes but an increased risk of CSF leak compared with the open dural flap approach. Mortality and neurological recovery, as measured by GCS, appear comparable between the two techniques. These findings highlight a trade-off between functional benefit and complication risk, emphasizing the need for careful patient selection and further high-quality randomized studies.

S371: Early versus Delayed Surgical Decompression in Spinal Cord Injury: A Systematic Review and Updated Meta-Analysis

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Background: The optimal timing of surgical decompression following spinal cord injury (SCI) remains controversial. Early intervention may improve neurological recovery, but its impact on functional outcomes, complications, and healthcare utilization is not fully established. This study aimed to compare early versus delayed decompression in SCI through an updated systematic review and meta-analysis.

Methods: A comprehensive literature search identified studies comparing early versus delayed surgical decompression in SCI. A total of 43 studies met inclusion criteria, comprising 9,669 patients in the early group and 28,760 in the delayed group. Outcomes assessed included neurological recovery, functional outcomes, complications, healthcare utilization, and perioperative parameters. Pooled risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI) were calculated using random-effects models.

Results: Early decompression was associated with significantly improved neurological recovery, including higher rates of ≥1 grade improvement (RR 1.19, 95% CI 1.05–1.36) and ≥2 grade improvement on the ASIA Impairment Scale (RR 1.89, 95% CI 1.35–2.66), along with greater improvement in ASIA Motor Score (MD 5.86, 95% CI 0.55–11.17). No significant differences were observed in AIS A conversion or neurological deterioration. Functional outcomes showed improvement in SCIM (MD 5.63, 95% CI 3.19–8.08) and FIM scores (MD 3.34, 95% CI 0.29–6.39), while independent ambulation rates were similar between groups.

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Early surgery was associated with a lower risk of pneumonia (RR 0.82, 95% CI 0.72–0.94), with no significant differences in overall complications, mortality, DVT, UTI, or pressure ulcers. Healthcare utilization analysis demonstrated reduced hospital length of stay (MD −2.27 days, 95% CI −3.45 to −1.09), although ICU stay was longer in the early group (MD 2.08 days, 95% CI 0.97–3.20). No significant differences were observed in discharge disposition or perioperative outcomes.

Conclusion: Early surgical decompression in SCI is associated with improved neurological recovery, better functional scores, reduced pneumonia risk, and shorter hospital stay without increasing overall complications or mortality. These findings support early intervention as a favorable strategy in SCI management.

S372: Comparing the Use of Subgaleal and Subdural Drains in Non-acute Subdural Hematomas: A Systematic Review and Updated Meta-Analysis

Presenting Author: *Yousef Joseph, DO, Las Vegas, NV*

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Background: Drain placement following surgical evacuation of non-acute subdural hematomas (SDH) is standard practice to reduce recurrence and improve outcomes. However, the optimal drain location-subgaleal versus subdural-remains debated. This study aimed to compare the safety and efficacy of subgaleal and subdural drains through an updated systematic review and meta-analysis.

Methods: A comprehensive literature search was conducted across major databases to identify studies comparing subgaleal and subdural drain placement in patients with non-acute SDH. A total of 25 studies met inclusion criteria, comprising 7,239 patients (3,230 in the subgaleal group and 4,009 in the subdural group). Outcomes analyzed included infection, mortality, seizures, pneumocephalus, favorable functional outcome, recurrence, and intracerebral hemorrhage. Pooled effect estimates were calculated using odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (CI).

Results: There were no statistically significant differences between subgaleal and subdural drains in infection (OR 0.94, 95% CI 0.60–1.48), mortality (OR 0.54, 95% CI 0.20–1.44), seizures (OR 0.68, 95% CI 0.43–1.08), pneumocephalus (OR 0.88, 95% CI 0.51–1.52), or favorable outcomes (OR 1.02, 95% CI 0.79–1.32). However, subgaleal drains were associated with a significantly lower recurrence rate (RR 0.87, 95% CI 0.76–0.98) and reduced risk of intracerebral hemorrhage (OR 0.55, 95% CI 0.30–0.99).

Conclusion: Subgaleal drain placement demonstrates comparable safety to subdural drains while offering advantages in reducing recurrence and intracerebral hemorrhage. These findings support the consideration of subgaleal drains as a preferable alternative in the surgical management of non-acute SDH. Further high-quality randomized controlled trials are warranted to strengthen these conclusions.

S373: Mortality Trends in Traumatic Brain Injury Among Adults Aged ≥25 Years in the United States: A CDC WONDER Population-Based Analysis (1999-2024)

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Background: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide, yet population-level mortality trends across demographic subgroups remain largely underexplored.

Understanding these disparities is critical for targeted prevention. This CDC WONDER analysis examines the TBI mortality trends in the U. S. from 1999 to 2024

Methods: We conducted a retrospective CDC WONDER analysis (1999–2024) using ICD-10 code followed by S06 (TBI). Age-adjusted mortality rates (AAMR) were stratified by sex, race, census region, and urbanization. Join point regression calculated Annual Per cent Change (APC) and Average Annual Per cent Change (AAPC) with $p<0.05$.

Results: From 1999-2024, 398,034 deaths were reported. The overall AAMR decreased significantly from 1999–2018 (APC: -0.27*, 95% CI: -0.50 to -0.04; p=0.023), increased non-significantly from 2018–2021 (APC: 4.28%, 95% CI: -2.75 to 11.81; p=0.223), then decreased significantly from 2021–2024 (APC: -3.78, 95% CI: -6.98 to -0.47; p=0.028), with a non-significant overall AAPC of -0.16 (95% CI: -1.04 to 0.72; p=0.716). By sex, males had consistently higher mortality than females (11.45 vs. 5.23 per 100,000 in 2021). Males showed a significant decline from 1999–2018 (APC: -0.60*, p =0.000052), a non-significant rise from 2018–2021 (APC: 4.47, p=0.227), then a significant decline from 2021–2024 (APC: -4.49,* p=0.015), with a non-significant overall AAPC of -0.48 (p=0.308). Females showed a significant overall increase (AAPC: 0.50*,

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p<0.001). By race, White individuals had the highest AAMR (8.88 in 2021) with a significant increase (AAPC: 0.51*, p<0.001).
Black individuals showed a significant overall decline (AAPC: -1.45*, p=0.032). By age, the highest AAMR was in adults aged 85+ years (100.81 per 100,000 in 2021) with a significant increase (AAPC: 2.37*, p<0.001). Adults aged 75–84 years also increased significantly (AAPC: 0.84*, p<0.001). Regionally, only the Midwest showed a significant overall increase (AAPC: 0.64*, p=0.008). By urbanization, large central metro areas declined significantly (AAPC: -1.11*, p=0.012), while medium metro, small metro, micropolitan, and non-core areas all increased significantly.
Conclusion: This study reveals impactful research mortality gaps in TBI across the U.S., 1999-2024. Age, sex, race, and geography strongly influence outcomes. These disparities demand aggressive neurological rescue and rehabilitation before this hidden epidemic worsens further.

S374: Drains Drains Versus No Drain After Burr Hole Craniotomy for Chronic Subdural Hematoma: A Systematic Review and Meta-Analysis

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Background: The role of postoperative drains following burr hole craniotomy for chronic subdural hematoma (CSDH) remains debated, with varying evidence regarding their impact on recurrence and clinical outcomes. This systematic review and meta-analysis aimed to compare the efficacy and safety of drain versus no-drain strategies after burr hole evacuation of CSDH.
Methods: A comprehensive literature search identified 10 studies meeting inclusion criteria, comprising a total of 895 patients. Outcomes assessed included postoperative complications, infections, mortality, morbidity, recurrence, functional recovery, radiological parameters, and length of hospital stay. Pooled risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI) were calculated using appropriate meta-analytic models.
Results: The use of drains was associated with a statistically significant reduction in overall morbidity (RR 0.78, 95% CI 0.66 to 0.93) and recurrence rates (RR 0.53, 95% CI 0.36 to 0.80). Mortality showed a trend toward reduction but did not reach statistical significance (RR 0.69, 95% CI 0.46 to 1.04). There were no significant differences between groups in postoperative complications (RR 1.09, 95% CI 0.67 to 1.76), postoperative infections (RR 0.88, 95% CI 0.55 to 1.40), or worse mobility at 6 months (RR 0.66, 95% CI 0.43 to 1.02). Radiological outcomes, including change in midline shift (MD 1.26, 95% CI -0.67 to 3.19) and maximal hematoma width (MD 3.60, 95% CI -0.14 to 7.33), were also comparable. Length of hospital stay did not differ significantly (MD -0.12, 95% CI -1.52 to 1.28).
Conclusion: The use of postoperative drains following burr hole craniotomy for CSDH significantly reduces recurrence and overall morbidity without increasing complications or infections. These findings support the routine use of drains in clinical practice, although further high-quality randomized studies are warranted to confirm long-term functional outcomes.

S375: Assessment of Stakeholders' Perceptions of Outcomes After Subarachnoid Hemorrhage: A Single-center Prospective Study

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Background: The Modified Rankin Scale (mRS) is commonly used to measure outcomes in stroke research, and poor outcomes in aneurysmal subarachnoid hemorrhage (aSAH) are typically defined as mRS > 2 or > 3. However, it remains unclear whether these provider-defined unfavorable outcomes align with patients' preferences. We aimed to assess differences between aSAH patients' and neurocritical care providers' perceptions of commonly used outcome measures.
Methods: We conducted a prospective study of consecutive patients with aSAH at an academic center from March to November 2024. After obtaining informed consent, surveys were administered to patients or their healthcare surrogates, as well as to their neurocritical care providers, including board-certified attending physicians and advanced practice providers. Survey questions, based on respondents' understanding, assessed the minimally or worst possible but acceptable outcomes at 3 months after discharge using the mRS and Glasgow Outcome Scale–Extended (GOS-E). Providers were also asked to rate mRS and GOS-E on a scale from 1 to 5, where 1 indicated poor and 5 indicated excellent utility for outcome assessment.
Results: Of 62 completed surveys, 24 were from patients or their healthcare surrogates and 38 from neurocritical care providers (mean years of experience 5 [SD 4.8]). Providers estimated higher minimally acceptable mRS scores at 3 months after discharge compared to patients/surrogates (median 3 [IQR 2–3] vs 2 [1–3]; p = 0.029). There was no significant difference in the minimally acceptable GOS-E scores between providers and patients/surrogates (median 4.5 [4–6] vs 4 [4–5]; p = 0.23). Providers also favored mRS over GOS-E as better outcome measurement tool (median 3 [3–4] vs 3 [2–3]; p = 0.001).

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Conclusion: Providers may perceive worse functional outcomes as acceptable compared to patients/surrogates and favor mRS over GOS-E, suggesting a gap in outcome expectations that warrants further research.

S376: Multimodal Neuromonitoring of Neurovascular Coupling may Prognosticate Neurological Outcome after Anoxic Brain Injury

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Background: Cardiac arrest (CA) results in anoxic brain injury, which impairs neurovascular coupling (NVC) and disrupts the brain's ability to meet metabolic demand with adequate cerebral perfusion. Prior studies establish a link between neural activation and changes in cerebral metabolic rate of oxygen (CMRO2) and have examined NVC through neural bursting and subsequent oscillations in either cerebral blood flow (CBF) or intracranial pressure (ICP) waveforms. However, no studies have shown a consolidated display of CMRO2, CBF, and ICP dynamics during burst-suppression in a model of global ischemia. We measured NVC through the relationship of neural bursting with CMRO2, CBF, and ICP before and immediately after acute anoxic brain injury to prognosticate post-CA neurological outcome.

Methods: Male rats (n=5) were anesthetized. Electrocorticography (ECoG) was used to record neural activity. Polyethylene tubing was used to monitor ICP. Laser speckle imaging and spatial frequency domain imaging were used to monitor CBF and cerebral oxygenation, respectively, and combined to calculate CMRO2. After 7 minutes of asphyxial CA, cardiopulmonary resuscitation was performed. A Neurological Deficit Scale (NDS) was used to evaluate neurological recovery at 20 hours post-CA. The CMRO2, CBF, and ICP oscillations in response to ECoG bursting were quantified using the area under the curve (AUC), with a smaller AUC indicating a smaller CMRO2, CBF, and ICP response to every neural burst.

Results: Our results demonstrate a significant negative correlation between the pre-CA CBF oscillation AUC and overall NDS score (R= -0.989, p=0.001), as well as the brainstem function (R= -0.889, p=0.044), motor assessment (R= -0.981, p=0.003), and behavior (R=-0.993, p=0.001) subscores. We also found a significant negative correlation between the post-CA CBF oscillation AUC and the overall NDS score (R= - 0.900, p=0.037) and brainstem function subscore (R= -0.910, p=0.032). Furthermore, our results demonstrate a significant negative correlation between the post-CA ICP oscillation AUC and the overall NDS score (R= -0.979, p=0.004), as well as the motor assessment (R= -0.955, p=0.011) and behavior (R= - 0.994, p=0.001) subscores.

Conclusion: These results suggest that a more efficient pre- and post-CA NVC mechanism may be associated with improved neurological outcome. In conclusion, our results highlight the importance of NVC in both normal and post-anoxic states in predicting neurological outcomes and the utility of monitoring neural activity, CMRO2, CBF, and ICP simultaneously.

S377: Not Just a Snore: When Stridor Signals Something Sinister in the ICU

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Background: Anti-IgLON5 disease is a rare autoimmune-neurodegenerative disorder characterized by sleep disturbances, bulbar dysfunction, and progressive respiratory compromise. Approximately 27% of patients present with bulbar syndrome including stridor and acute respiratory insufficiency, with nearly half requiring ventilatory support during disease course. Despite increasing recognition, optimal ICU airway management strategies remain poorly defined.

Methods: We conducted a comprehensive case series review examining airway management challenges in patients with anti-IgLON5 disease requiring ICU admission. Cases were analyzed for presenting respiratory symptoms, indications for intubation, tracheostomy timing and outcomes, ventilatory requirements, and response to immunotherapy.

Results: This case series highlights multifactorial respiratory failure in 3 patients with seropositive IGLON5 disease due to stridor and vocal cord paresis necessitating emergent airway management. All 3 patient's reported history of OSA with progression to stridor later in their disease course. Duration of symptoms was found to correlate with severity of airway disease on admission. All 3 patients requiring airway support during initial hospitalization.

Notably, Improvement in airway disease (as measured by successfully wean off respiratory support) was observed in all patients following initiation of appropriate immunotherapy treatment.

Conclusion: ICU airway management in anti-IgLON5 disease requires recognition of both obstructive and central respiratory pathophysiology. Approximately 20% of patients ultimately require tracheostomy, with 50% needing nocturnal or continuous ventilatory support. Our cases highlight how central hypoventilation may be unveiled or persist after tracheostomy, requiring continued mechanical ventilation despite relief of upper airway obstruction. Early immunotherapy initiation within the first year of disease onset represents the only modifiable factor associated with improved survival and should be prioritized alongside airway management. The association of obstructive sleep apnea with dysphagia should prompt consideration of anti-IgLON5 disease in the differential diagnosis.

S378: Sex Differences in Metacognitive Awareness and Cognitive Screening in a Post-Mild TBI Clinic

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Background: Mild traumatic brain injury (mTBI) can cause chronic cognitive symptoms, and discordance between patient-reported symptoms and objective cognitive testing results complicates management. In mTBI recovery, the sex-specific differences in metacognitive awareness during the sub-acute phase of injury is relatively unknown. This study aimed to evaluate sex-specific differences in concordance between subjective primary cognitive complaint and objective performance (metacognitive awareness), and to explore differences in global and processing speed testing between sexes in an mTBI cohort. We hypothesized that women would demonstrate greater subjective-to-objective concordance than men.

Methods: We analyzed 65 mTBI (GCS 13-15, loss of consciousness <30 min) patients (mean age=43 years, 49% female, 60% college-educated) evaluated within 6 months of injury (mean time to clinic=2.5 months) from a prospective longitudinal TBI clinic cohort (1/2023-4/2026). Objective cognitive status was measured via an education-adjusted Montreal Cognitive Assessment (MoCA), with a representative subset (n=14) also completing an age-adjusted WAIS-V Processing Speed Index (PSI). Primary cognitive complaint was defined as patient-reported cognition as the primary, most disabling symptom at the clinic visit with Rivermead Post-Concussion Symptoms Questionnaire (RPQ) cognitive symptom score >3. Metacognitive awareness was evaluated using point-biserial correlations between primary cognitive complaint and MoCA, stratified by biologic sex. Cognitive battery mismatch, defined as patients with "normal" global screening (MoCA >26) but reduced processing speed (PSI-standard-score <85), was examined as an exploratory secondary analysis.

Results: Of the 65 patients, 31% (n=20) endorsed cognition as their primary disabling complaint, with no difference between males and females (27% vs 33%, p=0.701). Rates of abnormal MoCA also did not differ between sexes (67% vs 60%, p=0.789). Sensitivity analysis showed age was not associated with MoCA (p=0.479). In females, primary cognitive complaint was modestly associated with lower objective MoCA performance (r=-0.363, p=0.049), whereas no association was observed in males (r=0.061, p=0.753), suggesting a lack of subjective-to-objective concordance in men on MoCA. Furthermore, a cognitive-battery mismatch was identified in a single female case (7% of the PSI-tested cohort).

Conclusion: We found self-reported cognitive disability is common in sub-acute TBI. Women exhibited higher metacognitive awareness post-mTBI than men, whose lack of concordance may lead to clinical under-recognition of cognitive deficits. While MoCA remains a robust global screen for most, the identified mismatch with speed-dependent metrics underscores the need for targeted neuropsychological assessment. Understanding the mechanisms driving these sex-specific phenotypes is essential for precision TBI-clinical management.

S379: Mapping the Social Exposome in Traumatic Brain Injury with a Machine Learning Approach to Identify Latent Social-Exposure Clusters

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Background: We sought to evaluate the feasibility of unsupervised machine learning (ML) to identify latent social exposome phenotypes and characterize their association with intensive care unit (ICU) discharge outcomes in moderate-severe traumatic brain injury (msTBI). Outcomes after TBI are heterogeneous. While individual social determinants of health (SDOH) are related to msTBI ICU outcomes, they are poorly incorporated into standard msTBI prognostic models. The emerging social exposome framework may address this gap by modeling SDOH as an interrelated totality of exposures rather than isolated variables.

Furthermore, characterizing these phenotypes is a critical step toward understanding how social context influences acute msTBI recovery.

Methods: We conducted a retrospective cohort study (09/2022 – 01/2026) of msTBI patients (admission GCS ≤ 12, positive with skull fracture or intracranial hemorrhage) at a single Level I trauma center. 22 patients with documented goals-of-care limitations (e.g., DNR/DNI) were excluded from outcome analyses. The primary outcome was discharge modified Rankin Scale (mRS). Three literature-guided variables modeled the social exposome: a composite race/ethnicity variable, insurance status, and state Area Deprivation Index (ADI). A Gower distance matrix accommodated mixed variable types, followed by hierarchical clustering using Ward's linkage. Optimal cluster number was determined by silhouette analysis and dendrogram inspection. Exploratory analysis included proportional odds regression of discharge mRS with cluster assignment as the primary predictor (adjusted for age, sex, admission GCS, and pupillary reactivity) and ROC-AUC analysis to compare discriminative performance of clinical-only versus social-augmented models.

Results: Of 166 registry patients, 149 met study criteria (25.5% female, median admission GCS 8, 19.6% with pupillary abnormality). Four distinct social exposome phenotypes were identified (silhouette width 0.541, k=4, suggesting substantial clustering). Phenotypes included one high social risk group (n=56, 100% government-insured, 100% Hispanic, mean ADI 5.7), two intermediate risk groups, and one low social risk group (n=31, 0% government-insured, racially and ethnically mixed, mean ADI 4.3). Exploratory-adjusted ordinal regression did not demonstrate an association between social exposome clusters and discharge mRS (all p-values > 0.10). The social-augmented model demonstrated similar discrimination to the clinical-only model (AUC 0.779 vs. 0.742), though this did not reach significance (p=0.164), supporting validation for larger samples.

Conclusion: We demonstrate the feasibility of utilizing ML to identify cohesive social exposome phenotypes in a neuro-ICU TBI population. This multidimensional phenotyping provides a platform for future studies to evaluate how clustered social factors influence TBI outcomes, including in larger, adequately powered cohorts with granular social exposures and long-term outcomes.

S380: Operationalizing the Neural Exposome in Mild TBI: Feasibility and Directional Trends of a Three-Domain Framework on Cognitive Trajectories using Principal Component Analysis

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Background: Patients recovering from mild traumatic brain injury (mTBI) are at increasingly recognized risk for adverse cognitive trajectories. However, the multidimensional nature of post-TBI exposures remains poorly characterized. The neural exposome defined by the National Institute of Neurological Disorders and Stroke (NINDS) as the totality of exogenous, endogenous, and behavioral exposures affecting neurological health, offers a theoretically grounded framework for capturing this complexity, but dimension-reduction approaches validating its structure in TBI populations are lacking. Our objective was to examine a NINDS-informed three-domain exposome framework in chronic mTBI using principal component analysis (PCA) and explore associations between domain-level composite risk scores and baseline-adjusted 6-month cognitive change.

Methods: We enrolled adults with mTBI presenting to a single-center TBI program. Fifteen variables were a priori organized into three NIH-NINDS neural exposome domains: Exogenous (PM2.5 air pollution, state-level area deprivation index, insurance coverage, household size, perceived stress), Endogenous (lifetime TBI burden, intracranial

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hemorrhage, adverse childhood events, education, depression severity), and Behavioral (brain health behaviors, cardiovascular lifestyle score, Mediterranean diet adherence, sleep disturbance, food insecurity).

Within-domain PCA was applied and PC1 retained as a composite risk score (higher = greater risk burden) after sign correction. Cognitive outcome was defined as residualized 6-month Montreal Cognitive Assessment (MoCA) adjusted for baseline. Exploratory quantile g-computation was performed to estimate mixture effects on baseline-adjusted cognitive change.

Results: Of 44 mTBI patients (50% female), PC1 explained 27.1%, 34.7%, and 37.9% of within-domain variance in the Exogenous, Endogenous, and Behavioral domains, respectively, exceeding the 20% expected under equal variance distribution and indicating shared structure within NINDS-defined domains. PM2.5 and area deprivation, intracranial hemorrhage and education, and brain health behaviors and cardiovascular score were the dominant contributors within Exogenous, Endogenous, and Behavioral domains, respectively. All three risk scores were negatively associated with cognitive change (Exogenous: $r = -0.23$; Endogenous: $r = -0.15$; Behavioral: $r = -0.04$), consistent in direction with the hypothesis that greater exposome burden is associated with worse-than-expected 6-month recovery, though none reached statistical significance.

Similarly, quantile g-computation demonstrated preliminary negative mixture effects across Exogenous ($\beta = -0.88$, 95% CI −4.57, 2.81), Endogenous ($\beta = -0.93$, 95% CI −2.53, 0.67), and Behavioral ($\beta = -0.21$, 95% CI −2.27, 1.85) domains.

Conclusion: PCA-derived composite scores provide a feasible, internally coherent approach to operationalizing the neural exposome in a mTBI cohort. Adequately powered prospective studies are warranted to evaluate preliminary negative directional trends and their consistency with the hypothesis that greater exposome burden is associated with impaired cognitive recovery.

S381: Efficacy and Safety of Hypertonic Saline Versus Mannitol for Intraoperative Brain Relaxation in Supratentorial Craniotomies: A GRADE Assessed Systematic Review and Updated Meta-Analysis

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Background: Optimal brain relaxation during supratentorial craniotomies is crucial for neurosurgical outcomes. Mannitol and hypertonic saline (HTS) are commonly used osmotic agents, but their comparative efficacy and safety remain debated. This systematic review and meta-analysis compared HTS and mannitol in achieving intraoperative brain relaxation using evidence from RCTs.

Methods: Following PRISMA guidelines, RCTs comparing HTS and mannitol were included. Primary outcomes were brain relaxation, need for a second dose, hospital stay, and focal neurological deficits. Secondary outcomes included fluid intake, urine output, serum osmolality, electrolytes, mean arterial pressure (MAP), and central venous pressure (CVP). Data were analyzed using a random-effects model. Risk of bias was assessed with Cochrane RoB 2, and evidence certainty with GRADE.

Results: Fourteen RCTs (989 participants: HTS 497, mannitol 492) were included. HTS reported an improved excellent brain relaxation (RR 1.39; 95% CI 1.14–1.70), reduced poor brain relaxation (RR 0.73; 95% CI 0.57–0.93), and the need for a second dose (RR 0.62; 95% CI 0.47–0.82). No significant differences were found for good brain relaxation (RR 0.92; 95% CI 0.78–1.08), focal neurological deficits (RR 0.53; 95% CI 0.27–1.03), or hospital stay (MD −0.08 days; 95% CI −0.37 to 0.21). For secondary outcomes, HTS reduced total fluid intake (MD−460.33 mL; 95% CI −880.60 to −40.06) and urine output (MD −389.70 mL; 95% CI −578.19 to −201.21), while increasing serum sodium (MD 5.73 mmol/L; 95% CI 3.56–7.89) and serum osmolality (MD 7.84 mOsm/kg; 95% CI 5.10–10.57). No significant differences were observed in serum potassium (MD 0.57 mmol/L; 95% CI −0.74–1.89), MAP (MD 0.13 mmHg; 95% CI −3.67–3.94), or CVP (MD 0.16 mmHg; 95% CI −0.93–1.25). Heterogeneity ranged from $I^2 = 0$ to 93%, and overall certainty of evidence was moderate to very low.

Conclusion: HTS provides favourable excellent brain relaxation and reduces the need for repeat osmotic therapy compared to mannitol, with similar neurological and hemodynamic safety. Mild increases in serum sodium and osmolality remain within clinically acceptable limits. HTS is a safe and effective alternative to mannitol, supporting further large-scale trials.

S382: Changes in Cerebral Glucose Metabolism Following Hemicontusive Cervical Spinal Cord Injury in Mice: A Whole-Brain Autoradiographic Study

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Background: Spinal cord injury (SCI) disrupts communication between the brain and spinal cord, leading to significant functional and structural reorganization within the brain, changes that extend beyond the site of injury and involve multiple neural circuits. Understanding how the brain reorganizes during the subacute phase following SCI is critical for identifying patterns of neuroplasticity and potential therapeutic targets.

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This study investigates whole-brain functional reorganization one week after SCI using high-resolution metabolic mapping techniques in an experimental mouse model.

Methods: Adult female mice were subjected to a right-sided moderate contusive SCI at the cervical 5 (C5) level. The injury was confirmed through glial fibrillary acidic protein (GFAP) immunohistochemical staining. To assess brain-wide functional changes, we applied [14C]-2-deoxyglucose autoradiography, which enabled high-resolution mapping of glucose uptake. Regional cerebral glucose uptake was analyzed by statistical parametric mapping from autoradiographic images of the 3D-reconstructed brain. Functional outcomes were evaluated by comparing SCI animals to sham-lesioned controls using motor performance tests (grip strength, rotarod).

Functional connectivity between select regions was examined by interregional correlation analysis.

Results: Compared to sham controls, SCI animals exhibited significant motor deficits, as demonstrated by reduced grip strength and impaired rotarod performance. Metabolic mapping revealed decreased glucose uptake in key sensorimotor regions, including the cortex, basal ganglia, and thalamus. In contrast, increased glucose uptake was observed in several limbic system structures (amygdala, nucleus accumbens, lateral septum, hippocampus), as well as in the cerebellum. These metabolic changes were predominantly bilateral, despite the unilateral nature of the injury, indicating involvement of both ascending and descending neural pathways across hemispheres.

Furthermore, functional metabolic connectivity between the ventral posterolateral thalamic nucleus and the primary somatosensory cortex was reduced bilaterally, suggesting disrupted communication within sensory processing circuits.

Conclusion: Our findings demonstrate widespread and bilateral brain reorganization during the subacute phase following unilateral contusive SCI. The observed alterations in regional glucose metabolism and connectivity highlight the widespread neural adaptations after injury across both sensorimotor and limbic circuits. This study underscores the value of whole-brain metabolic mapping in identifying patterns of neuroplasticity and provides a foundation for future research aimed at understanding post-injury clinical symptomatology and for evaluating targeted therapeutic strategies.

S383: Efficacy of Intravenous 20% Mannitol vs 3% Hypertonic Saline in Reducing Intracranial Pressure in Nontraumatic Brain Injury: A systematic Review and Updated Metanalysis of RCTs

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Background: Optimal osmotherapy for intraoperative brain relaxation and intracranial pressure (ICP) control in nontraumatic brain injury remains debated. This systematic review and updated meta-analysis of randomized controlled trials (RCTs) compared intravenous 20% mannitol with 3% hypertonic saline (HTS).

Methods: A comprehensive literature search identified RCTs comparing 20% mannitol and 3% HTS in patients undergoing neurosurgical procedures for nontraumatic brain injury. Seven RCTs met inclusion criteria, comprising 404 patients (202 in each group). Primary outcomes included brain relaxation grades, need for repeat dosing, and neurological complications. Secondary outcomes assessed fluid balance, serum electrolytes, osmolality, and perioperative hemodynamics. Pooled risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI) were calculated using a random-effects model.

Results: HTS significantly improved intraoperative brain relaxation, increasing the likelihood of excellent relaxation (RR 1.39, 95% CI 1.14–1.70) and reducing poor relaxation (RR 0.73, 95% CI 0.57–0.93). There was no significant difference in good relaxation (RR 0.92, 95% CI 0.78–1.08). HTS reduced the need for a second osmotic dose (RR 0.62, 95% CI 0.47–0.82). A trend toward fewer focal neurological deficits was observed (RR 0.53, 95% CI 0.27–1.03). Fluid balance favored HTS, with lower total fluid intake (MD −460.33 mL) and urine output (MD −389.70 mL). HTS was associated with higher serum sodium (MD +5.73 mEq/L) and osmolality (MD +7.84 mOsm/kg), while potassium levels were comparable. No significant differences were observed in hospital stay, mean arterial pressure, or central venous pressure.

Conclusion: Compared with 20% mannitol, 3% hypertonic saline provides superior intraoperative brain relaxation and reduces the need for repeat osmotherapy, with favorable fluid dynamics and stable hemodynamics. These findings support HTS as an effective alternative to mannitol in neurosurgical management of nontraumatic brain injury, although careful monitoring of serum sodium is warranted.

S384: Outcomes of Decompressive Craniectomy in Severe Traumatic Brain Injury: A Retrospective Cohort Study (2003–2021)

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Background: Decompressive craniectomy (DC) is an important and possibly life-saving medical procedure performed on patients with severe traumatic brain injury (TBI) who suffer from refractory intracranial pressure hypertension on an international scale. Evidence on DC is varied globally particularly between high versus low-resource settings.

Methods: Data on 135 patients who underwent DC between 2003 and 2021 was reviewed and analyzed for this

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retrospective cohort study. Functional outcomes were evaluated at 1, 3 and 6 months using the Glasgow outcome (GOS) Classification scale. Outcomes were compared with the cohort from Aga Khan University Hospital, Pakistan.

Results: Overall outcomes were marginally better than the outcomes of the cohort. 22% of patients were dead at 3 months postoperative, 10% were in a vegetative state, 15% with severe disability, 19% moderate disability, and good recovery was 34%. Documented common postoperative complications included hydrocephalus, infection, and CFS leakage.

Conclusion: Despite limited ICU resources and increased complication rates, DC resulted in acceptable and comparatively favourable outcomes. The study reinforces the role of DC as a critical intervention in resource-limited neurosurgical settings.

S385: Rising Mortality of Brain Herniation in the United States: Insights from 25 Years of Data from CDC-WONDER

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Background: Brain herniation is a life-threatening neurologic emergency caused by increased intracranial pressure leading to displacement of brain tissue. It represents a final common pathway of various intracranial pathologies and is associated with high mortality. Despite advances in neurocritical care, national trends in mortality due to brain herniation remain poorly characterized.

Methods: CDC Wide-Ranging Online Data for Epidemiological Research (WONDER) database was used to extract the mortality data associated with Brain herniation from 1999 to 2024. Individuals over 25 years of age were identified through International Classification of Diseases, Tenth Revision (ICD-10) code, G93.5. Age-adjusted mortality rates (AAMR) were calculated per 100,000 people. Temporal trends were evaluated using Joinpoint regression software, and average annual percent changes (APC) were calculated.

Results: Between 1999 and 2024, a total of 101,222 deaths were attributed to brain herniation. Mortality rates declined from 1999 to 2007 (APC −3.4%), followed by a subsequent increase from 2007 to 2024 (APC +2.8%). AAMR for males was higher compared to females. Among females, mortality rates declined significantly from 1999 to 2003 (APC −5.1%), followed by a drastic increase from 2009 to 2024 (APC +2.96%). In contrast, among males, mortality decreased from 1999 to 2006 (APC −4.6%) and subsequently increased from 2006 to 2024 (APC +2.6%). Among Hispanics, mortality rates initially declined from 1999 to 2005 (APC −6.1%), followed by a marked increase between 2013 and 2021 (APC +5.5%). In the non-Hispanic population, mortality decreased from 1999 to 2007 (APC −3.3%), followed by a subsequent rise through 2024 (APC +2.8%). A rising mortality trend was observed among African Americans (AAPC +1.2%), Asians (AAPC −0.3%) and Whites (AAPC −0.5%). AAMR were highest for Northeast followed by Midwest and South. Rural population experienced a slightly higher mortality rate compared to urban.

Conclusion: In conclusion, brain herniation presents as a fatal condition with continuously rising trends in the last 15 years. These findings highlight the urgent need for targeted public health strategies, improved neurocritical care infrastructure, and equitable access to advanced medical services.

S386: Disparities In Mortality Trends Due To Encephalopathy And Sepsis; A CDC-WONDER Based Retrospective Analysis of 25 Years Data

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Background: Sepsis-associated encephalopathy (SAE) represents a severe manifestation of systemic infection, characterized by diffuse brain dysfunction mediated by neuro inflammation, endothelial injury, and blood–brain barrier disruption. It is associated with high mortality and significant neurologic morbidity. However, national trends and demographic disparities in SAE-related mortality have not been well established.

Methods: The CDC-WONDER database was used to extract death certificate data for adults aged ≥55years using specific ICD-10 codes for encephalopathy and sepsis. Crude mortality rates (CMR) and age-adjusted mortality rates (AAMRs) per 100,000 population were calculated. The AAMRs were assessed by demographic variables, including race, geographic density, sex, age, and US census region. Temporal trends were identified by calculating annual percent change (APC) using JoinPoint regression analysis.

Results: From 1999 to 2024, a total of 47,417 deaths among U.S. adults aged ≥55 years were associated to coexisting encephalopathy and sepsis. The overall AAMR was 2.17 (95% CI: 2.15 - 2.19). Males had higher overall AAMR (4.68) compared to females (3.56) demonstrating an increasing trend from 2014 to 2022 (APC: 10.09%; 95% CI: 8.45-11.33; $p = 0.00$). Black or African Americans exhibited the highest AAMR (3.84) which increased significantly from 1999 to 2022 (APC: 7.79%, 95% CI: 7.34-8.87, $p = 0.01$). Non-Hispanic population showed higher AAMR 2.17(95%

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CI: 2.15-2.18). The highest mortality was observed in the South (AAMR: 2.6), which increased significantly from 1999 to 2021 (APC: 10.34%, 95% CI: 9.80-11.32). Significant variations in AAMR were observed among different states, with the District of Columbia recording the highest (4.05) and New York the lowest (0.79). By 2013 Urbanization, the Large Central Metro area showed the highest AAMR (1.84) meanwhile there increasing trend from 2015 to 2020 in all areas.

Conclusion: Mortality trends associated with sepsis and encephalopathy demonstrated marked demographic and regional disparities over the past years underscoring the need for population specific interventions, including earlier recognition, access to healthcare resources, surveillance and region-specific public health strategies.

S387-LB: Long-Term Multidisciplinary Follow-Up in Pediatric TBI: Accidental vs. Abusive Head Trauma

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Background: Pediatric traumatic brain injury (TBI) follow-up care remains poorly characterized, particularly among patients with abusive head trauma (AHT), a leading cause of morbidity in young children. This study evaluated discharge referral and subspecialty follow-up patterns comparing young children hospitalized for AHT versus accidental head trauma (Acc) to understand long-term follow-up patterns.

Methods: A retrospective analysis of 2,065 children aged 0–5 years with moderate to severe TBI hospitalized at a level I trauma center was performed, comparing AHT (n=190) vs. Acc. Referral and visit trends across 14 subspecialties over five years post-discharge were compared using Fisher's exact test and logistic regression.

Results: Compared to Acc counterparts, the AHT cohort had higher odds ($p<0.001$ unless noted) of outpatient visit within the first year with: gastroenterology/nutrition (4.6), neurology (6.6), neurosurgery (2.5, $p<0.01$), ophthalmology (6.2), physical medicine and rehabilitation (PM&R, 4.7), social support (5.1), and surgery (2.7). Follow-up visit rates to neurology, PM&R, and ophthalmology remained significantly higher for the AHT cohort during the first five years ($p<0.01$). In both cohorts, referrals significantly increased odds of follow up ($p<0.001$) and shortened time-to-first-visit ($p<0.01$). There were no differences observed in time-to-first-visit or number of referrals between AHT and Acc cohorts..

Conclusion: Children hospitalized with AHT demonstrated persistently greater utilization of subspecialty follow-up care, suggesting increased long-term care needs. Referrals increased follow-up rates and reduced time-to-first-visit in all TBI patients. Evidence-informed, standardized referral and multidisciplinary follow-up models may improve continuity of care and ultimately improve outcomes for young children with TBI, especially for AHT.

S388: SAH Survivorship Through the Patient Lens: Early Feasibility of a Patient-Centered PROM Battery and Photovoice Methodology

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Background: Despite being the rarest form of stroke, subarachnoid hemorrhage (SAH) remains the leading cause of long-term morbidity in stroke patients younger than 65 years. Even those classified as having a "favorable outcome" in clinical trials report persistent difficulties with memory, cognition, and fatigue, and remain unable to reintegrate into society even decades after hemorrhage. There are currently no therapeutic options to address these long-term disabling symptoms. Contributing to this gap, available outcome tools are borrowed from other diseases, such as ischemic stroke, and focus on motor deficits, while SAH survivors primarily experience cognitive, memory, psychological, and social challenges. This misalignment leaves critical gaps in understanding and addressing SAH survivorship. SAH-LENS aims to evaluate the feasibility and scoring reliability of patient-centered outcome measures (PROMs) and to apply Photovoice as a method to elicit patient-prioritized recovery experiences.

Methods: SAH-LENS is an ongoing prospective observational cohort study enrolling adults within five years of SAH. We selected and harmonized 15 validated PROM tools to create a feasible battery spanning cognition, fatigue, sleep, emotional health, pain, reintegration, and reproductive health. We conducted guided interviews, which were independently scored by trained raters to assess inter-rater reliability.

Photovoice is a qualitative methodology utilizing participant-taken photography with structured guided interviews previously applied in ischemic stroke, but novel in the SAH

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population. Over four weeks, participants photograph their post-SAH experiences in response to standardized prompts, followed by structured interviews to explore the meaning behind their images. Thematic analysis will identify common themes, barriers to reintegration, and potential areas for intervention.

Recruitment is ongoing.

Results: Three participants (2 female, 1 male) completed initial quantitative assessments a median of 1.8 years post-SAH (range 1.0–2.8); median age at SAH onset was 59 years (range 21–68). Modified Rankin Scale (mRS) at discharge ranged 1–2; Hunt & Hess ranged 1–2; Fisher grade ranged 1–4. Despite favorable discharge mRS scores, 1/3 screened below Montreal Cognitive Assessment-BLIND ceiling (18/22), 2/3 reported insomnia symptoms (including 1/3 with clinically meaningful burden), 1/3 reported reduced reintegration into normal life, and fatigue-associated cognitive symptoms ranged from none to severe.

Across independently scored items (2–3 raters), pooled item-level agreement was 90.5%.

Conclusion: SAH-LENS demonstrates feasibility and high-scoring reliability of a harmonized, patient-centered outcomes approach. Ongoing Photovoice data collection is expected to provide qualitative context for survivorship domains not captured by conventional measures.

S389: Low Preoperative Seizure Rate in Infants with Congenital Heart Disease Undergoing Surgery with Cardiopulmonary Bypass

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Background: Complex congenital heart disease (CHD) in infants often requires surgical correction with cardiopulmonary bypass (CPB). This places them at risk of neurologic injury and seizures, which are often subclinical. Post-operative neurologic risk has been well established, but questions remain about the pre-operative period. The most recent American Clinical Neurophysiology Society guidelines recommend postoperative EEG monitoring and do not provide a recommendation regarding preoperative monitoring, a practice still in place at some hospitals (Wusthoff, J Clin Neurophysiol, 2025). Data on preoperative seizure risk are limited, with some studies suggesting rates as high as 16-20% (Pittet, J Clin Neurophysiol, 2022). Records of neonates who underwent corrective surgery for CHD with CPB and neuromonitoring at a single center were reviewed to evaluate seizure risk and preoperative EEG clinical utility.

Methods: Retrospective chart review was conducted on patients who underwent neuromonitoring at American Family Children's Hospital (Madison, WI) between 2018 and 2021. Inclusion criteria included: 1). age 0-12 months at admission; 2). CHD; 3). surgical repair requiring CPB; and 4). preoperative EEG monitoring.

Exclusion criteria included: 1). preterm birth; 2). hypoxic-ischemic encephalopathy; and/or 3). confirmed or suspected genetic syndromes. CHDs were assigned to Class I-IV per Clancy et al. (J Thorac Card Surg, 2000). EEG backgrounds and seizures were scored per Tsuchida et al. (J Clin Neurophysiol, 2013).

Results: 76/87 patients met inclusion criteria. 29 patients were CHD Class I, 27 Class II, 1 Class III, and 19 Class IV. 9 patients had abnormal EEGs (5 with diffuse slowing, 3 with excessive sharp wave transients, and 1 with background asymmetry). No patients exhibited electrographic seizures.

Conclusion: In this cohort, EEG abnormalities were uncommon and preoperative seizures were not observed. While further research into perioperative seizure risk stratification is needed, these rates are notably lower than in previously reported cohorts and add to the limited existing literature. These data suggest that routine preoperative EEG in infants undergoing congenital heart disease repair with cardiopulmonary bypass may not be necessary and that the clinical utility of such neuromonitoring may be low.

S390: Cross-Domain Neural Exposome Burden is Associated with Worse-Than-Expected Cognitive Recovery After Mild TBI: An Unsupervised Dimension-Reduction Approach

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Background: Mild traumatic brain injury (mTBI), the most common form of TBI, has heterogenous cognitive recovery trajectories, suggesting a multifactorial process. The neural exposome, defined by the National Institute of Neurological Disorders and Stroke as the totality of exogenous,

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endogenous, and behavioral exposures affecting neurological health, provides a cumulative burden framework for understanding divergent cognitive trajectories post mTBI. However, dimension-reduction approaches characterizing exposome structure in clinical mTBI populations remain limited. We examined whether a cross-variable neural exposome composite, derived through unsupervised dimension reduction, can separate baseline-adjusted 6-month cognitive trajectories in mTBI.

Methods: We enrolled 44 adults (50% female) with mTBI (GCS 13-15, initial evaluation within 3 months of injury) in a longitudinal clinic cohort. A 13-variable subset was retained via a forward-selection procedure, applied to the full 15-variable set prior to outcome analysis, optimizing within-sample exposome coherence across candidate variable combinations: PM2.5 air pollution, area deprivation index, insurance coverage, household size, perceived stress, lifetime TBI burden, intracranial hemorrhage, adverse childhood events, education, brain health behaviors, Mediterranean diet adherence, sleep disturbance, food insecurity. Cognitive outcome was the residual from regressing 6-month Montreal Cognitive Assessment (MoCA) on baseline MoCA, with patients dichotomized at a residualized change cutoff of −1 into worse-than-expected (residual ≤ −1; n=15) and not-worse-than-expected (n=29) groups. Univariate associations were tested with Mann-Whitney, chi-square, or Fisher's exact tests (Benjamini-Hochberg FDR-corrected). Principal component analysis (PCA) was applied to the full 13-variable exposome matrix; sign correction was applied so that higher first principal component (PC1) scores reflect greater cumulative neural exposome burden.

PC1 score was then compared between cognitive outcome groups using Mann-Whitney testing, with a centroid permutation test as a multivariate sensitivity analysis.

Results: PCA yielded a PC1 explaining 16.0% of variance, with dominant loadings from education, area deprivation, insurance coverage, air pollution, and adverse childhood events, suggesting their strong influence on PC1. The cumulative exposome burden score (PC1 score) was significantly elevated in the worse-than-expected cognitive recovery group relative to the not-worse-than-expected group (median PC1: 1.34 vs −0.76; Mann-Whitney U=322, p=0.010), indicating that greater aggregate neural exposome burden was associated with poorer 6-month outcome. Multivariate centroid permutation testing confirmed this separation (observed distance=1.49, p=0.037).

Conclusion: A cross-domain neural exposome burden composite stratified mTBI 6-month cognitive trajectories in an unsupervised framework. These 13 variables, selected for their collective coherence as a burden index, provide preliminary support for a cumulative exposome approach to post-mTBI cognitive decline in larger, adequately powered longitudinal studies.

S391: Mild Traumatic Brain Injury Facilitates Development of Anterior Insula Hyperactivation to Fearful Stimuli in Trauma Survivors with Post-Traumatic Stress Disorder

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Background: Mild traumatic brain injury (mTBI) may rapidly alter neurocognitive function and has been associated with an increased risk for post-traumatic stress disorder (PTSD). However, neuroimaging investigations during the acute post-trauma phase remain sparse. We previously reported greater left anterior insular cortex (aIC) activation during the cognitive appraisal of fearful versus neutral emotional faces in survivors who did and did not exhibit probable PTSD at 3 months, but not at 2 weeks, after a motor vehicle collision (MVC). Given previous studies suggesting that mTBI may lead to increased cortical activation in the early post-trauma period, we hypothesize that aIC activation within 2 weeks post-MVC may be elevated among probable PTSD survivors who sustained an mTBI compared to those who did not sustain mTBI.

Methods: In this secondary hypothesis-driven analysis, previously reported task-related activation at both 2 weeks and 3 months after trauma was extracted from the aIC region of interest and compared among groups of survivors diagnosed with probable PTSD at 3 months with (n=5) and without (n=11) mTBI in the emergency department. An exploratory analysis of change over time included two time points and additional groups of survivors without probable PTSD with (n=10) and without (n=12) mTBI.

Results: At 2 weeks, aIC activation was significantly greater in the probable PTSD with mTBI group than in the probable PTSD without mTBI group (mean = 0.125, SD = 0.053 vs. 0.014, SD = 0.111) (Welch's t (13.86) = 2.71, two-sided p = 0.017). aIC activation in probable PTSD survivors with and without mTBI was not significantly different at 3 months after MVC. The time and time × group interactions were not significant in brain activation and post-traumatic stress symptoms, but within-group tests suggest that decreases in post-traumatic stress symptoms over time were significant in groups without mTBI.

Conclusion: These preliminary results are consistent with the hypothesized association between mTBI and greater aIC activation to negative emotional stimuli in the early post-trauma period among survivors with probable PTSD, but do not support post-trauma brain changes in survivors with mTBI, probable PTSD, both conditions, or neither condition. These preliminary findings warrant further investigation into the relationship between mTBI and probable PTSD-related cortical alterations during the acute post-trauma period.

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S392: NITE RN: Feasibility and Preliminary Educational Outcomes of a Night-Shift Neurology Resident-Led Teaching Initiative for Registered Nurses in the Neurological ICU

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Background: Night-shift registered nurses are often the first clinicians to detect neurologic deterioration, yet face significant educational barriers - including leaner staffing, fewer bedside teaching opportunities, and limited access to structured learning compared to day shift. Compounding this, night-shift ICU positions are disproportionately filled by early-career nurses and recent graduates, who may have had limited exposure to the breadth of high-acuity neurologic conditions encountered in the Neuro ICU. Timely recognition and escalation of neurologic emergencies, including acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, intracranial hypertension, status epilepticus, and neuromuscular respiratory failure, is critical to patient outcomes. Formal, scalable educational programs targeting this population have not been well characterized.

Methods: NITE RN is a prospective educational quality improvement study conducted in the neurological ICU. Neurology residents select and deliver approximately 10–15 minute case-based micro-teaching sessions during night shift, targeting registered nurses at the bedside. Each session incorporates neurologic red flags, bedside escalation points, and case discussion. Post-session surveys assess knowledge (true/false questions across seven neurologic emergency domains) and satisfaction (Likert scale). Preliminary data from the first five sessions are reported here; formal paired pre- and post-session knowledge assessments are planned for subsequent sessions.

Results: Twenty-nine registered nurses participated across five preliminary sessions. Knowledge assessments completed by 14 respondents in sessions 3–5 demonstrated 99% overall accuracy (97/98 correct responses) across domains covering altered level of consciousness, pupillary abnormalities, focal neurological deficits, seizure recognition, ICP and EVD red flags, autonomic vital sign changes, and respiratory deterioration. On satisfaction surveys across all 29 respondents, 100% rated sessions as "agree" or "strongly agree" for both clarity of objectives (65.5% strongly agree) and clinical applicability of content (65.5% strongly agree). Qualitative feedback identified subarachnoid hemorrhage management, hemorrhagic transformation of ischemic stroke, and seizure and EEG interpretation as priority topics for future sessions. Implementation feedback surfaced actionable concerns regarding staffing constraints and advance notification logistics, informing ongoing program refinement.

Conclusion: These preliminary data demonstrate that a resident-delivered night-shift neurology micro-teaching curriculum is feasible and well-received among Neuro ICU nurses. Next steps include expansion with formal paired pre- and post-session knowledge quizzes to measure learning gains, and exploration of nursing continuing education credit designation to recognize participation and broaden institutional reach. NITE RN offers a scalable, interprofessional model for improving neurologic emergency recognition and escalation among early-career nurses during overnight ICU care.

NEUROGENETICS AND GENE THERAPY

S393-K: Longitudinal Sway and Gait Changes and Discrimination of Fall Risk in Adults With X-Linked Adrenoleukodystrophy

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Background: X-linked adrenoleukodystrophy (ALD) is the most common leukodystrophy and peroxisomal disorder, with a prevalence of approximately one in 14,000–17,000 live births. The clinical phenotype is heterogeneous and includes adrenal insufficiency, myeloneuropathy, and cerebral demyelination.

Myeloneuropathy is the most prevalent presentation and develops in all affected men and in 80-90% of women, although disease severity is generally greater in men due to X-linkage. There are no FDA-approved treatments for myeloneuropathy. Quantifying disease progression in X-linked adrenoleukodystrophy (ALD) remains a bottleneck for clinical trials due to low sensitivity of conventional functional scales. We tested whether instrumented sway and gait from body-worn inertial sensors (Opal/APDM) change over two years and discriminate fallers from non-fallers in men and women with X-ALD myeloneuropathy.

Methods: Sway was recorded in four standing paradigms (feet apart/together × eyes open/closed). Gait was recorded during the 6-MWTat two academic medical centers. Features were modelled with linear mixed-effects models adjusted for sex and walking-aid use, with Benjamini–Hochberg correction within each variable × paradigm pair. Baseline AUC thresholds defined an anchored minimal clinically important difference (MCID). Patients were classified into four MCID trajectories: Stayed Below-, Stayed Above-, Crossed Into-, or Crossed Out of risk.

Results: 118 patients (68 male, 50 female; mean age 36.5 years men, 52.5 years women) had a fully assessable baseline. After Benjamini-Hochberg-correction, 18 pairwise sway contrasts were significant pooled (4 male, 12 female), concentrated in eyes-open paradigms. Gait performance declined over two years (speed -0.083 m/s; stride length -0.059 m; both $p < 0.001$). Baseline feet-together eyes-

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closed sway discriminated patients who reported falls at any frequency (any-fallers) with AUCs up to 0.88 (23/76 pairs ≥ 0.80). Patients above the Sway Area MCID at both baseline and 2-year follow-up visits had near-100% any-faller rates versus near-0% below (BH-corrected $p = 0.012$).

Conclusion: Eyes-open sway paradigms detect longitudinal change over 2-years in both men and women with X-ALD myeloneuropathy. Eyes-closed sway paradigms discriminate any-fallers vs. non-fallers. The fall-anchored Sway Area MCID translates continuous change into a clinical responder definition for trial enrichment.

S394-K: Allele-Specific Antisense Oligonucleotide with Enhanced Specificity for Timothy Syndrome Type 1

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Background: Timothy syndrome type 1 (TS1) is a multisystem disorder caused by a heterozygous pathogenic variant in the alternatively spliced exon 8A of CACNA1C, the α1 subunit of the L-type calcium channel CaV1.2. We have previously shown that the TS1 p.G406R variant caused delayed channel inactivation, resulting in excessive calcium influx in TS1 cortical neurons, activity-dependent changes in neuronal morphology, and GABAergic neuron defect. Interestingly, the TS1 variant also interferes with alternative splicing, amplifying its own expression and interfering with the developmental shift in exon utilization from exon 8A to exon 8, which is the major isoform in the adult brain. We designed an antisense oligonucleotide (ASO) to affect this splicing, but it was not TS1 allele specific. To preserve developmentally regulated expression, we sought to develop an ASO that is TS1 allele specific to treat this disorder.

Methods: We designed ASOs via gapmer, walking, and modification optimization and tested them via qPCR for CACNA1C exons 8 and 8A for splicing efficiency. We tested top ASO hits for efficacy in rescuing calcium-dependent immediate early gene expression via qPCR, as well as whole-cell patch clamp electrophysiology for barium current, capacitance, and voltage-dependent inactivation.

Results: Gapmers did not improve efficiency. We identified an ASO directly over the TS1 allele that specifically reduced TS1 exon 8A expression without reducing control exon 8A or exon 8 expression, termed ASO.B4. ASO.B4 rescued immediate early gene expression changes, specifically FOS and EGR expression. ASO.B4 also rescued electrophysiology measures including the known deficit in voltage-dependent inactivation.

Conclusions: These data provide evidence that the novel ASO.B4, optimized for its enhanced specificity, effectively rescues the pathological gating defects of L-type calcium channel kinetics in TS1, while leaving control CACNA1C exon 8A expression intact. We hypothesize this could reduce side effects from developmentally regulated isoform-specific expression.

S395-K: Development of Antisense-Oligonucleotide Therapy for Histone 3.3-Related Bryant-Li-Bhoj Syndrome

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Background: Bryant-Li-Bhoj syndrome (BLBS) is a syndromic neurodevelopmental disorder with neurodegenerative features caused by heterozygous variants in either the H3F3A or H3F3B gene, both encoding the identical histone 3.3 (H3.3) protein. BLBS is caused by a range of missense variants throughout the H3F3A or H3F3B genes, and available clinical, cell and mouse data point to a gain-of-function mechanism. Although the shared disease mechanism across diverse variants remains incompletely understood, knock-down of the altered gene could ameliorate the disease phenotype. Antisense-oligonucleotide (ASO)-mediated knockdown of the affected gene or allele therefore could be therapeutic. Here, we investigate two alternate approaches that exploit the unique biology behind H3.3 production. In the first approach, we target both alleles of H3F3A or H3F3B. Given the inherent redundancy of H3.3 being encoded by two loci, this approach is expected to reduce the H3.3 protein no more than approximately 50%, allowing the targeting of only the gene affected by the pathogenic variant. The second approach targets the pathogenic variant in an allele-specific manner, thereby more selectively reducing the affected H3.3 protein, while preserving the three remaining alleles.

Methods: We have designed and screened 2'-methoxyethyl and phosphorothioate-backbone modified gapmer ASOs with both gene-specific and allele-specific designs. ASOs were transfected into 293T cells and H3F3A transcript level was determined by qPCR.

Results: Gene-specific ASO effectively reduced H3F3A transcript by over 90% in a cell culture system. Allele-specific ASO was designed for the recurrent T45I mutation in H3F3A, and while it achieved robust target knockdown, only a marginal selectivity towards the targeted allele was observed, highlighting the challenge of achieving high allele discrimination for single-nucleotide variants.

Conclusions: These data demonstrate ASOs as a potential therapeutic option for BLBS. ASOs were designed to target sequences with complete conservation between human and mouse, allowing for expedited evaluation of safety and efficacy in vivo, with particular attention to the tolerability of partial global H3.3 reduction.

NEUROINFLAMMATION AND NEUROINFECTION

S396-K: Allogenic Engineered T Cell Receptor Therapy for Progressive Multifocal Leukoencephalopathy

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Background: PML is a fatal disease of the central nervous system caused by JC polyomavirus (JCV). Survival is dependent on early diagnosis and ability to establish T cell immunity. Adoptive transfer of polyomavirus-specific T cells is possible; however, current delays in creating HLA-matched anti-viral T cells can be fatal. Off the shelf therapies are starting to become available, but the need to travel to receive them and the lack of consistent matching can result in mixed responses. We need an off the shelf option that can be rapidly deployed that takes advantage of recent engineering advancements to make effective allogenic T cells with a more consistent efficacy for a diverse array of patients.

Methods: PBMCs from healthy donors from a class I subtype were stimulated with peptide libraries tiled across the JCV VP1 protein. Multiple rounds of stimulation were performed to identify an epitope that induced the largest CD8+ T cell activation (i.e., INF-gamma, TNF-alpha, CD137, and CD69 expression). For these antigens, high-affinity antigen-specific CD8+ T cells were isolated using tetramers. Single-cell T cell receptor (TCR) sequencing identified the high-affinity, VP1-specific TCR-alpha/beta chain pairs.

Candidate TCRs were both virally integrated via lentivirus and then precisely introduced with genome editing via CRISPR-Cas9 into the TRAC (T cell receptor alpha constant) locus into CD8 and CD4 donor T cells for further characterization. These T cells then underwent in vitro validation through antigen:MHC presentation on K562 cells and PML isolated non-cytolytic strains of JCV infected astrocytes. Further in vivo testing was completed by flank tumors of A375 tumor lines transduced to express antigen:MHCs of interest. The TCR also underwent further safety studies via alanine, X-scans, and autoreactivity scans.

Further cell editing is being explored through both epigenetic edits and single gene knock-outs.

Results: A highly conserved region, as determined by a screen of >700 isolated viral copies of JCV isolated from PML patients, of the JCV VP1 protein (VP1 100-108) was identified as an antigen for HLA-A2*01 CD8+ T cells. Fourteen high avidity TCRs specific for VP1 100-108 were isolated, and ten demonstrated specific binding to VP1 100-108 HLA-A2 tetramers. The top two candidates were retrovirally edited into T cells and showed complete clearance of K627 cells expressing HLA-A2 compatible MHC with VP1100-108 at an ET of 2:1 after 48 hours of co-culture. Subsequently, we treated JCV infected astrocytes which showed CD137 activation of treatment T cells and 30-50% clearance of the infected astrocytes in increasing order of E:T after 72hr of co-culture. Based on this, we then used CRISPR-Cas9 editing to knock-in our TCR of choice and avoid any endogenous TCR effect. These T cells again showed efficacy in vitro. We then injected a A375 tumor line expressing HLA-A2 compatible MHC and VP1 100-108 into mice and showed complete tumor prevention and tumor growth reversal with our candidate T cell treatment. We have now explored this candidate TCR and found it to have a low risk of cross-reactivity via alanine and X-scan. In parallel, we have been optimizing editing techniques to allow for us to downregulate the expression of beta 2 microglobulin and CIITA, and upregulate CD47 for increased allogenic cell persistence. Other immunogenic regions of VP1 and candidate TCRs have been similarly identified for HLA-A3 allele.

Conclusions: We identified immunogenic epitopes from the JCV VP1 protein that bind HLA-A2 and A3 and isolated HLA restricted TCRs. For HLA-A2*01 we have demonstrated recognition and activation to the epitope of interest both in vitro and in vivo. We have further shown that targeting this epitope alone can clear around 40% of virally infected cells in vitro. While additional in vitro and in vivo validation are in progress, we believe these cells will offer a rapid, "off-the-shelf", allogeneic anti-JCV T cell therapy for PML patients who are unable to immune reconstitute.

SLEEP DISORDERS AND CIRCADIAN RHYTHMS

S398-LB: Circadian and Non-Circadian Sleep Disorders as Predictors of Neurodegenerative Diagnosis: Evidence From Three Retrospective Cohorts

Presenting Author: *Nicole Ash, M.A.S, Clinical Research, San Diego, CA*

Background: Circadian rhythm dysfunction has emerged as a potential contributor to neurodegenerative disease, yet its relationship to incident neurodegenerative outcomes remains incompletely understood. Sleep disturbances are increasingly recognized as modifiable risk factors for cognitive decline and dementia, although prior studies have often evaluated sleep disorders broadly without distinguishing circadian from non-circadian etiologies. We evaluated the association between circadian rhythm disorders (CRD), other sleep disorders, and neurodegenerative diagnoses in a large multi-center electronic health record cohort.

Methods: Sleep disorders were common among patients with neurodegenerative diagnoses and were more frequently

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documented following diagnosis. In matched analyses, CRD was associated with significantly increased odds of neurodegenerative outcomes compared to controls, including Alzheimer's disease (OR 3.01), dementia (OR 2.84), and mild cognitive impairment (MCI) (OR 6.51) (all $p < 0.001$). CRD was also associated with a higher hazard of neurodegenerative diagnosis (HR 6.93, 95% CI 5.40–8.91, $p < 0.001$) and shorter time to diagnosis.

When compared to NCSD, CRD demonstrated more modest associations, with no significant differences for Alzheimer's disease or dementia and a modest increase in MCI (OR 1.35, $p = 0.001$; HR 1.30, 95% CI 1.14–1.50)

Results: Circadian rhythm disorders were associated with increased likelihood and slightly earlier occurrence of neurodegenerative diagnosis in a large, multi-center cohort. Differences across comparator groups highlight the heterogeneity of sleep-related risk and support circadian dysfunction as a clinically relevant and potentially modifiable factor in neurodegenerative disease.

Conclusion: We conducted a retrospective cohort study using de-identified electronic health record data from the University of California Health Data Warehouse (OMOP format) from 2012–2024. Three analytic cohorts were evaluated: (1) a descriptive cohort of patients with neurodegenerative diagnoses to characterize the temporal distribution of sleep disorders before and after diagnosis; (2) a matched cohort comparing patients with circadian rhythm disorders (CRD) to individuals without sleep disorders; and (3) a matched comparator cohort comparing CRD to non-circadian sleep disorders (NCSD). Neurodegenerative outcomes included Alzheimer's disease, dementia, and mild cognitive impairment (MCI). Logistic regression models estimated odds ratios (ORs) and 95% confidence intervals (CIs) for neurodegenerative outcomes, while Cox proportional hazards models evaluated time to neurodegenerative diagnosis.

S399-LB: Diurnal Variation in Brain Diffusion MRI in a Large Preadolescent Cohort

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Background: Recent studies in healthy adults show diurnal variations in brain diffusion measures [Thomas, Neuroimage 2018; Carlucci, Nat Comm 2023]. We analyzed the dependence of diffusion metrics on the time-of-day (TOD = scan time) in 8,661 children in the Adolescent Brain and Cognitive Development (ABCD) study, the largest longitudinal brain development study in the U.S. We further assessed whether TOD effects vary by sex.

Methods: On DTI, TOD effects were most pronounced on MD, where 12/42 regions showed diurnal variations. MD showed a trough during the morning, peak early afternoon, followed by a slow TOD decline. MD varied up to 1% across TOD. Fewer regions showed diurnal effects on TD, but their TOD courses resembled MD time courses. Only one region showed diurnal FA variation. Finally, TOD variations in girls and boys were parallel but boys had higher diffusivities. On RSI, HNI and RNI exhibited contrasting TOD patterns: HNI generally decreased across the day (strongest effects in fornix and inferior longitudinal fasciculus), whereas RNI increased across the day (strongest effects in inferior superior frontal cortex).

Results: This is the first study to assess hourly diurnal variations in brain DTI and RSI in preadolescents, separately for girls and for boys. MD variations were consistent with prior findings in younger adults who were scanned at two time points [Thomas, Neuroimage 2018]. TOD effects on RSI differed from those on DTI, and indicate a shift of water from the extracellular to the intracellular compartment across the day.

Ongoing analyses will further evaluate longitudinal diurnal changes in diffusion metrics across adolescence. Understanding diurnal variations in diffusion measures is important since they may be linked to glymphatic system alterations in neurological disorders, including neurodegenerative conditions.

Conclusion: We analyzed baseline DWI (4,156 girls, 4,505 boys, age 9-10 years), using the 2026 7.0 release. DWI involved 96 diffusion directions (4 b-values). We assessed the mean (MD), radial (RD) and transverse (TD) diffusivities and fractional anisotropy (FA) in major white matter tracts [Hagler, Neuroimage 2019]. We additionally evaluated restriction spectrum imaging (RSI) metrics reflecting hindered (HNI) and restricted (RNI) normalized isotropic diffusion. Diffusion measures were analyzed in 1-hour bins; scans before 10am and after 6pm comprised separate bins. Subject numbers across the 10 TOD bins were similar (range N=547-1,128 per bin). A linear mixed effects model was fitted with TOD and sex as independent variables and age, race, parent income and scanner as covariates (significance=$p<0.05$ FDR-corrected).

S400:Sleep Apnea in Paralympic Ontario-Resident aThletes with Spinal Cord Injury (SPORTS) Study: A Prospective Study

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Background: Given that sleep-related breathing disorders (SRBDs) in para-athletes with spinal cord injury (SCI) are understudied, we proposed a trial to evaluate the effectiveness of CPAP therapy in para-athletes with SCI who developed moderate-to-severe SRBDs in improving psychosocial and cognitive outcomes, and sports performance.

Methods: In this prospective study, adults living with chronic SCI who are high-performance para-athletes underwent a home-based sleep screening test that quantified the

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apnea-hypopnea index (AHI). Those with moderate-to-severe SRBD (AHI>15 events/hour) were assessed for levels of sleep quality, fatigue, mental health (i.e., mood, anxiety, stress), cognition, health-related quality of life, social participation, and sports performance before and after a 4-month trial of CPAP therapy.

Results: We recruited 11 para-athletes with SCI of whom four individuals met criteria for moderate-to-severe SRBD. Participants with severe-to-moderate SRBD were older (p=0.030), had a longer time since SCI (p=0.056), and greater body mass index (p=0.047) than those in the no/mild SRBD group. While severe/moderate SRBD group included only curling para-athletes, individuals with no/mild SRBD play a variety of sports (p=0.024). There was no significant differences between both groups regarding their sex/gender, race/ethnicity, level of education, household income, level and severity of SCI, neck circumference, oropharynx opening, and degree of disability. Both study groups had similar levels of fatigue (p=0.210), mental health (p=0.108), cognition (p=0.444), quality of life (p>0.117) and participation (p=0.886), but the participants in the no/mild SRBD group had greater daytime alertness (p=0.053). Among those with moderate-to-severe SRBDs, a 4-month trial of CPAP therapy improved sleep adequacy (p=0.002) and problems (p=0.045), but there were no significant effects on their levels of fatigue, mental health, cognition, quality of life, and participation. There was a trend towards improvement of the recovery (p=0.059), stress (p=0.068), and sports-specific recovery (p=0.078) as assessed using the Recovery-Stress Questionnaire for Athletes (RESTQ-76 Sport). There was no significant impact on sports performance as assessed using the Acute Recovery and Stress Scale.

Conclusion: Our preliminary results suggest that older age, longer time since SCI, and higher BMI are risk factors for moderate-to-severe SRBD among para-athletes with SCI. While moderate-to-severe SRBD adversely affects daytime alertness, there were no significant differences between the study groups regarding the individuals' levels of fatigue, mental health, cognition, health-related quality of life, and social participation. Among those four para-athletes with moderate-to-severe SRBDs, a 4-month trial of CPAP trial was already sufficient to improve sleep quality and nearly improve sports performance in this small cohort.

S402*: Clinical Predictors of Phenoconversion in Isolated REM Sleep Behavior Disorder

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Background: Isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is a prodromal α-synucleinopathy in older (>65-70 years) adults, strongly associated with Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Phenoconversion determinants in iRBD remain unclear, especially in younger cohorts. We assessed rates and predictors in our large iRBD cohort.

Methods: We conducted a retrospective cohort study of 162 participants from the Mayo Clinic RBD Registry with ≥1 year of follow-up. We analyzed demographics, iRBD characteristics, antidepressant use, comorbidities, and neurodegenerative biomarkers and determined phenoconversion categories including persistent iRBD, PD, DLB, mild cognitive impairment (MCI), and MSA. Kaplan–Meier and Cox proportional hazards models estimated phenoconversion risk using age, sex, and antidepressant use as predictors ($p < 0.05$).

Results: Among 162 participants 117 [72%] were men, with mean age of 63.5 ± 10.9 years. Baseline mean MoCA score was 26.3 ± 2.8, mean TUG was 8.2 ± 2.1 seconds, and mean BSIT score was 8.3 ± 2.2. 36 (22.2%) had psychiatric comorbidity, 25 (15.4%) received antidepressant medications, and 45 (27.8%) had cardiovascular co-morbidity. Median follow-up was 6.2 years (IQR 2.2–8.0), and median symptom duration was 6.5 years (0.1–26.1). At last follow-up, 122 (75.3%) remained as iRBD, while overall 40 (24.,7%) phenoconverted, of which 13 (8.0%) developed PD, 17 (10.5%) DLB, 5 (3.1%) MCI, 1 (0.6%) MSA, and 4 (2.5%) other diagnoses. Median time to phenoconversion was 6 years (0–18). Cumulative phenoconversion rates were 2.5% at 1 year, 9.7% at 3 years, 12.1% at 5 years, 30.1% at 10 years, 33.9% at 12 years, and 48.6% at 15 years. Older age at PSG remained independently associated with phenoconversion risk after adjustment for sex (HR 2.48 per 10-year increase, 95% CI 1.55–3.99, $p = 0.0002$). Antidepressant use trended toward association with decreased phenoconversion, (HR 0.28, 95% CI 0.08–1.06, $p = 0.061$).

Conclusion: In our younger average aged iRBD cohort, phenoconversion risk was approximately 34% at 12 years, with age as the only independent predictor. Antidepressant use trended toward lower risk for conversion. Compared with prior cohorts, conversion rates were lower, suggesting heterogeneous risk across cohorts, and confirming that age is the strongest influence of conversion risk, which is informative for patient counseling and future neuroprotective trial design.

S401: Autonomic Regulation via Dermal Vibrotactile Triggering of Piezoelectric Channels: An Emerging Nonmedication Approach to Symptom Relief

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Background: Piezo ion channels enable interpretation of sensory information conveyed through the Somatic Nervous System (SNS) of the Peripheral Nervous System (PNS) to be communicated between neurons in the brain, and also bidirectionally between the brain and the PNS. Piezo channels allow electrical current to pass through them. In this way, ion channels enable neurons to communicate with each other, so that the brain's neural networks can properly function. Haptic Vibrotactile Trigger Technology (VTT) prompts a sensory response by using electrical current-producing vibrations to stimulate the skin's mechano-receptors and is communicated via the PNS to the brain. Outcomes from several IRB-approved randomized clinical trials evaluated the efficacy of a non-drug, topical patch with VTT in patients with sleep disorders, pain, stress/anxiety issues, and in elite athletes.
Methods: Subjects were provided a topical patch with VTT, or a placebo patch without VTT. Over 14 days, responses to validated scales were collected and functional measurements were taken to evaluate the efficacy of the VTT patch and any change in sleep patterns, pain severity and interference, stress and anxiety levels, and any change in athletic performance.
Results: Outcomes demonstrated the reduction of sleep awakenings, time to fall asleep, improvement in sleep, reduced anxiety, stress, depression, pain relief, and improved athletic strength and performance.
Conclusion: The bi-directional sensory communication promoted by VTT may be able to boost the functioning of the piezoelectric channels. Evolving VTT treatments may be beneficial in people with diminished functioning of their piezoelectric channels and lead to breakthrough approaches for treating various disorders as well as improving athletic performance, endurance, and prevention of injuries.

S403: Pre–Shift Work Sleep Quality Predicts Early-Career Turnover in Newly Hired Nurses: A Prospective Cohort Study

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Background: Early-career nurse turnover remains a critical issue in the context of persistent nursing shortages. Given that newly hired nurses are inevitably exposed to shift work (SW), which adversely affects sleep, this study aimed to investigate the impact of sleep-related factors on early-career turnover risk. Specifically, we examined whether pre-SW subjective sleep quality is associated with post-SW sleep and early-career turnover.
Methods: A prospective cohort of 791 newly hired nurses was recruited from two national tertiary hospitals. Baseline subjective sleep quality was assessed prior to shift work (SW) exposure using the Pittsburgh Sleep Quality Index (PSQI). Also, participants provided baseline and 6–12 months follow-up data after SW exposure, during which chronotype, resilience, sleep outcomes (sleep quality and daytime sleepiness), and mental health outcomes (depression, anxiety, and stress) were assessed using validated self-report questionnaires. We followed participants for one year after the initiation of SW to assess early-career turnover.
Results: In 791 newly hired nurses, poorer subjective sleep quality at baseline and at 6–12 months after shift work exposure was significantly associated with an increased risk of early-career turnover. Notably, sleep duration showed the strongest association with turnover among the sleep domains. Baseline subjective sleep quality was also significantly associated with resilience and demonstrated a protective effect against early-career turnover.
Conclusion: Pre-SW sleep quality was significantly associated with resilience and subsequent mental health outcomes. Furthermore, baseline sleep quality predicted early-career nurse turnover one year after shift work exposure. These findings suggest that sleep vulnerability prior to shift work may play a critical role in early-career nurse turnover, highlighting the importance of targeted interventions-such as optimizing sleep quality and enhancing resilience-to mitigate early shift work–related mental health challenges.

BEHAVIORAL NEUROLOGY & DEMENTIA

M100-K: Interrogating Amygdala-predominant Lewy Body Disease with Spatial Proteomics

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Background: Lewy body disease (LBD) often coexists with Alzheimer's (AD), resulting in more cognitive decline than from either alone. LBD's hallmarks, asyn-positive Lewy bodies and neurites, propagate from the enteric system or olfactory bulb to the amygdala, which acts as a gatekeeper before spread to other structures. The amygdala-predominant LBD (AP-LBD) type is a special pattern of LBD that is quite prevalent in sporadic and familial early-onset AD (EOAD). Notably, AP-LBD does not conform with the most used staging systems for LBD and has received little attention. We found a link between asyn seeding-competent fibrils in cerebrospinal fluid (CSF) and the transition of LBD from the amygdala into connected regions, supporting its gatekeeper role. The factors permitting asyn propagation in the amygdala remain

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unknown. Our goal is to use spatial proteomics in EOAD cases with AP-LBD to identify pathways of spread and selectively vulnerable cell populations within amygdala subfields.
Methods: We identified all postmortem EOAD cases with AP-LBD from the UCSF Neurodegenerative Disease Brain Bank (n=57), 20 of which have banked CSF for asyn seeding amplification testing. We are using spatial proteomics (Nanostring GeoMx DSP with morphology, pathology, AD, and PD modules) with 50 um ROIs to select and compare neurons with phosphorylated asyn, phosphorylated tau, both, or neither. ROIs were chosen across the central nucleus, basolateral nuclei, and cortical nucleus of the amygdala.
Results: Pending analysis, we will report the proteomic differences between subfields, between different neuronal phenotypes, and their correlations to CSF seeding assay result. Of 19 CSF samples tested thus far, 53% were positive for asyn seeding; an additional sample is pending.
Conclusions: Proteomic variation among amygdala subfields and distinct neuronal phenotypes may uncover molecular determinants of selective neuronal vulnerability, deepening our understanding of AP-LBD pathobiology and facilitating the development of targeted diagnostic and therapeutic interventions.

M101-K: Neural Replay Events Emerge During Periods of Cortical Beta Suppression

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Abstract: Neural replay, temporally compressed reactivations of task-related activity during rest1, has emerged as a candidate mechanism for stabilizing newly acquired skills2–4. However, the oscillatory conditions that allow replay to emerge in humans is unknownIn particular, whether neural replay events are linked to specific brain oscillatory states remains unclear. Here we test the hypothesis that replay emerges preferentially during transient beta-band oscillatory suppression, a neural state that is associated with increased plasticity and learning5–9.
We analyzed magnetoencephalography (MEG) data from a repository of 31 participants performing a well-characterized motor sequence learning task in which 10-second bouts of sequence typing alternated with 10-second rest periods4,10. We implemented a previously described neural replay detection pipeline4,11. To characterize oscillatory dynamics around replay, source-level MEG data were bandpass filtered in the beta range, Hilbert transformed, and epoched trial-by-trial from 1 s before to 1 s after replay onset. Beta power surrounding replay was examined relative to rest baseline and compared with matched randomly selected rest time points.
Replay events were associated with a transient reduction in beta power surrounding event onset. At the group level, replay-locked averaging revealed a clear beta power decrease preceding replay onset, with a second drop centered near the replay event. This replay-related beta profile was not observed for randomly selected control periods, suggesting that the effect was not explained by fluctuations in rest-related beta activity.
These findings provide evidence that human motor replay is embedded within a low-beta state and suggest that transient beta suppression may mark a cortical state that facilitates replay. This aligns with recent animal literature showing that elevated beta-band bursting competes with the neural replay events that are causal drivers of performance gains9.
These results identify beta dynamics as a candidate target for testing how oscillatory brain state shapes offline motor learning.

M102-K: β-Amyloid Induces Microglial Expression GPC4 And APOE Leading to Increased Neuronal Tau Pathology and Toxicity

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Background: Heparan sulfate proteoglycans (HSPGs) are emerging as critical regulators of protein aggregation and intercellular propagation in neurodegeneration, yet their cell-type–specific regulation and function in Alzheimer's disease (AD) remain incompletely defined. Here, we identify a proteoglycan remodeling program in microglia triggered by β-amyloid (Aβ) pathology.
Methods: Human iPSC-derived microglial models were used to examine proteoglycan remodeling following exposure to fibrillar Aβ. Surfaceome profiling using HRP-WGA–based proximity labeling identified cell-surface proteins selectively altered by amyloid pathology. Functional studies in iPSC models assessed the role of Glypican 4 (GPC4) in tau aggregate binding, uptake, trafficking, and seeding.
Pathological relevance was evaluated in human AD brain tissue, and in vivo functional validation was performed using Drosophila models of amyloid- and tau-associated neurotoxicity.
Results: Surfaceome profiling of human iPSC-derived microglia reveals that fibrillar Aβ selectively induces the upregulation of multiple HSPGs, with prominent enrichment of the glypican family member Glypican 4 (GPC4), a GPI-anchored HSPG not previously linked to microglial biology. Aβ fibrils drive a robust increase in microglial cell-surface heparan sulfate and GPC4 expression, a response not recapitulated by monomeric peptides or canonical inflammatory stimuli, indicating an amyloid-specific glycan remodeling program.
Functionally, GPC4 acts as a key determinant of proteopathic cargo handling via their heparan sulfate chains, facilitating tau aggregate binding, uptake, and intracellular

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trafficking. Proteolytic shedding of GPC4 further generates a soluble HSPG pool capable of acting in trans to enhance tau internalization into neighboring cells. Mechanistically, GPC4 cooperates with the heparan sulfate–binding protein APOE to amplify tau uptake and seeding, suggesting the formation of a proteoglycan-centered extracellular complex that promotes proteopathic spread. In vivo, glial expression of the GPC4 ortholog exacerbates amyloid- and tau-ass**oc**iated toxicity, while in human AD brain, microglial GPC4 is enriched in peri-plaque regions and strongly associates with local neuritic tau pathology.

Conclusions: Together, these findings position microglial HSPG remodeling as a mechanistic link between amyloid deposition and tau propagation. This work highlights proteoglycans, particularly GPC4, not merely as passive scaffolds, but as active regulators of proteopathic signaling, uptake, and intercellular spread in neurodegenerative disease.

M104: Trends in Fracture-Associated Mortality Among Individuals with Mental and Behavioral Disorders in the United States (1999-2019)

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Background: Individuals with mental and behavioral disorders are at increased risk of fractures and related mortality, potentially due to falls, comorbidities, and medication effects. National temporal and demographic patterns in fracture-associated mortality in this population remain incompletely characterized.

Methods: We conducted an observational study using CDC WONDER multiple cause-of-death data (1999-2019). Fracture-associated deaths were identified using relevant ICD-10 codes among individuals with mental and behavioral disorders listed as contributing conditions. Crude and age-adjusted mortality rates (AAMRs) per 100,000 were calculated and Joinpoint regression estimated annual percent change (APC) and average APC (AAPC) with 95% confidence intervals (CI). Stratifications were done by age, region, race/ethnicity, urbanization, and sex.

Results: A total of 144,360 deaths were identified. AAMRs increased from 1.03 in 1999 to 2.36 in 2019 (AAPC 3.74%). Mortality was concentrated among older adults, with those ≥85 years accounting for 59.5% of deaths and having the highest crude mortality rate (76.1). Most deaths occurred in nursing homes/long-term care (40.0%) and inpatient settings (31.8%). Non-Hispanic White individuals and non-Hispanic American Indian/Alaska Native populations had the highest overall AAMRs in the study period (2.36 and 2.24 respectively). Urban AAMRs increased from 0.94 to 2.22 (AAPC 3.84%), while rural rates rose from 1.48 to 3.08 (AAPC 3.32%). Census-wise analyses demonstrated increasing mortality across all U.S. Census regions, with the Midwest showing the highest overall rise (AAPC 4.12%, 95% CI 3.33-5.24) and the Northeast showing the smallest increase (AAPC 3.32%). The highest state-level AAMRs were seen in Montana (5.92) and Vermont (5.82). Sex differences showed higher AAMRs among females with steeper increases (AAPC 4.13%) compared to males (AAPC 3.27%).

Conclusion: Fracture-associated mortality among individuals with mental and behavioral disorders has nearly doubled from 1999-2019, with the greatest burden seen among older adults. Mortality remained higher in rural populations and among non-Hispanic White and American Indian/Alaska Native individuals, with regional variations, particularly in the Midwest. Females experienced higher rates and steeper increases than males. These findings highlight the need for improved fracture prevention and post-fracture management in high-risk populations.

M105: Methamphetamine-Driven Dopaminergic Signaling Enhances Microglial HIV Infection in Human Brain Organoids

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Background: HIV-associated neurologic complications affect nearly half of people with HIV and are driven in part by

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persistent viral reservoirs in microglia and macrophages, leading to chronic neuroinflammation.

Methamphetamine (METH) use is more prevalent among people with HIV and is associated with increased viral burden and cytokine levels, though the mechanisms underlying this interaction remain unclear. Prior work from our group demonstrated that dopamine enhances HIV replication and cytokine release in myeloid cells, suggesting that METH-induced dopaminergic signaling may exacerbate HIV neuropathogenesis.

Methods: We developed human iPSC-derived cortical (low dopaminergic tone) and midbrain (high dopaminergic tone) organoids with co-cultured microglia to model region-specific neuroimmune interactions. Organoid identity and microglial incorporation were validated by qPCR, immunostaining, and transcriptomic profiling. METH-induced dopamine release and neuronal activity were assessed using live-cell imaging and multi-electrode arrays.

Organoids were infected with CCR5-tropic HIV-ADA +/- chronic METH treatment from 5 to 20 days-post-infection (DPI; n=3-7 per group). HIV viral capsid (p24Gag) and cytokine secretion were quantified in culture supernatants using AlphaLISA assays. Antiretroviral therapy (Biktarvy) was used to attenuate HIV replication, and pharmacologic modulation with the dopaminergic agonist apomorphine was used to probe a direct dopamine signaling effect. Follow-up studies (n=4 per group) assessed astrocyte activation in microglia-deficient organoids treated with A1-inducing cytokines (TNFα, IL-1α, and C1q) for 24h. Microglia-dependent neuroinflammation was evaluated in uninfected midbrain organoids +/- microglia treated with either lipopolysaccharide (LPS) or chronic METH.

Results: Measurements of p24Gag secretion demonstrated that HIV replication required microglial integration and was suppressed by Biktarvy, consistent across two independent differentiations. HIV p24Gag localized exclusively to microglia by immunostaining, with infected cells forming multinucleated giant cells. METH increased HIV replication in midbrain organoids (∼3.5-fold) by 14 DPI but not cortical organoids. Consistent with a dopamine-dependent mechanism, apomorphine increased viral replication in cortical organoids (∼4-fold). HIV infection induced CCL2 secretion in a microglia-dependent manner and was attenuated by Biktarvy. Activated astrocytes released CCL2 when treated with A1-inducing cytokines ($p<0.01$) in microglia-deficient midbrain organoids. In contrast, CCL2 secretion in response to LPS ($p<0.05$) or METH ($p<0.05$) required microglia integration, highlighting dynamic intercellular crosstalk between dopaminergic neurons, microglia, and astrocytes.

Conclusion: Our findings show that regional dopaminergic tone modulates microglial HIV infection and neuroinflammatory signaling in a human organoid model, with CCL2 as a possible feed-forward myeloid recruitment pathway, This work implicates dopamine as an intermediate link between METH exposure and accelerated HIV neuropathogenesis and highlights neurotransmitter–immune interactions as potential therapeutic targets.

M106*: Association Between Generative AI Integration and Perceived Cognitive Failures Among Healthcare Professionals: Implications for Workforce Cognitive Load

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Background: The rapid integration of Large Language Models (LLMs) into professional workflows has raised concerns regarding 'cognitive offloading' or executive dysfunction. While AI enhances efficiency, its impact on the executive function and attentional control of high-functioning individuals remains poorly understood.

Methods: The objective was to analyze the association between generative artificial intelligence usage frequency and self-reported perceived cognitive failures in healthcare professionals using the Cognitive Failures Questionnaire (CFQ). We conducted a STROBE-compliant cross-sectional study of 384 healthcare professionals categorized by AI chatbot use frequency (Never, Occasionally, Frequently). The CFQ total and subscale scores were analyzed using Kruskal-Wallis and Mann-Whitney U tests, with chi-square for categorical variables. Multivariable linear regression adjusted for age and sex assessed associations, reporting 95% confidence intervals and a significance level of $p < 0.05$. Internal consistency was evaluated using Cronbach's alpha.

Results: A total of 384 actively working healthcare professionals (median age 27 years [Q1-Q3: 25-30]; 62.5% female) were included. Frequent AI chatbot use (27.3%) demonstrated a frequency-dependent association with higher Cognitive Failures Questionnaire scores (median 40 vs. 33–36; $H = 20.314$, $p < 0.001$). This pattern was most pronounced in distractibility ($H = 28.20$, $p < 0.001$), followed by forgetfulness ($H = 13.48$, $p < 0.001$) and false triggering ($H = 8.01$, $p = 0.018$), suggesting greater perceived alterations in attentional control and executive functioning. Post-hoc analyses confirmed that the effect was primarily localized to the frequent-use group ($p < 0.001$). In adjusted models, AI use remained independently associated with higher CFQ scores ($\beta = 0.21$, $p < 0.001$), while female sex was associated with lower scores ($p = 0.030$) and age showed no significant effect.

Although scores remained within normative ranges, the observed gradient suggests a subclinical shift in cognitive self-monitoring in a young, high-functioning population. Internal consistency was good ($\alpha = 0.883$).

Conclusion: Frequent AI chatbot use is independently associated with a subclinical increase in perceived cognitive failures, particularly in attention. Although scores remain within normative ranges, the frequency-dependent pattern suggests changes in cognitive self-monitoring or reliance on digital tools, highlighting the need for longitudinal studies to clarify causality and long-term cognitive effects.

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M109: The Shifting Hierarchy of Death: A 25-Year Analysis of Neurodegenerative, Cancer, and Ischemic Heart Disease Mortality in the United States (1999–2023)

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Background: To characterize diverging mortality trends across cancer, ischemic heart disease (IHD), and neurodegenerative diseases in the United States over 25 years, and to identify demographic subgroups where the neurodegenerative burden is rising most rapidly. Decades of advances in cardiovascular prevention and oncologic treatment have driven substantial declines in IHD and cancer mortality. In contrast, neurodegenerative diseases - including Alzheimer's disease, Parkinson's disease, and ALS - lack comparable disease-modifying therapies, and deaths attributed to these conditions have increased steadily. Characterizing this divergence is essential for informing neurology workforce planning, research prioritization, and public health policy.

Methods: Mortality data from the CDC WONDER Underlying Cause of Death database were analyzed for 1999–2023. Age-adjusted mortality rates (AAMRs) per 100,000 were calculated using the 2000 U.S. standard population. Joinpoint regression estimated annual percent change (APC) and average annual percent change (AAPC), stratified by sex and race/ethnicity.

Results: Over the study period, cancer accounted for 10,243,227 deaths, IHD for 8,280,332, and neurodegenerative diseases for 2,820,123. Cancer AAMR declined from 1126.2 to 819.3 (AAPC −1.34; 95% CI −1.50 to −1.18) and IHD declined more steeply from 1301.6 to 515.8 (AAPC −3.77; 95% CI −4.29 to −3.25), with the sharpest IHD decline during 2002–2010 (APC −5.64). Neurodegenerative AAMR increased from 170.3 to 290.3 (AAPC 2.11; 95% CI 0.79 to 3.44), with the steepest rise between 1999 and 2005 (APC 5.51). Declines in cancer and IHD mortality were consistent across both sexes and all racial/ethnic groups. Neurodegenerative mortality increased significantly in males (AAPC 1.81; 95% CI 0.74 to 2.90) and females (AAPC 2.29; 95% CI 0.81 to 3.79), and across Hispanic, non-Hispanic Asian or Pacific Islander, non-Hispanic Black, and non-Hispanic White populations.

Conclusion: While IHD and cancer mortality have declined across all major demographic groups, neurodegenerative disease mortality has risen steadily and universally - a divergence that reflects the absence of effective disease-modifying therapies and an underprepared public health infrastructure. These findings argue for proportional investment in neurodegenerative disease research, neurology workforce development, and care delivery models capable of meeting this expanding burden.

M110: Sepsis-Related Mortality Among Older Adults with Alzheimer's Disease in the United States, 1999–2023: A CDC WONDER Population-Based Analysis of Demographic and Regional Disparities

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Background: To characterize temporal trends and demographic and geographic disparities in sepsis-related mortality among older adults with Alzheimer's disease (AD) in the United States from 1999 to 2023. Sepsis is a leading cause of death among older adults, and AD amplifies vulnerability through impaired immune function, blunted febrile response, and delayed recognition of infection. Despite the clinical relevance of this comorbidity, population-level mortality patterns at their intersection remain poorly characterized. Identifying high-risk demographic and geographic subgroups is essential for targeting early detection and equitable preventive care.

Methods: Mortality data were obtained from the CDC WONDER Multiple Cause of Death database for adults aged ≥55 years from 1999 to 2023, using ICD-10 codes to identify deaths with both sepsis and AD listed. Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated using the 2000 U.S. standard population.
Joinpoint regression estimated annual percent change (APC) and average annual percent change (AAPC), stratified by sex, race/ethnicity, age group, and U.S. census region.

Results: A total of 45,254 sepsis-related deaths occurred among adults with AD over the study period. Overall AAMR remained essentially stable, declining modestly from 2.2 to 2.0 (AAPC −0.46; 95% CI −2.40 to 1.52; p=0.65), indicating no statistically significant trend. Nearly half of deaths (45.7%) occurred in medical facilities. Adults aged 85 and older accounted for 57.6% of deaths. Non-Hispanic Black individuals had the highest AAMRs across the study period (3.3 to 3.7), exceeding rates in all other racial/ethnic groups. Females had higher AAMRs than males throughout. Geographically, the West region carried the highest mortality burden (AAMR 2.1 to 3.1) compared to other census regions.

Conclusion: Sepsis-related mortality among older adults with Alzheimer's disease remained stable over 25 years at the national level, yet substantial disparities persist by race, age, sex, and geography. Non-Hispanic Black individuals, adults aged 85 and older, and residents of the Western United States bear a disproportionate burden. Given that

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nearly half of deaths occur in medical settings, healthcare systems serving these populations should prioritize early sepsis recognition protocols specifically adapted for cognitively impaired patients, alongside equity-focused interventions addressing the structural determinants driving racial and regional disparities.

M111: An Escalating Crisis: A 25-Year CDC WONDER Analysis of Fall-Related Mortality in Older Adults with Neurodegenerative Diseases (1999–2023)

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Background: To evaluate trends in fall-related mortality among older adults with neurodegenerative diseases in the United States from 1999 to 2023, including disparities by sex, race/ethnicity, census region, and urbanization level. Falls are the leading cause of injury-related death among older adults, and neurodegenerative diseases - which impair gait, balance, and cognition - substantially amplify this risk. Despite the clinical burden, population-level mortality trends at this intersection remain poorly characterized and fall prevention strategies in cognitively impaired populations remain underdeveloped.

Methods: Death certificate data from the CDC WONDER Multiple Cause of Death database were analyzed for fall-related mortality among adults aged ≥55 years with neurodegenerative diseases from 1999 to 2023. Age-adjusted mortality rates (AAMRs) per 100,000 persons were calculated using the 2000 U.S. standard population.

Joinpoint regression estimated annual percent change (APC) and average annual percent change (AAPC), stratified by sex, race/ethnicity, census region, and NCHS 2013 urbanization classification.

Results: Between 1999 and 2023, 57,294 fall-related deaths occurred among adults aged ≥55 years with neurodegenerative diseases. AAMR increased more than fourfold, from 1.34 to 5.58 (AAPC 6.26%; 95% CI 4.79–7.74). Distinct acceleration phases were identified: rapid early rise from 1999–2002 (APC 14.22; 95% CI 4.05–25.38), modest increase through 2013 (APC 3.00; 95% CI 1.81–4.21), marked re-acceleration from 2013–2021 (APC 9.05; 95% CI 7.57–10.54), and apparent stabilization from 2021–2023 (APC 1.97; 95% CI −6.06–10.69), though the latter trend did not reach statistical significance. Males had consistently higher AAMRs than females throughout (1.92 vs. 1.08 in 1999; 5.96 vs. 5.30 in 2023). Non-Hispanic White individuals had the highest overall AAMR (3.41) and steepest increase (AAPC 6.51; 95% CI 5.17–7.86), with particularly rapid acceleration from 2014–2021 (APC 10.28). The West had the highest regional AAMR (4.10), followed by the Midwest (3.72), South (2.58), and Northeast (1.68). Small metropolitan (AAMR 3.30) and medium metropolitan areas (2.94) had higher rates than large central metropolitan areas (2.24), suggesting elevated risk across a range of community settings beyond exclusively rural populations.

Conclusion: Fall-related mortality among older adults with neurodegenerative diseases increased more than fourfold over 25 years, with marked re-acceleration after 2013 - a pattern that may reflect increased survival to advanced disease stages, evolving care transitions, or shifting demography of the neurodegenerative population. Disparities across sex, race, geography, and urbanization level underscore the need for targeted fall prevention protocols specifically designed for cognitively and motorically impaired populations, with particular attention to small and medium metropolitan communities where risk is highest.

M112: Trends, Disparities and Shifting Patterns of Mortality in Alzheimer's Disease with Mental Health in the United States: a CDC WONDER Analysis

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Background: Alzheimer's disease (AD), by incidence and mortality, constitutes the largest burden in neurodegenerative diseases occurring amongst older adults today. Mental health problems encompassing behavioral and psychiatric comorbidities are most prevalent among AD patients, lending towards the trend in AD's overwhelming mortality. This study examines mortality trends in AD patients with co-existing mental health disorders amongst older adults in the United States.

Methods: Data were extracted from the CDC WONDER Multiple Cause of Death database from 1999-2025 using the ICD-10 codes G30.0, G30.1, G30.8, and G30.9 for AD and F01-F99 for Mental health disorders as underlying cause of death among adults aged ≥ 65 years. Age-adjusted mortality rates (AAMR) per 100,000 were standardized to U.S population. Joinpoint regression analysis was used to calculate annual percent change (APC) and average annual percent change (AAPC), with $p < 0.05$ considered significant, denoted by an asterisk (*).

Results: From 1999-2025, a total of 308,309 deaths occurred due to AD with Mental Health Disorders in the United States. Considerable increase in AAMR was seen from 12.41 in 1999 to 38.83 in 2025 (AAPC: 4.13*%; 95% CI: 3.49 to 4.94). Mortality rates rose sharply from 1999-2001 (APC: 16.58*%), stabilized trend from 2001-2014 (APC: 1.18%), surging again from 2014-2020 (APC: 9.99*%), and finally plateauing through 2025 (APC: 0.44*%). Females showed higher mortality rates (AAPC: 4.31*%) as compared to males (AAPC: 3.63*%). Age group analysis revealed that individuals aged 85+ years had a notable rise in mortality

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throughout the study span (AAPC: 4.07*%). Regionally, the South region showed the highest trend (AAPC: 4.40*%), followed by the Midwest (AAPC: 3.82*%). Non-Hispanics had greater mortality rates (AAPC: 4.18*%) than the Hispanics (AAPC: 3.95*%). Amongst non-Hispanics, the most pronounced rise was shown by Blacks or African Americans (AAPC: 5.18*%), followed by Whites (AAPC: 4.32*%). Non- metropolitan regions (AAPC: 5.92*%) experienced higher mortality than the metropolitan regions (AAPC: 4.79*%)

Conclusion: From 1999-2025, AD associated mental health disorders caused a significant rise in mortality among older adults. Persistent geographic and demographic mortalities underscore urgent need for long-term public health intervention and neuropsychiatric care to mitigate this growing burden.

M113-LB: Auditory Cortex Connectivity Disruption in Behavioral Variant Frontotemporal Dementia

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Background: Behavioral variant frontotemporal dementia (bvFTD), the most common frontotemporal lobar degeneration syndrome, is characterized by progressive behavioral and cognitive decline with prominent frontal and anterior temporal atrophy (Seeley, Continuum, 2019; Boeve, Continuum, 2022). bvFTD is also associated with impaired sound processing, auditory emotion recognition, and sound localization, suggesting selective vulnerability of the auditory cortex (Johnson et al., Alzheimer's & Dementia, 2025). Prior studies report reduced gray matter density in this region (Aylward et al., Otology & Neurology, 2020), but changes in auditory network connectivity and its relationship to auditory-based cognitive functions remain unclear. In this study, we examined resting-state auditory-network connectivity in the bvFTD continuum and its associations with auditory working memory and socio-emotional function.

Methods: Resting-state fMRI data from 18 mild to moderate bvFTD and 35 controls from the ALLFTD database were preprocessed using the CONN toolbox. Seed-based whole-brain connectivity was examined for the secondary auditory cortices planum polare (PP) and planum temporale (PT), regions involved in acoustic processing (Upadhyay et al., The Journal of Neuroscience, 2008). Age, sex, handedness, and gray matter volume were included as covariates. Group differences between bvFTD and controls were assessed using a voxel-wise threshold of $p < 0.001$ and cluster-FDR $p < 0.05$. Regression analyses of auditory working memory and socio-emotional measures–Digit Span, California Verbal Learning Test (CVLT) immediate free recall, and Interpersonal Reactivity Index Perspective Taking (IRI-PT) Test–were assessed using a voxel-wise threshold of $p < 0.001$ and cluster-FDR $p < 0.05$. Benson Complex Figure scores were evaluated as a nonverbal control task.

Results: Individuals with bvFTD showed reduced connectivity in perisylvian, insular, and parietal association regions with both the PP and PT seeds (PT > PP). Digit Span and CVLT positively correlated with connectivity in auditory seeds, particularly the PT seed (PT > PP) based on cluster size. The IRI-PT was positively associated with PP connectivity. Connectivity correlations with the Benson test revealed regions outside the perisylvian zone.

Conclusion: These findings support the selective functional vulnerability of the associative auditory cortex in bvFTD. The pronounced decreases in PT and PP connectivity and their association with Digit Span, CVLT, and IRI-PT suggest that auditory-based impairment in bvFTD can contribute to verbal working memory, memory encoding and social perspective taking. Lack of perisylvian connectivity for the visual task supported the specificity of our findings.

M114: Effects of Non-Invasive Cervical Vagus Nerve Stimulation on Neuroinflammation, Brain Oxygenation, and Behavior in Alzheimer's Transgenic Mice

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Background: Vagus nerve stimulation (VNS) delivers mild electrical pulses to the vagus nerve, a parasympathetic nerve that modulates brain activity and inflammatory pathways. VNS is FDA-approved to treat migraines, epilepsy, and depression, yet emerging research suggests broader therapeutic applications. Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline, with chronic neuroinflammation playing a central role in its pathology. Cytokines, especially IL-1β, are key mediators of this pro-inflammatory response, contributing to cognitive impairment and increased anxiety when chronically elevated. Recent studies demonstrate that VNS reduces levels of inflammatory cytokines in the brain, particularly in models where inflammation is experimentally induced via lipopolysaccharide injection in mice.

Methods: We hypothesized that the effects of VNS may present a promising strategy for reducing neuroinflammation and associated behavioral impairments in AD. To test this, male and female transgenic 5x Familial Alzheimer Disease (5xFAD) mice (n=8) and Wild-Type (WT) mice (n=11) received 2 sets of non-invasive right unilateral cervical VNS using GammaCore. Each set consisted of two 2-minute stimulations with a 3-minute interval (20V; 60mA; 25Hz; 1ms bursts of 5kHz sine waves). Behavioral activity was assessed using Open Field Testing (OFT) and EthoVision XT

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software before and after VNS, while brain oxy- and deoxyhemoglobin concentrations were measured using Spatial Frequency Domain Imaging (SFDI) before, during, and after treatment. Concentrations of pro-inflammatory cytokine IL-1β were measured in right-hemisphere brain homogenates using ELISA.

Results: When we compared IL-1β concentrations between 5xFAD and WT mice post-VNS, we found that IL-1β concentrations were not significantly different ($p=0.8601$). Since 5xFAD mice are known to have higher baseline IL-1β concentrations, this suggests a reduction in IL-1β in 5xFAD mice to that of WT levels. Analysis of SFDI revealed a significant increase in deoxygenated hemoglobin in WT mice post-VNS compared to pre-VNS ($p=0.0137$) whereas 5xFAD did not show significant changes, suggesting changes in cerebral oxygenation demands post-VNS in WT mice only. Mean velocity of locomotor activity analyzed with OFT revealed significant reductions in average velocity across all 10 minutes of recording in 5xFAD mice post-VNS compared to pre-VNS ($p<0.02$), which was not observed in WT mice.

Conclusion: Our findings suggest that VNS attenuates hyper-active neuroinflammation and modulates cerebral oxygenation, leading to lower anxiety and enhanced short-term cognitive performance in 5xFAD mice.

M115: Low levels of Insulin Signaling proteins in HIV Brains are Associated with Neurocognitive Impairment and CSF Viral Load

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Background: HIV-associated neurocognitive impairment (HIV-NCI) persists in people with HIV (PWH) despite effective antiretroviral therapy (ART), with emerging evidence implicating disruptions in brain metabolic and related signaling pathways. The insulin/insulin-like growth factor-1 (IGF-1) pathways are integral to brain bioenergetic homeostasis. We hypothesize that the expression of key markers of glucose metabolism and insulin/IGF-1 signaling is downregulated in the brains of PWH with HIV-NCI.

Methods: We performed biochemical analysis of Insulin Receptor substrates (IRs) 1 and 2 and hexokinase 1 (HK1) and pyruvate kinase M2 (PKM2) in postmortem dorsolateral prefrontal cortex (DLPFC) lysates collected from 24 decedents, stratified by neurocognitive status.

Results: Immunoblot analyses demonstrated a significant reduction in IRs1 expression in HIV-NCI compared to NUI. IRs2 exhibited a similar downward trend. In contrast, glycolytic enzymes HK1 and PKM2 levels were significantly elevated in HIV-NCI. IRs2 and PKM2 were significantly associated with the global deficit score (GDS) and cerebrospinal fluid viral load (CVL), with IRs2 exhibiting inverse associations with both measures. HK1 also demonstrated a modest association with CVL; notably, none of the examined markers correlated with plasma viral load (PVL).

Conclusion: Given the central role of insulin receptor substrate proteins in both insulin/IGF-1 signaling, reduced IRs1/2 may prevent homeostatic IGF-1 signaling in the HIV-infected brain. The concomitant increase in HK1 and PKM2 may represent a compensatory glycolytic response to impaired upstream signaling. Disruption of insulin/IGF-1 pathways may contribute to neuronal vulnerability by reducing glucose utilization efficiency and promoting neurodegenerative processes.

M117: Interpretable Mathematical Foundations for Reliable Event-Based Modeling of Alzheimer's Disease Progression

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Background: Alzheimer's disease unfolds over decades, yet most available data are cross-sectional, requiring disease progression to be inferred from static snapshots. Event-Based Models (EBMs) have emerged as a leading framework for reconstructing biomarker trajectories and informing early detection and staging. However, EBMs rely on strong assumptions, including irreversible biomarker transitions and a shared progression across individuals, assumptions that are routinely violated in heterogeneous, high-dimensional data such as cerebrospinal fluid proteomics. Despite this, EBM-derived sequences are often interpreted as definitive, without a principled way to determine which inferred relationships are reliable. This lack of reliability quantification limits clinical interpretability and undermines trust in model-driven staging.

Methods: We develop an interpretable mathematical framework to quantify the reliability of EBM-derived biomarker orderings. Rather than treating a single inferred sequence as ground truth, we systematically stress-test it through local perturbations, swapping adjacent biomarkers and evaluating the resulting change in model evidence. We prove that this change admits a decomposition into two interpretable components: a visibility term, capturing whether patient data meaningfully inform a given region of the disease timeline, and a contrast term, capturing the strength and direction of biological evidence between competing orderings. These subject-level contributions aggregate into a cohort-level stability measure that directly characterizes the reliability of each local relationship.

Results: Applied to cerebrospinal fluid proteomic data from the Emory Healthy Brain Study, this framework reveals that apparent global structure in disease progression conceals substantial and systematic local uncertainty. While EBMs recover coherent large-scale trajectories, many local biomarker relationships are weakly supported or exhibit conflicting evidence across patients. We identify three clinically actionable regimes: stable relationships supported consistently across individuals, weak relationships driven by limited data coverage, and heterogeneous relationships reflecting true biological

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divergence. Critically, instability is concentrated in early-stage regions, precisely where accurate staging is most important for early intervention, patient stratification, and clinical trial design.

Conclusion: This work establishes a principled foundation for determining when disease progression models can be trusted and when they cannot. By explicitly separating robust structure from uncertainty, it transforms EBMs from descriptive tools into interpretable, falsifiable models. Clinically, this enables more reliable biomarker sequencing and highlights regions of disease progression where caution is required, particularly in early-stage disease. More broadly, this framework introduces a new standard for transparency and reliability in machine learning–driven disease modeling, with direct implications for precision neurology and therapeutic development.

M118: Redox-Mediated Regulation of Neuroinflammatory STING Pathway via Protein S-Nitrosylation Contributes to Damage in Alzheimer's Disease Brain

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Background: Alzheimer's disease (AD) is characterized by progressive neurodegeneration accompanied by chronic neuroinflammation that contributes to synaptic dysfunction and consequent cognitive decline. The cGAS–STING pathway has emerged as a key mediator of innate immune activation in AD; however, mechanisms underlying its aberrant activation in the human brain remain poorly understood.

Methods: Here, we identify protein S-nitrosylation of STING (SNO-STING) as a redox-dependent mechanism driving pathological STING activation. Using redox proteomics and mass spectrometry, we detect elevated SNO-STING in postmortem human sporadic AD brains, as well as in hiPSC-derived microglia exposed to amyloid-β and α-synuclein oligomers and in 5xFAD transgenic mice.

Results: Mechanistically, S-nitrosylation promotes STING oligomerization and downstream type I interferon signaling, leading to a sustained neuroinflammatory response. Functionally, this pathway contributes to early synaptic dysfunction and neuronal injury, processes central to AD progression. Importantly, we identify a specific cysteine residue where the S-nitrosylation reaction on STING occurs. We show that a non-nitrosylatable mutant STING prevents the excessive inflammatory response, indicating that this cysteine residue is a potential therapeutic target for AD.

Conclusion: These findings define a disease-relevant mechanism of STING activation in AD and support redox modulation of innate immune signaling as a potential therapeutic approach for neurodegenerative diseases in general.

M119: Nonalcoholic Fatty Liver Disease, ApoE Genotype, and Neurocognitive Function in Middle-Aged Adults in the Dominican Republic: The HIGACOGNI Study

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Background: Nonalcoholic fatty liver disease (NAFLD) is a growing public health concern, and its association with cognitive decline is emerging. We investigated the relationship between NAFLD stage, cardiometabolic factors, Apolipoprotein E (ApoE) genotype, and neurocognitive performance in middle-aged adults in the Dominican Republic.

Methods: This multicenter cross-sectional study included 157 participants (40-65 years) classified into steatosis (n=51), steatohepatitis (n=50), and controls without NAFLD (n=56). We assessed cognitive function using a comprehensive neuropsychological battery and evaluated ApoE genotype, metabolic profiling, and cardiometabolic risk factors. Propensity score matching and multivariable logistic regression models adjusted for cardiometabolic variables were used to evaluate associations.

Results: NAFLD was present in 64.3% of participants. Orientation deficits differed significantly by NAFLD stage (26.8% in controls, 21.6% with steatosis, 44% with steatohepatitis; p=0.03). Fasting glucose was associated with an increased odds of abstract reasoning impairment (OR 1.15, p=0.05), but showed inverse associations with the language and orientation domains. Diabetes demonstrated a paradoxical protective association with orientation impairment (p=0.03). ApoE ε3-ε4 genotype was associated with reduced odds of orientation impairment (OR 0.03, p=0.03) but increased odds of construction deficits (OR 23.8, p=0.05). Hypertension was associated with lower odds of abstract reasoning impairment (p=0.05).

Conclusion: NAFLD stage alone was not independently associated with global cognitive impairment. Instead, cognitive performance was more strongly related to cardiometabolic variables and ApoE genotype, with domain-specific and heterogeneous effects. These findings suggest that metabolic dysfunction and genetic susceptibility may mediate cognitive vulnerability in NAFLD. Early identification and targeted management of cardiometabolic risk factors may represent an opportunity to mitigate cognitive decline in at-risk populations. The project advances understanding of the liver-brain axis and highlights the importance of personalized medicine approaches in preventing cognitive decline.

M120: Gut Microbiota Alterations in Alzheimer's Disease and Mild Cognitive Impaired Patients in the Dominican Republic: A Translational Study

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Background: Alzheimer's disease (AD) and mild cognitive impairment (MCI) are major contributors to dementia in Latin America, with the region expected to experience a significant increase in dementia prevalence by 2050. The gut-brain axis has emerged as a key area of research, with evidence suggesting that gut microbiota alterations may influence neurodegeneration. However, data on Hispanic populations are lacking, and the role of regional dietary and ethnic factors remains unclear.

Methods: This prospective-translational study characterized gut microbiota in 88 participants (≥60 years) with AD, MCI, and controls in the Dominican Republic. Clinical, cognitive, and functional assessments were performed using validated tools, including the Montreal Cognitive Assessment (MoCA), Neuropsychological Battery from the Taub Institute at Columbia University, and the Lawton and Brody Instrumental Activities of Daily Living Scale. Stool samples were analyzed using 16S rRNA gene sequencing. Bioinformatic processing used Quantitative Insights into Microbial Ecology Version 2 (QIIME2) and R. Alpha and beta diversity, taxonomy, and differential abundance were evaluated. Dietary influences were assessed using PERMANOVA.

Results: No significant differences in alpha diversity (Shannon index 4-5, Simpson index 0.94-0.99, $p>0.05$) or beta diversity ($p>0.05$) were observed between groups. Firmicutes (51.9%) and Bacteroidota (34.1%) dominated the microbiota. Higher Desulfobacterota abundance was found in MCI and AD (0.54% and 0.61%, respectively, vs. 0.34% in controls; $p<0.05$). The Firmicutes/Bacteroidota ratio was lower in men with MCI (1.09) compared to controls and AD (1.70). MCI and AD were associated with increased levels of Bilophila, Odoribacter, and Parabacteroides ($p<0.05$) and reduced levels of Mitsuokella and Eubacterium ruminantium. Dietary interactions, e.g., mango, lettuce, and carrot, influenced specific taxa ($p<0.05$).

Conclusion: This translational study pioneers gut microbiota characterization in AD and MCI in the Dominican Republic, identifying microbial alterations in cognitive impairment and highlighting regional dietary and ethnic factors. The findings support the gut-brain axis hypothesis and have implications for developing microbiota-targeted therapies and personalized medicine approaches for AD and MCI. Longitudinal and multi-omics studies are warranted to clarify causality and therapeutic potential. The study's results contribute to the growing evidence on the role of gut microbiota in neurodegenerative diseases and highlight the need for culturally tailored strategies for dementia prevention and management in Latin American populations.

M121*: Neurodegeneration Meets Infection: A Population-based Analysis of Sepsis Mortality in Alzheimer's Disease (CDC WONDER 1999–2024)

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Background: Alzheimer's disease (AD) is the leading cause of mortality in the U.S. Sepsis has been shown to increase mortality in patients with AD. This study examined the trends and disparities in United States (U.S.) adult mortality due to coexisting Alzheimer's disease (AD) and sepsis.

Methods: Data were extracted from the CDC WONDER for the period 1999–2024. Age-adjusted mortality rates (AAMRs) per 100,000 population and annual percentage changes (APCs) with 95% confidence intervals (CIs) were calculated. Temporal trends in mortality were assessed using joinpoint regression analysis and stratified by age, sex, ethnicity, and geographic characteristics, including state, rural–urban classification, and census region.

Results: A total of 46,667 deaths related to AD and sepsis were reported between 1999 and 2024, with higher AAMRs observed in females. Among females, mortality increased from 1999 to 2017 (APC +2.3%), followed by a marked decline from 2017 to 2024 (APC −6.5%). Similarly, in males, mortality rose from 1999 to 2018 (APC +2.1%) and subsequently declined sharply from 2018 to 2024 (APC −7.2%). Among Hispanics, mortality rates increased from 1999 to 2016 (APC +4.3%), followed by a significant decline from 2016 to 2024 (APC −6.2%). In contrast, among non-Hispanics, mortality rose more modestly from 1999 to 2017 (APC +2.1%), before declining sharply from 2017 to 2024 (APC −6.4%). African Americans exhibited considerably higher AAMRs compared with Whites. Among Black individuals, mortality declined from 2016 to 2024 (APC −4.1%), whereas Whites experienced a more pronounced decline over a shorter period from 2018 to 2024 (APC −8.2%).

Mortality rates were highest in the West and South, intermediate in the Midwest, and lowest in the Northeast, with varying temporal trends across regions. Mortality rates were consistently higher for non-metropolitan areas throughout the study period.

Conclusion: Our analysis of CDC WONDER data from 1999 to 2024 indicates an initial increase followed by a significant decline in mortality rates related to sepsis and AD after 2016–2018 in the U.S. Females consistently exhibited higher rates than males, with notable racial, ethnic, and geographic disparities, including higher mortality in non-metropolitan areas and in the West and South. These findings emphasize the importance of implementing targeted interventions to address the evolving burden of sepsis and AD mortality.

M122: Temporal Trends in respiratory failure contributing mortality among Parkinson's Disease decedents in the United States, 1999–2024: A CDC WONDER population based analysis

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Background: Respiratory failure is an established but poorly studied risk factor for death among individuals suffering from Parkinson's disease (PD). The present study evaluates the temporal trend of age-adjusted mortality rate (AAMR) for respiratory failure as a multiple cause of death (MCOD) among deceased patients with PD as the underlying cause of death (ICD-10: G20; J96) in adults aged ≥65 years in the United States.

Methods: Data on mortality was retrieved from the CDC WONDER database (1999-2024) using the ICD-10 coding system. Individuals with a PD (G20) diagnosis as the underlying cause of death and respiratory failure (J96) as one of the contributing causes of death were selected. Only individuals aged ≥65 years were included in the analysis. Joinpoint regression analysis was applied to estimate significant inflection points and annual percent change (APC).

Results: In total, AAMR had a biphasic acceleration profile (two joinpoints): initially, modest acceleration (APC +2.07, 1999 to 2012), followed by significant acceleration (APC +5.85*, 2012 to 2017) then a deceleration trend (APC +1.67, 2017 to 2024). In females, there was a stable increase throughout (APC +2.75*); however, in males, a steep increase was observed during the mid period (APC +7.48, 2014 to 2017). Black or African American descendants consistently showed an increased rate of increase (APC +4.01*); on the other hand, white decedents showed notable mid-acceleration (APC +6.69*, 2013 to 2017). Geographically, the South had the greatest acceleration rate (APC +7.20*, 2012 to 2017); while the Northeast and Midwest showed uniform increases (APC +3.12* and +3.64*, respectively).

Conclusion: There is an observed increase of deaths due to pulmonary function failure among Parkinson's disease patients aged above 65 years after 26 years of monitoring, showing a notable rise from 2012 to 2017. There are also observed inequalities along racial and geographic lines in terms of this health problem.

M123: Distinct Patterns of Mnemonic Similarity Task Performance in Alzheimer's Disease Variants: lvPPA and MCI/AD

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Background: The Mnemonic Similarity Task (MST), a sensitive measure of hippocampal pattern separation (Stark, Frontiers in Behavioral Neuroscience, 2023), detects memory deficits in Alzheimer's disease (AD) and amnestic mild cognitive impairment (MCI/AD). Although hippocampal atrophy is not characteristic of the logopenic variant of primary progressive aphasia (lvPPA), parietotemporal degeneration may disrupt consolidation of object representations, potentially producing similar impairments (der Linden, Journal of Neuroscience, 2017). We therefore assessed whether MST performance distinguishes these AD-related phenotypes from healthy aging.

Methods: MST data were collected from 115 participants (50 lvPPA, 27 MCI-AD, 38 healthy controls). Four metrics were derived: Lure Discrimination Index (LDI; ability to distinguish similar from repeated items), Corrected Recognition (REC; probability of responding "old" to repeated items minus "old" responses to novel items), Hit rate (EXC; accuracy for identifying repeated items as "old"), and Percent Correct (PC; overall accuracy). Group differences were assessed using one-way ANOVA (MST metrics as dependent variables; diagnosis as the grouping factor), followed by Games–Howell post hoc tests to account for unequal variances and multiple comparisons.

Results: All MST metrics showed significant group effects (LDI: $F = 8.55$, $p = 0.003$; REC: $F = 12.19$, $p < 0.001$; EXC: $F = 6.54$, $p < 0.001$; PC: $F = 17.24$, $p < 0.001$). Post hoc analyses revealed differences between healthy controls (HC) and both patient groups for LDI, REC, and PC (all $p < 0.05$). For EXC, a significant difference was observed only between HC and MCI/AD ($p = 0.002$). No differences were detected between lvPPA and MCI/AD. Exploratory analyses of EXC distributions suggested a symmetric profile in MCI/AD and a right-skewed distribution in lvPPA. Stratification by quantiles indicated that 73% of participants in the upper 60% of EXC scores were lvPPA (30/41), compared to 46% in the lower 40% (13/28; Fisher's exact test: $OR = 3.1$, $p = 0.04$).

Conclusion: These findings demonstrate that both lvPPA and MCI/AD are associated with comparable impairments in mnemonic discrimination (LDI), recognition (REC), and overall accuracy (PC) relative to healthy controls, suggesting shared disruptions in memory processes despite distinct clinical presentations. In contrast, deficits in hit rate, (old item recognition, EXC) were specific to the MCI/AD group, potentially reflecting greater involvement of hippocampal-dependent memory mechanisms. Exploratory analyses suggested that a subset of lvPPA showed preserved performance in this metric. This pattern, not captured by mean comparisons, highlights the potential value of distributional approaches.

M124-LB: Modeling Amyloid and Tau Biomarker Trajectories Across the 2024 NIA-AA Clinical Staging of Alzheimer's Disease in ADNI

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Background: The 2024 National Institute on Aging-Alzheimer's Association (NIA-AA) revised criteria define Alzheimer's disease (AD) biologically by Core 1 biomarker positivity, with 6 clinical stages for biomarker-positive

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individuals. Whether biomarker burden concords with this 6-stage clinical gradient is unknown; this analysis tests five amyloid and tau biomarkers against the gradient in Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods: 1,645 participants were staged (Stages 1–6: 301, 148, 482, 497, 163, 54). All five biomarkers correlated with clinical stage (all $P < .001$): four rose and CSF Aβ42 fell (expected direction, consistent with amyloid sequestration into plaques). Concordance strength ($|\rho|$), highest to lowest: plasma p-tau217 (0.53), tau PET MTL (0.52), CSF Aβ42 (0.44), amyloid PET (0.37), CSF p-tau181 (0.30). Adjacent-stage differences were non-uniform: Stages 1–2, none meaningful; Stages 2–3 and 3–4, all five meaningful; Stages 4–5, only tau PET MTL met the criterion ($d = 0.36$), with amyloid PET, CSF Aβ42, and plasma p-tau217 at $d = 0.18$–0.20; Stages 5–6, none meaningful.

Results: AD biomarkers partially concorded with the NIA-AA 2024 clinical stage gradient, but varied widely. The strongest (plasma p-tau217) and weakest (CSF p-tau181) trackers were both tau markers. Biomarker burden changed most steeply entering Stages 3 (MCI) and 4 (mild dementia); smaller change entering Stage 5 (moderate dementia); none at either end of the gradient.

Conclusion: Data were collected from each participant's last available visit. AD positivity defined by one of four Core 1 markers: amyloid positron emission tomography (PET) ≥ 25 Centiloid, cerebrospinal fluid (CSF) Aβ42 < 980 pg/mL, CSF phosphorylated tau-181 (p-tau181) > 24 pg/mL, or elevated plasma phosphorylated tau-217 (p-tau217). These four, plus tau PET medial temporal lobe (MTL), were the five biomarkers analyzed. Among AD-positive participants, stages followed the revised criteria: Stage 1, neither impairment nor decline; Stage 2, no impairment but documented longitudinal decline on the Clinical Dementia Rating Sum-of-Boxes (slope > 0.5/year), Mini-Mental State Examination (slope < −1/year), Everyday Cognition (mean > 1.5), or Neuropsychiatric Inventory (total ≥ 4); Stage 3, neuropsychological impairment (a cognitive composite ≥ 1.5 SD below normative, or two composites ≥ 1.0 SD below) or Functional Activities Questionnaire score 3–8; dementia Stages 4–6 by the Clinical Dementia Rating Global score. Spearman rank correlation (ρ) assessed each biomarker's concordance with clinical stage.

Cohen's d indexed standardized differences between adjacent stages; a difference was considered meaningful when $|d|$ reached 0.2 with a 95% CI excluding zero.

M125: Trends in Dementia-Associated Mortality Among Diabetes Mellitus Patients in the United States (1999–2023): A Retrospective Analysis

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Background: Diabetes Mellitus(DM) is a leading risk factor of cognitive decline and dementia through common inflammatory, metabolic, and vascular pathways. This study aims to examine Dementia-Associated Mortality trends among adults with Diabetes Mellitus.

Methods: The Multiple Cause-of-Death data using CDC WONDER were analyzed for DM and Dementia-related deaths from 1999 to 2023 in adults ≥25 years. The International Classification of Diseases, Tenth Revision(ICD-10 codes) were used to find deaths due to DM (E10–E14) as the underlying cause and Dementia (F01, F02, G30) as the Multiple Cause of Death (MCD). Age-adjusted mortality rates (AAMRs)/100,000 were determined and stratified by year, sex, race/ethnicity, and geographic region. Joinpoint regression was used to analyze trends in AAMRs using annual percent change (APC).

Results: Between 1999 and 2023, there were a total of 131,572 deaths among adults aged ≥25 years with DM and Dementia.

The overall AAMR increased from 1.76 per 100,000 in 1999 to 3.04 in 2003, with an average APC of 12.63 (95% CI: 4.23 to 21.71), decreased to 2.40 in 2007 (APC: -8.43, 95% CI: -17.54 to 1.68), then declined slowly to 2.10 in 2023 (APC: -0.47, 95% CI: -1.28 to 0.36). Mortality rates varied by sex; in 1999, rates were 1.70 for males and 1.76 for females, while in 2023, rates were 2.23 for males and 2.01 for females. Death rate varied according to morbidity. Type 1 DM and Dementia decreased significantly (AAPC: -7.42), Type 2 DM and Dementia increased significantly (AAPC: +4.60), no significant change in Parkinson's Disease and DM (AAPC: -0.75, $p>0.05$). Among racial groups in 2023, Black or African Americans had the highest AAMR (4.07), followed by American Indian or Alaska Natives (2.78), Whites (1.93), and Asians (1.86). The Midwest region had the highest average AAMR (2.63), followed by the South (2.48), West (2.43), and Northeast (1.99) regions.

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Conclusion: Our findings reported that the Dementia-associated mortality among adults with DM in the United States (1999-2023) showed dynamic trends, increasing sharply followed by a gradual decline. Blacks, males, and the Midwest region displayed the highest AAMR. These findings highlight the need for targeted interventions and preventive strategies to reduce the disease burden.

M126: Alzheimer's Disease–Related Mortality in the United States (1968-2023): A CDC WONDER Database Study

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Background: Alzheimer's disease (AD) is a leading cause of morbidity and mortality among older adults in the United States. We evaluated long-term national trends in AD-related mortality and demographic disparities.

Methods: We performed a population-based analysis using the CDC WONDER Multiple Cause of Death database from 1968–2023. Adults aged ≥65 years with AD listed as the underlying cause of death were included. Age-adjusted mortality rates (AAMRs)/100,000 population were calculated using the 2000 U.S. standard population. Temporal trends and annual percentage changes (APC) were estimated using Joinpoint regression and stratified by sex, race, age group, and geographic region.

Results: A total of 2,621,149 Alzheimer's disease-related deaths were recorded among U.S. adults aged 65 years and older. The age-adjusted mortality rate (AAMR) increased substantially from 2.75 (95% CI: 2.47–3.03) per 100,000 in 1968 to 216.95 (95% CI: 215.68–218.22) in 2023. Mortality increased sharply between 1975 and 1986 (APC: +30.29; 95% CI: 26.09–34.63), followed by continued but slower increases through 2008 (APC: +4.01; 95% CI: 3.44–4.58). A non-significant decline occurred between 2008 and 2013 (APC: −1.69; 95% CI: −4.05 to 0.73), followed by a transient significant increase from 2013 to 2016 (APC: +9.25; 95% CI: 1.95– 17.07). Rates stabilized from 2016 to 2021 (APC: +0.19; 95% CI: −1.75 to 2.17) and showed a non-significant decline from 2021 to 2023 (APC: −6.01; 95% CI: −11.88 to 0.26). Mortality was consistently higher among females than males in recent years, reaching 248.05 per 100,000 in females compared to 169.45 per 100,000 in males in 2023. AAMRs were higher among White individuals than Black individuals throughout the study period, with rates of 228.23 and 192.23 per 100,000, respectively, in 2023. Mortality increased markedly with advancing age, peaking among adults aged 85 years and older, who accounted for 1,618,815 (61.8%) of all deaths. Significant regional variation was observed, with the highest recent AAMRs in the West (258.82 per 100,000) and Midwest (232.48 per 100,000), while the Northeast demonstrated the lowest rates (135.80 per 100,000) in 2023.

Conclusion: AD mortality in the United States increased substantially over the past five decades, with persistent disparities by sex, race, age, and region.

M127: National Trends and Disparities in Mortality among U.S. Older Adults, with Coexisting Alzheimer's Disease and Hypertension, 1999-2023

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Background: Hypertension is the most prevalent modifiable cardiovascular risk factor globally, while Alzheimer's disease (AD) leads to dementia in the United States. Midlife hypertension accelerates cognitive decline and AD progression, yet

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the national mortality burden of their coexistence remains uncharacterized.

Methods: Using CDC WONDER Multiple Cause-of-Death data (1999–2023), deaths in adults ≥65 years with AD (ICD-10: G30) as the underlying cause and hypertension as a contributing cause were analyzed. AAMRs/100,000 were calculated using the 2000 U.S. standard population and stratified by sex, race/ethnicity, urbanization, census region, and place of death. Joinpoint regression identified temporal trends via APC and AAPC with 95% CIs.

Results: A total of 504,360 deaths were attributed to coexisting AD and hypertension between 1999 and 2023. The overall AAMR rose from 14.51 per 100,000 (95% CI: 14.10–14.91) in 1999 to 60.00 (95% CI: 59.40–60.70) in 2023, representing a more than fourfold increase. Four distinct trend phases were identified: a steep rise from 1999 to 2001 (APC: 37.57; p=0.046), a gradual increase through 2007 (APC: 6.67; p=0.012), a plateau through 2014 (APC: −1.14; p=0.429), and another significant surge through 2021 (APC: 6.52; p<0.001), followed by a non-significant decline through 2023 (APC: −5.38; p=0.341). Females accounted for 77.33% of total deaths, with consistently higher AAMRs than males across the entire study period (67.5 vs. 48.1 per 100,000 in 2023). Among racial groups, Non-Hispanic Black or African American individuals had the highest AAMR (57.14; 95% CI: 54.57–59.72), followed by Whites (45.11), Hispanics (39.69), American Indian/Alaska Natives (35.28), and Asians or Pacific Islanders (27.94). Non-metropolitan areas had higher overall AAMRs than metropolitan areas (48.74 vs. 41.45). Regionally, the West recorded the highest average AAMR (52.59), followed by the South (49.39), Midwest (46.47), and Northeast (28.11). At the state level, Mississippi had the highest AAMR (129.95), and Massachusetts had the lowest (21.54).

Conclusion: AD and hypertension-associated mortality quadrupled from 1999 to 2023, with disproportionate burden among women, Non-Hispanic Black individuals, rural residents, and Western and Southern populations. Targeted hypertension management, equitable dementia care, and prevention strategies are urgently needed for high-risk subgroups.

M128: Temporal Trends in Mortality Among U.S. Adults With Coexisting Dementia and Sepsis, 1999–2023

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Background: Dementia and sepsis represent two converging public health burdens with a well-established bidirectional relationship, with dementia predisposing to worse sepsis outcomes, and sepsis accelerating long-term cognitive decline. This study aims to examine temporal trends in dementia- and sepsis-associated mortality among U.S. adults from 1999 to 2023.

Methods: Mortality data were obtained from the CDC WONDER Multiple Cause-of-Death database for adults aged ≥25 years from 1999 to 2023. Dementia was identified using ICD-10 codes F01, F03, and G30; sepsis using codes A02.1, A20.7, A22.7, A26.7, A32.7, A40, A41, and B37.7. Age-adjusted mortality rates (AAMRs)/100,000 were calculated using the 2000 U.S. standard population and stratified by year, sex, race/ethnicity, age group, census region, and urban-rural classification. Temporal trends were assessed using Joinpoint regression, reporting annual percent change (APC) and average annual percent change (AAPC) with 95% confidence intervals.

Results: A total of 254,450 deaths were attributed to co-occurring dementia and sepsis between 1999 and 2023, with women accounting for 59.71% of deaths. The overall AAMR rose from 4.54 per 100,000 in 1999 to a peak in 2015, followed by a decline to 5.44 in 2023 (AAPC: 0.47; 95% CI: −0.63 to 1.58). Three distinct trend phases were identified: a sharp increase from 1999 to 2001 (APC: 12.56), a period of relative stabilization from 2001 to 2020 (APC: 0.05), and a declining phase from 2020 to 2023 (APC: −4.36). Males had consistently higher AAMRs than females throughout the study period (average AAMR: 6.26 vs. 5.89). Among racial groups, Non-Hispanic Black or African American individuals carried the greatest burden with an average AAMR of 10.30, nearly double that of Non-Hispanic Whites (5.76). Geographically, the South recorded the highest average AAMR (7.08), followed by the West (5.73), Northeast (5.42), and Midwest (5.31). Non-metropolitan areas had higher mortality than metropolitan areas (average AAMR: 6.32 vs. 6.08). The District of Columbia had the highest AAMR (10.23), while Arizona had the lowest (2.61).

Conclusion: Dementia- and sepsis-associated mortality in U.S. adults showed a modest overall increase from 1999 to 2023, with notable disparities across sex, race/ethnicity, geography, and age. These findings underscore the need for equity-centered prevention strategies, early detection programs, and integrated care models targeting high-risk populations.

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M129: National Trends and Disparities in Mortality Involving Chronic Obstructive Pulmonary Disease and Dementia in the United States, 1999-2023

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Background: Chronic obstructive pulmonary disease (COPD) and dementia are major public health concerns, and limited research has examined their combined impact on mortality. This study aims to describe the trends, demographic differences, and geographic variations of mortality involving both dementia and chronic obstructive pulmonary disease (COPD) in the United States from 1999 to 2023.

Methods: The CDC WONDER database was used to gather data on age-adjusted mortality rates (AAMRs) and crude mortality rates (CMRs) of dementia and COPD (ICD-10: J40–J47 and F01–F03, G30). The analysis was conducted separately for men and women, for different races and ethnicities, age groups, and place of death. Joinpoint regression was used to assess mortality trends and estimate the Annual Percent Change (APC).

Results: Between 1999 and 2023, there were 540,121 deaths in the U.S. linked to both conditions. The national age-adjusted mortality rate rose from 5.48 to 10.40 per 100,000 people. There were two main periods of growth: a sharp increase from 1999 to 2003 and a slower rise from 2003 to 2023. The crude mortality rate also went up, from 1.52 in 1999 to 1.91 in 2023, with an average of 1.63. Males had a higher average age-adjusted mortality rate than females, but the rate increased more for females over time. The highest mortality rates were in the South and in rural areas. Older adults had the highest crude mortality rates, while middle-aged adults had lower rates. The elderly population showed some improvement over time. Most deaths happened in nursing homes.

Racial differences persisted, with Non-Hispanic White individuals having the highest age-adjusted mortality rate.

Conclusion: Considerably higher mortality rates of dementia and COPD comorbidity have been observed. The findings highlight the growing need for proportionate chronic disease management and enhanced healthcare service delivery and access for socioeconomically disadvantaged populations.

M130: When Psychiatry Masks Neurodegeneration: Sex-Specific Diagnostic Pathways in Frontotemporal Dementia

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Background: Frontotemporal dementia (FTD), particularly the behavioral variant (bvFTD), frequently presents with psychiatric symptoms that overlap with primary psychiatric disorders, contributing to misdiagnosis and diagnostic delay.

Emerging evidence suggests that women may be disproportionately affected by psychiatric-first presentations, yet sex-specific diagnostic trajectories remain poorly characterized. This study aimed to quantify psychiatric-first presentations in women with FTD and identify clinical and objective factors associated with diagnostic reclassification.

Methods: A systematic review was conducted in accordance with PRISMA guidelines. PubMed, Embase, and Cochrane Library were searched from 1991 through January 2026. Studies including women with confirmed FTD and reporting psychiatric-first presentation, diagnostic delay, or diagnostic triggers were included. Extracted variables included initial psychiatric diagnoses, neuroimaging findings, genetic mutations, and clinical features associated with diagnostic reclassification.

Results: Thirty-seven studies comprising 915 women with FTD were included. Psychiatric-first presentation occurred in 6.78% of cases, yet was reported across 94.6% of studies, indicating a consistent diagnostic pathway. Initial diagnoses were most commonly psychosis or schizophrenia-spectrum (37.7%) and depressive disorders (28.3%), followed by bipolar or mania (11.3%). Diagnostic delay was frequently reported and was longest in psychotic-spectrum presentations (median 48 months), compared to mood disorders (36 months). Structural neuroimaging abnormalities were reported in 73.0% of studies, with frontotemporal involvement in 54.1%. Imaging contributed to diagnostic reclassification in 94.6% of studies, representing the most consistent trigger for diagnostic revision.

Genetic findings contributed in 54.1% of studies, most commonly involving C9orf72 mutations (40.7%), which were strongly associated with psychotic and manic presentations. Cognitive decline was reported as a diagnostic trigger in

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97.3% of studies, although standard screening tools were often insensitive in early disease.

Conclusion: Psychiatric-first presentation represents a reproducible and clinically significant diagnostic pathway in women with FTD, associated with identifiable patterns of misdiagnosis and prolonged delay. Structural neuroimaging emerges as the most reliable trigger for diagnostic reclassification. These findings support earlier integration of neurologic evaluation and biomarker-informed assessment in women with atypical, progressive, or treatment-resistant psychiatric symptoms, and provide important implications for improving diagnostic accuracy in neurodegenerative disease.

M131: Structural Abnormalities Of Perivascular Spaces By Brain Free Water Imaging In People with HIV

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Background: Perivascular spaces (PVS) are a neuroimaging marker of cerebral small vessel disease associated with vascular dysfunction and cognitive decline. PVS is also thought to play an important role in clearance of brain's metabolic byproducts. Conventional MRI sequences (T1, T2, FLAIR) are commonly used to visualize PVS but have limited sensitivity to smaller structures. Brain free-water imaging (BFWI), which enhances free water contrast, improves visualization of PVS. However, scalable methods integrating BFWI with conventional imaging for automated PVS quantification are limited. In this study, we developed a scalable pipeline for automated PVS segmentation leveraging BFWI alongside conventional MRI and evaluated differences in PVS burden and morphology between people with HIV (PWH) and people without HIV (PWoH).

Methods: Multi-contrast MRI data (BFWI, T1, FLAIR) from 217 participants (156 PWH virologically controlled, 61 socio-demographically similar PWoH; age 52.91 $\pm$ 9.08 vs. 52.50 $\pm$ 10.98; sex 32.7% vs. 42.6% female; race 59.6% vs. 63.9% black) were analyzed (Clinicaltrails.gov ID: NCT01875588). Candidate PVS regions were generated using a rule-based approach and refined with CSF segmentation to create pseudo-labels. These were used to train an nnU-Net model iteratively with quality control and retraining. Final segmentations were refined using feature-based filtering. PVS burden and morphology were quantified, and group differences and associations with clinical and neuropsychological measures were assessed, including interaction effects by HIV status.

Results: Our proposed approach enabled automated PVS segmentation across a multi-contrast cohort. While overall PVS burden did not differ between groups, differences emerged in the distribution of PVS metrics. Measures of variability (standard deviation and interquartile range) showed significant interactions between groups with atrophy, with group differences primarily observed in individuals with less atrophy. Median and mean PVS measures demonstrated similar context-dependent patterns. Additionally, relationships between PVS measures and clinical, cognitive, and inflammatory markers differed by HIV status, with significant interaction effects, although within-group associations were not consistently significant after covariate adjustment. These findings suggest altered perivascular organization and heterogeneity in HIV.

Conclusion: This framework enables scalable quantification of PVS and suggests that HIV is associated with altered perivascular organization and heterogeneity. Distributional, morphological, and relational PVS features may serve as markers of microvascular change and provide insight into perivascular processes related to fluid dynamics and waste clearance.

M132: Effect Modification by Demographics in the Relationship between Midlife Adiposity and Late-life Brain Amyloid: The Atherosclerosis Risk in Communities (ARIC) Study

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Background: Midlife obesity, defined as a body mass index (BMI) of at least 30, has been identified as a risk factor for increased late-life brain amyloid deposition visualized on florbetapir positron emission tomography (PET). In this Atherosclerosis Risk in Communities (ARIC) study, we assessed for effect modification by demographic characteristics on the association between midlife adiposity and late-life brain amyloid in a community-based population.

Methods: This study included all ARIC participants with at least one PET scan from late-life (visit 5; ages 67-95) who were dementia-free at time of scan (n=801). Adiposity measures (categorical BMI, sex-specific waist circumference (WC), sex-specific waist-to-hip ratio (WHR)) were measured at midlife (visit 1; ages 45-64) and defined using World

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Health Organization cutpoints. In logistic regressions linking adiposity measures with amyloid positivity (standardized uptake value ratio >1.2), we included interaction terms between adiposity measures and potential modifiers (sex; APOE ε4), adjusting for demographics and vascular and metabolic risk factors.

Results: In sex-stratified models, obese BMI (OR 2.77, 95% CI 1.30-5.91) and high risk WHR (OR 2.74, 95% CI 1.38-5.43) at midlife were associated with increased odds of amyloid positivity in males but not females. The interaction between high risk WHR and sex was significant (p-interaction=0.01), indicating the effect of high WHR on amyloid positivity differs by sex, but no statistically significant interaction was found for obese BMI. Obese BMI in midlife was also associated with increased odds of amyloid positivity in APOE ε4 non-carriers (OR 2.21, 95% CI 1.36-3.59) but not carriers (OR 0.93, 95% CI 0.38-1.22) (p-interaction=0.04). No significant associations were seen for WC.

Conclusion: The association between adiposity in midlife and amyloid positivity in late-life is stronger in males when adiposity is measured as high risk WHR, but not when defined by obese BMI. Additionally, obese BMI in midlife has a stronger effect on amyloid positivity in APOE ε4 non-carriers (vs carriers). These findings establish demographic subgroups in whom adiposity may be particularly important to the development of Alzheimer's disease-related pathology and demonstrate the importance of utilizing multiple clinical adiposity measures.

M133-LB: Association of Midlife Obesity and Adiposity Measures with Late-life Changes on Brain MRI: The Atherosclerosis Risk in Communities (ARIC) Study

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Background: Midlife obesity is known to be associated with late-life dementia risk, but mechanisms by which this may occur are not clear, and most studies have assessed limited measures of obesity. In this Atherosclerosis Risk in Communities (ARIC) Study, we investigated the association of midlife obesity with late-life cerebrovascular and neurodegenerative changes on brain magnetic resonance imaging (MRI).

Methods: In ARIC participants with late-life brain MRI scans, categorical adiposity measures (body mass index [BMI], sex-specific waist circumference [WC], sex-specific waist-to-hip ratio [WHR]) were measured at visit 1 (midlife; ages 45-64) and defined using standard clinical cutpoints. Brain MRI measures taken at visit 5 (late-life; ages 67-90) consisted of cerebrovascular (cerebral microbleeds [CMB], subcortical microbleeds [SCMB], lacunar infarcts, white matter hyperintensity [WMH] volume) and neurodegenerative (total brain volume [TBV], total cortical thickness [CTh], temporoparietal meta-ROI [TMR] volume, TMR CTh) outcomes. Multivariable (demographic and vascular/metabolic risk factor-adjusted) logistic regressions assessed the relationship between midlife adiposity measures and binary (yes/no) late-life outcomes (CMB, SCMB, lacunes); linear regressions evaluated continuous outcomes (WMH volume [log-transformed], TBV, total CTh, TMR volume, TMR CTh; all standardized z-scores).

Results: Among 1860 participants, compared to normal BMI, midlife obese BMI was associated with decreased late-life TBV (β1 -0.07, 95% CI -0.13, -0.01), TMR volume (β1 -0.14, 95% CI -0.22, -0.06), and TMR CTh (β1 -0.19, 95% CI -0.31, -0.07). Underweight BMI was associated with increased odds of lacunes (OR 3.78, 95% CI 1.01, 14.19). Substantially increased-risk WC was associated with increased odds of SCMB (OR 1.53, 95% CI 1.12, 2.09) and lacunes (OR 1.59, 95% CI 1.16, 2.17) as well as increased WMH volumes (β1 0.17, 95% CI 0.07, 0.28), decreased total CTh (β1 -0.12, 95% CI -0.23, -0.01), and decreased TMR volume (β1 -0.11, 95% CI -0.18, -0.04) and CTh (β1 -0.17, 95% CI -0.28, -0.07). High-risk WHR was independently associated with increased WMH volume (β1 0.15, 95% CI 0.06, 0.25) and decreased TMR volume (β1 -0.07, 95% CI -0.13, -0.00) and CTh (β1 -0.12, 95% CI -0.22, - 0.02).

Conclusion: Midlife obesity (measured as obese BMI, substantially increased-risk WC, or high-risk WHR) was associated with greater cerebrovascular burden and decreased brain volumes and CTh, particularly in regions usually affected by Alzheimer's disease, in late-life. These findings were independent of other risk factors and highlight midlife as a critical period influencing future risk of developing dementia-related brain pathology and emphasize the value of considering multiple measures of adiposity.

M134-LB: Functional Differences in Primary Human Microglia Across Alzheimer's Disease and SuperAgers

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Background: Alzheimer's disease (AD) is characterized by amyloid-β and phospho-tau accumulation, collectively termed Alzheimer's disease neuropathologic changes (ADNC), which drive neuroinflammation and neurodegeneration. Microglia, the resident immune cells of the central nervous system, play a central role in this process. While initially protective through amyloid clearance, microglia can transition into a chronic disease-associated state that contributes to ongoing

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neurodegeneration. SuperAgers, individuals aged 80 years and older with exceptional episodic memory performance, represent a unique model of cognitive resilience because they maintain preserved cognition despite the presence of ADNC. Preliminary findings from our group suggest that SuperAger microglia exhibit a distinct phenotype more closely resembling younger microglia, potentially reflecting resistance to age-and disease-associated dysfunction. However, the functional mechanisms underlying this resilience remain poorly understood.

Methods: Compared to controls, AD microglia demonstrated significantly reduced phagocytosis, evidenced by a lower proportion of bead-positive cells ($p<0.05$). Control microglia also exhibited significantly higher mean fluorescence intensity (MFI), a surrogate marker of phagocytic uptake per cell, compared to AD microglia ($p<0.05$). In contrast, SuperAger microglia appear to have increased phagocytic activity and higher MFI relative to both AD and control microglia, suggesting preserved or enhanced functional capacity.

Results: These findings demonstrate functional differences in phagocytosis among AD, control, and SuperAger microglia and support the hypothesis that preserved microglial function may contribute to cognitive resilience in aging.

Ongoing studies will further characterize intracellular cytokine-associated phenotypes and phagocytosis of amyloid β to better define mechanisms of neuroimmune resilience in SuperAgers. Identifying pathways that preserve microglial homeostasis may reveal novel therapeutic targets and biomarkers to mitigate neuroinflammation and slow progression of AD.

Conclusion: Primary human microglia were isolated and cultured from AD, cognitively normal control, and SuperAger post-mortem cases using a method established in our lab. After the cells were grown to confluence, they were lifted from the flask and made into a single cell suspension. Cells were incubated with 1μm fluorescent latex beads to quantify phagocytic activity. Flow samples were run on a A8 BDFACSDiscover flow cytometer and analyzed using FlowJo v11.

M135: How Much Brain Atrophy Is Too Much? It Depends on Who You Are – Normative Brain Volume Z-Scores Predict 5-Year Transition To Mild Cognitive Impairment/Alzheimer's Disease In Cognitively Normal Adults

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Background: Brain atrophy is routinely reported in clinical practice, yet clinicians lack practical thresholds linking imaging to real-world outcomes. Although the link between atrophy and cognitive decline in aging is well established, it remains unclear how much atrophy is normal for a given individual and when it signals elevated risk. We validated a sex-, age-, and estimated total intracranial volume (eTIV)-adjusted normative brain-volume model and tested whether its z-scores predict 5-year transition from cognitively normal (CN) to mild cognitive impairment (MCI) or Alzheimer disease (AD).

Methods: A generalized additive model for location, scale, and shape (GAMLSS) was trained on 21,977 healthy participants from 80 international cohorts (age 4–96 years; 56% female). In the Alzheimer's Disease Neuroimaging Initiative (ADNI), we identified baseline CN participants with linked structural MRI and longitudinal follow-up. The primary endpoint was 5-year CN-to-MCI/AD transition (n=558; age 73.1±6.7 years, 54.7% female, baseline Mini-Mental State Examination [MMSE] 29.0±1.4). Secondary endpoints were baseline cognition (MMSE, Montreal Cognitive Assessment, and ADNI Executive Function [ADNI-EF, ADNI-EF2] and Language [ADNI-LAN] composites) and 5-year Clinical Dementia Rating (CDR) global ≥0.5 progression (n=609). Cox proportional-hazards models and Kaplan-Meier curves by z-score tertile estimated risk; incremental z-score value beyond age and sex was tested.

Results: For the primary endpoint, 41/558 participants (7.3%) transitioned from CN to MCI/AD within 5 years. Each 1-standard-deviation (SD) decrease in baseline brain-volume z-score increased transition hazard by 36% (HR 1.362, 95% CI 1.034–1.795, p=0.028). Kaplan-Meier curves by tertile separated significantly (log-rank χ^2=8.01, p=0.018), with 5-year event rates of 10.2%, 8.6%, and 3.2% from lowest to highest tertile. For the secondary CDR endpoint, 130/609 (21.3%) progressed; each 1-SD decrease raised hazard by 24% (HR 1.239, 95% CI 1.056–1.453, p=0.0085). Lower z-scores also tracked worse baseline cognition (MMSE β=0.150, p=0.0019; ADNI-LAN β=0.058, p=0.028; ADNI-EF β=0.062, p=0.022; ADNI-EF2 β=0.068, p=0.0057) and added incremental predictive value beyond age and sex (ΔR^2=0.0117, 0.0056, 0.0056, 0.0089; all p≤0.028).

Conclusion: Whether a given degree of atrophy is concerning depends on who the person is. By referencing each brain against age-, sex-, and eTIV-matched norms, individualized z-scores separate what is expected for an individual's demographics and head size from genuinely pathological deviation. In cognitively normal adults, these z-scores flag elevated 5-year risk of diagnostic transition and CDR progression and track concurrent cognitive burden – so once individual characteristics are taken into account, the same absolute brain volume can be reassuring in one person and a red flag in another.

M136: Investigating Speech Behaviors in Mild Cognitive Impairment Using Human-Computer Interaction: A Comparative Study of Speech Tasks in Chinese Context

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Background: This study aimed to investigate speech behavior of patients with mild cognitive impairment (MCI) through human-computer interaction (HCI) technology, and to compare the screening effectiveness of different speech tasks in the Chinese environment

Methods: A total of 17 participants were enrolled from Beijing Tiantan Hospital. MCI was defined by neuropsychologically confirmed impairment in at least one cognitive domain, accompanied by a concurrent complaint of subjective cognitive decline. Speech data were elicited via human-computer interaction using picture description tasks ("Cookie Theft" and "Cat Rescue") and verbal fluency tasks. Audio recordings were processed using OpenAI's Whisper for automated speech recognition and subsequent semantic feature extraction. The most statistically significant variables were selected and integrated into a Linear Discriminant Analysis (LDA) classifier, which was validated using leave-one-out cross-validation (LOOCV).

Results: In the picture description tasks, the MCI group exhibited a significantly decreased proportion of nouns rate(0.24 ± 0.05 vs. 0.27 ± 0.04) and an increased word frequency level (0.29 ± 0.06 vs. 0.24 ± 0.03) compared to the HC group ($p < 0.05$). Additionally, the "Cat Rescue" task performed better than in "Cookie Theft" task. The MCI group produced fewer correct words(12.60 ± 2.07 vs. 19.00 ± 3.58), a reduced number of semantic clusters (6.20 ± 1.10 vs. 10.50 ± 1.87), and a decreased number of switches (NOS) (5.20 ± 1.10 vs. 9.50 ± 1.87) in the verbal fluency task.

Conclusion: Speech-based interaction technology is a viable and novel approach for the assessment of MCI. Both picture description tasks and verbal fluency tasks demonstrate robust discriminative power in its adjunctive diagnosis.

M138: Diagnostic Performance of CSF Protein 14-3-3 For Prion Disease In The Modern Era

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Background: CSF protein 14-3-3 has been incorporated into diagnostic criteria for Creutzfeldt–Jakob disease for decades. Advances in MRI and RT-QuIC enable detection of prion disease at earlier symptomatic stages, when neuronal injury biomarkers such as 14-3-3 may be below detection. To improve sensitivity, the US National Prion Disease Pathology Surveillance Center (NPDPSC) lowered the positivity threshold from >4,000 to >2,000 AU/mL. The impact of this change on diagnostic performance remains uncertain.

Methods: We analyzed CSF biomarker data from 629 participants evaluated at academic centers (Washington University in St. Louis and Mayo Clinic; 2016–2025) for prion disease (definite, n=9; probable, n=37), non-prion rapidly progressive dementia (RPD; n=147), and typically progressive dementia (n=436). Biomarkers were measured using standardized NPDPSC protocols, including RT-QuIC assays and ELISA measures of 14-3-3 and total tau. Brain MRIs were assessed for prion-associated changes. Diagnostic performance was summarized using sensitivity, specificity, accuracy, and likelihood ratios. Survival associations were assessed using Cox models.

Results: At the revised threshold (≥2,000 AU/mL), 14-3-3 showed high sensitivity (100%) but very low specificity (≤6.1%) and low accuracy (≤28.5%), with positive likelihood ratios approximating 1. Elevated 14-3-3 levels were common in non-prion RPD (93.9%) and typically progressive dementias (95.6%). In contrast, total tau (≥1,150 pg/mL), RT-QuIC, and MRI demonstrated high diagnostic accuracy. Higher 14-3-3 concentrations were modestly associated with shorter survival (Hazard Ratio=1.02 per 1000 AU/mL), comparable to total tau but weaker than RT-QuIC and MRI. Using the prior cutoff (≥4,000 AU/mL), 14-3-3 showed limited specificity and accuracy; an optimized threshold (9,800 AU/mL) improved accuracy but remained inferior to other markers.

Conclusion: Despite its historically outsized role, CSF protein 14-3-3 provides minimal incremental clinical value for prion disease diagnosis compared with RT-QuIC, total tau, and MRI.

M139: Creutzfeldt–Jakob Disease Initially Misdiagnosed as Alzheimer's Disease: Lessons from Reported Cases

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Background: Overlap in clinical presentation, imaging findings, and laboratory profiles can challenge differentiation of patients with rapidly progressive Alzheimer's disease (AD) and Creutzfeldt–Jakob disease (CJD), contributing to delays in diagnosis and impacting management. This study aimed to characterize clinical features, neuroimaging, and biomarkers to improve identification of patients with probable or definite CJD who were initially misdiagnosed as having rapidly progressive AD

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Methods: We systematically searched PubMed and Embase using MeSH and EMTREE synonyms for CJD and AD. We included patients with CJD who were initially diagnosed with AD. Clinical features and results from biomarker, imaging, and CJD-specific tests were extracted. In addition to the systematic review, two AD mimic cases were identified from prospectively evaluated patients with RPD at Mayo Clinic in Florida

Results: Of 210 articles, 8 articles (10 cases) were included through systematic review, supplemented by two additional Mayo Clinic cases. Four cases were female (40%). Age at symptomatic onset ranged from 52 to 82 years.

Median survival from symptom onset was 18.5 months (range ~5 months–6 years). Patients were initially diagnosed with amnestic (n=4) or variant presentations of AD (n=6), supported by CSF AD biomarkers in 3 cases (low Aβ42, n=3; elevated ptau181, n=3) and findings on FDG-PET in 6/6 cases. Subsequent testing established prion disease as the cause of impairment, with prominent MRI cortical ribboning or restricted diffusion present in 7/10 cases (80%), RT-QuIC for prions detected in 7/8 cases (including 2 on repeat testing). CSF total tau >1200 pg/mL in 6/9 cases, and t-tau/ptau181 ratio >14 in 4/6 cases. Both Mayo Clinic cases from a prospective cohort presented with atypical AD-like phenotypes (amnestic–aphasic and logopenic PPA), no early prion red flags, and DWI-negative MRI. CSF showed mixed AD biomarker profiles but markedly elevated t-tau and 14-3-3 in both cases, with RT-QuIC negative in one and positive in the other. Final diagnoses were definite and probable CJD, with delays to clinical suspicion of 1.3 and 4.6 months, respectively.

Conclusion: CJD may be misdiagnosed as AD, particularly in the presence of AD-consistent CSF biomarkers, AD-like FDG-PET patterns, and absence of MRI findings typical of CJD. These findings support routine use of prion-specific biomarkers (e.g., RT-QuIC) in patients with RPD.

M140: Neurodegenerative Disease Mechanisms: Predicting Antioxidant Therapeutic Potential in Alzheimer's and Parkinson's Diseases

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Background: The proteostasis network comprises molecular chaperones, the ubiquitin-proteasome system, and the autophagy-lysosomal system, which collectively regulate protein synthesis, folding, and degradation to maintain cellular function. However, oxidative stress caused by rising levels of reactive oxygen or nitrogen species can disrupt this network, leading to neurodegeneration. Specifically, oxidative stress amplifies aging processes by oxidizing proteins and lipids and forming cross-linked aggregates that are resistant to degradation. This study aims to evaluate whether oxidative stress represents a sufficient therapeutic target or requires integration with proteostatic and neuroinflammatory pathways.

Methods: Following the PRISMA 2020 guidelines, a bibliometric analysis was conducted in the Web of Science database and analyzed with Bibliometrix in RStudio and Excel. Keywords included "neuroinflammation", "proteostasis & aggregation", and "antioxidant therapies". Out of 69,548 articles across searches, the 100 most relevant and highly cited papers were included.

Results: The most-cited authors included Dr. Dennis J. Selkoe and Christopher M. Dobson, who together accounted for over 30,000 citations. The most-cited articles typically originated from well-known institutions, possibly due to reputation advantages and greater resource abundance. Interestingly, there was a spike in publications in 2017, potentially suggesting a shift from single-pathway explanations to systemic disruptions in neurodegeneration. Keyword co-occurrence visualizations revealed three distinct clusters. One represented how oxidative stress is intertwined with apoptosis, mitochondrial pathways, and post-translational modifications, while the others represented neuroinflammation and proteostasis pathways. This suggests that neurodegeneration arises from a convergent network of factors, with oxidative stress occupying a central yet intermediary position within it.

Alone, antioxidant-based therapies have had limited effectiveness in mitigating the progression or prevention of neurodegenerative diseases. While oxidative stress plays a significant role in the pathophysiology of these diseases, it may not be sufficient as a singular therapeutic target.

Conclusion: Our findings underscore the complexity of neurodegenerative disease mechanisms and the need for multifaceted approaches. Across reviewed studies, it is mentioned how neuroinflammation and proteostasis dysregulation are not just peripheral symptoms but proponents of the neurodegenerative process in both Alzheimer's and Parkinson's. Future research should assess the effectiveness of antioxidant therapies beyond their effects on neurodegeneration and develop therapies with high mitochondrial affinity and improved blood-brain barrier penetration. Additionally, identifying early biomarkers is essential for timely intervention before irreversible neuronal loss. The interplay between other treatment targets and oxidative stress needs to be researched in order to combine these novel therapies with existing treatments for Alzheimer's and Parkinson's disease that ultimately account for multiple disease pathways.

M141: Associations between Midlife Alcohol Use and Dementia: The Atherosclerosis Risk in Communities Study

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Background: Excessive alcohol use is responsible for approximately 3.3 million deaths globally each year, with an estimated 178,000 deaths in the US. As individuals age, their susceptibility to brain aging increases, and chronic alcohol exposure can worsen this cognitive decline. However, current research remains inconsistent, with studies reporting conflicting findings regarding whether midlife alcohol consumption is associated with dementia risk. We hypothesized that heavy alcohol consumption in midlife would be associated with an increased risk of dementia, with an elevated but lower risk for light/moderate consumption for developing dementia, each vs no alcohol use.

Methods: Participants aged 45-64 years from 4 U.-S. communities were recruited into the Atherosclerosis Risk in Communities (ARIC) study in 1987-1989 and were followed with a combination of in-person visits and ongoing surveillance through 2022. Self-reported midlife alcohol consumption at baseline was categorized into 5 levels based on daily use): non-drinkers (0 drinks/day), light drinkers (women: ≤1 drink, men: ≤2 drinks), moderate drinkers (women: 2-3 drinks, men: 3-4 drinks), heavy drinkers (women: ≥4 drinks, men: ≥5 drinks), and former drinkers (do not drink but report past drinking). Dementia was defined using a combination of in-person and telephone-based neuropsychological testing, informant interviews, and hospitalization dementia codes. Cox proportional hazards models were used to test the associations between midlife alcohol consumption and risk of dementia and mortality, separately, adjusted for demographic, vascular, and lifestyle factors, including smoking.

Results: 15,340 individuals (mean age 54.2y; 55.2% female) were included, of whom 8,710 (57%) were non-drinkers, 2,923 (19%) former drinkers, 2,812 (18%) light drinkers, 719 (5%) moderate drinkers, and 176 (1%) heavy drinkers. Overall, risk of dementia was increased only in former drinkers when compared to non-drinkers [HR 1.09, 95% CI, 1.00-1.19)], while no association was observed with light [HR 0.94 (0.86-1.04)], moderate [HR 1.08 (0.92-1.28)] or heavy [HR 0.83 (0.55-1.26)] drinking. In contrast, all midlife alcohol use categories were associated with increased mortality, most notable in heavy drinkers [HR for death 1.42 (1.20-1.68)], followed by former [1.21 (1.15-1.27)], and moderate [1.20 (1.10-1.32)] drinkers, when compared to non-drinkers.

Conclusion: Former drinkers have an increased risk of developing dementia, compared to non-drinkers, while other groups of drinkers show no increased risk. Moreover, mortality risk was highest among heavy drinkers. Further studies are needed to show whether this unexpected lack of association with dementia in heavy drinkers is due to death prior to the potential development of dementia in this group.

M142: Practical Factors Influencing the Use of Confirmatory Blood-Based Biomarkers in Alzheimer's Care

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Background: Advances in blood-based biomarkers (BBMs) are reshaping the diagnostic pathway of Alzheimer's disease. Despite increasing adoption, site-level factors influencing real-world implementation at centers using BBMs for confirming amyloid pathology without follow-up PET or CSF remain poorly understood. This study examined workflow, resource, and organizational factors that facilitate or hinder BBM use for confirmation of amyloid pathology.

Methods: Using a multi-site approach, we conducted 13 semi-structured interviews with physicians and allied healthcare providers across three clinical sites (a rural single-physician practice, an urban academic medical center, and a multi-physician private practice) that had experience using BBMs in routine clinical practice for confirming amyloid pathology (without follow-up PET or CSF testing). Two focus groups were held. Transcripts were analyzed using the Consolidated Framework for Implementation Research (CFIR) to identify operational barriers, drivers of adoption, communication processes, and workflow adaptations relevant to confirmatory BBM use.

Results: CFIR-aligned themes were consistent across sites. Intervention characteristics (relative advantage, adaptability) favored confirmatory BBMs over CSF or PET because they required minimal infrastructure, fit existing clinic flow, and were met with strong patient receptivity. Outer-setting drivers differed by clinic type: some practices adopted confirmatory BBMs to offset limited access to PET or procedural services, while others used them to improve efficiency within complex academic systems. Inner-setting barriers centered on resources and implementation climate; insurance variability, assistance-program navigation, and potential out-of-pocket costs were universal constraints that added staff workload. Process needs focused on execution: participants emphasized the need for clear follow-up protocols, structured counseling for interpretation, and reliable laboratory integration to

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reduce logistical errors. Despite these challenges, strong organizational receptivity and perceived implementation success underscored the value of confirmatory BBMs in supporting timely evaluation and patient experience.

Conclusion: Confirmatory BBMs were viewed as clinically acceptable and operationally adaptable across diverse practice settings. Tailored workflows, effective financial navigation, and clear communication processes emerged as key factors for successful adoption. Despite differing resources and contexts, sites reported shared implementation needs, suggesting these learnings may be transferable to clinics newly incorporating confirmatory BBMs. These findings highlight both common and site-specific influences on BBM implementation and the importance of continued evaluation to guide their evidence-aligned use in clinical practice.

M143: From First Visit to Disclosure: How Confirmatory Blood-Based Biomarkers Are Changing Diagnostic Timing in Alzheimer's Disease

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Background: The rapid availability of blood-based biomarkers (BBMs) for Alzheimer's disease (AD) has outpaced descriptions of how they are integrated into diagnostic workflows. Uncertainty remains regarding their placement in the diagnostic sequence, including use as triage tools that require CSF or amyloid PET for positive results, use as confirmatory tools without follow-up testing, and the timing from cognitive assessment to biomarker testing.

Methods: This prospective, multi-site observational study included adults aged ≥55 years evaluated for cognitive decline at three diverse neurology practices (a rural single-physician practice, an urban academic medical center, and a multi-physician private practice), all with experience using BBMs in practice for triage and/or confirmatory use. Data were extracted from electronic medical records and summarized descriptively. Outcomes included time from cognitive health assessment (CHA) to BBM and PET testing, test-to-result (clinician) and test-to-disclosure (patient) intervals, use of BBMs with or without PET or CSF follow-up, and diagnostic outcomes.

Results: Among 185 patients, 166 (89.7%) underwent BBM testing, of whom 56.7% had an abnormal result. For most patients (89.2%), BBMs were used to confirm amyloid pathology. Amyloid PET was performed in 17 patients (9.2%), with 70.6% positivity; of whom 12 also received BBM testing. Median (Q1, Q3) time from CHA to BBM testing was 0 days (0, 11) versus 50 days for PET (12, 97). Test-to-result intervals were 13 days for BBM (9, 15) and 7.5 days for PET (2, 9.5), with patient disclosure occurring at 19 days for BBM (11, 29) and 18 days for PET (9, 36). Across the cohort, 46.5% received a final diagnosis of AD (final diagnoses reflected clinician judgment informed by the full evaluation).

Conclusion: Across three U.S. neurology practices, BBMs were performed at or near the initial neurology evaluation, whereas PET typically occurred weeks later. Despite similar processing intervals once tests were completed, earlier ordering of BBMs resulted in a shorter overall interval from first visit to the availability of biomarker information compared with PET. BBMs served as the primary test for most patients, with PET used less frequently. Together, these real-world patterns suggest that BBMs may support efficient diagnostic workflows by facilitating timely access to biomarker evidence of amyloid pathology.

M144: Noninvasive, Brain-Specific Inhibition of BMP Signaling For The Prevention Of Tauopathy

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Background: Tauopathies, including Alzheimer's disease and related neurodegenerative disorders, are defined by progressive accumulation of neuronal hyperphosphorylated tau (pTau) and lack effective therapies. Aging is the strongest shared risk factor across these disorders, implicating age-regulated pathways as therapeutic targets. Our laboratory has shown that bone morphogenetic protein (BMP) signaling increases in the aging brain of both mice and humans and drives tau phosphorylation. Experimental BMP pathway activation increases pTau, whereas inhibition with the endogenous antagonist, noggin, reduces pTau in multiple patient-derived iPSC lines and mouse models of tauopathy. In vivo, both stereotactic viral injection and genetic overexpression of noggin reduce pTau burden and neuronal death and improve hippocampus-dependent cognition in P301S and APOE4

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knock-in mouse models. While this establishes BMP inhibition as a compelling therapeutic strategy, stereotactic viral delivery and germline genetic overexpression lack translational feasibility. This limitation is particularly relevant as advances in predictive biomarkers increasingly enable identification of individuals in preclinical stages of Alzheimer's disease, highlighting the need for noninvasive approaches suitable for prevention.

Methods: To enable brain-wide, noninvasive modulation of BMP signaling in vivo, we employed a systemic gene delivery approach using the BBB-penetrant AAV-PHP.eB capsid to drive astrocyte-restricted expression in the CNS of noggin under a shortened GFAP promoter (GfaABC1D). Because noggin is a secreted BMP antagonist, astrocyte-derived expression enables paracrine inhibition of neuronal BMP receptor signaling. Adult P301S mice received intravenous AAV administration at 8–10 weeks of age and were aged for 6 months prior to assessment of cognitive and pathological outcomes. Downstream readouts include biochemical and immunohistochemical measures of canonical BMP signaling (pSMAD1/5/8), tau phosphorylation (AT8), and spatial memory performance (Barnes maze). Ongoing studies address multiple tauopathy-relevant models (P301S, APOE4 KI, 5xFAD) and intervention points throughout disease stages.

Results: A single systemic AAV tail vein injection achieves efficient, brain-wide transduction with astrocyte-restricted expression that is maintained at >3 months post-injection. Noggin is secreted from astrocytes and detected in the media of treated astrocyte cultures, and reduces canonical BMP signaling in vivo, as reflected by decreased pSMAD1/5/8 IHC. In 5xFAD mice, preliminary stereotactic hippocampal delivery of noggin reduces pTau (AT8) and shows a trend toward improved spatial memory on the Barnes maze. Systemic administrations have been completed in P301S, APOE4, and 5xFAD cohorts, and analyses of tau pathology and behavioral outcomes are ongoing.

Conclusion: These findings support noninvasive, brain-specific BMP inhibition as a translational strategy for early intervention in tauopathy by targeting an upstream driver of tau pathology.

M145*: Heterotypic Co-Assembly of α-Synuclein and Tau Drives Pathology in Synucleinopathies: Implications for Therapeutic Targeting

Presenting Author(s): *Satkarjeet Gill, MBBS, Tomball, TX*

Background: Pathological aggregation of α-synuclein (α-Syn) is a defining hallmark of Parkinson's disease (PD); however, increasing evidence implicates tau co-pathology as a critical contributor to disease progression and neurodegeneration. The mechanistic interplay between αSyn and tau remains incompletely understood, particularly regarding how tau pathology evolves over time and influences α-Syn-mediated toxicity.

Methods: We utilized the human wild-type α-synuclein overexpressing mouse model (hSyn) to examine the temporal progression of behavioral impairments and associated pathological changes. Motor and cognitive performances were longitudinally assessed, and brain tissues were analyzed for α-Syn and tau aggregation, hyperphosphorylation, and synaptic integrity. To determine the therapeutic potential of tau targeted immunotherapy, hSyn mice received TTCM2-a conformation-selective IgG2b antibody that recognizes discontinuous β-strand-rich epitopes within the tau microtubule-binding region, exhibiting high specificity for aggregation-prone tau oligomers.

Results: Motor deficits emerged around 9 months of age and progressively worsened, followed by cognitive impairments at later stages. These behavioral declines correlated with marked accumulation of α-Syn aggregates and hyperphosphorylated tau species in the cortex, midbrain, and hippocampus. Treatment with TTCM2 significantly reduced pathogenic tau oligomers, attenuated α-Syn aggregation, and restored synaptic marker expression. These molecular improvements were accompanied by robust recovery of motor coordination and cognitive performance.

Conclusion: Our findings identify tau oligomers as key amplifiers of α-synuclein-induced neurotoxicity, driving both pathological propagation and behavioral dysfunction. Selective targeting of tau oligomers with TTCM2 effectively disrupted the synergistic tau-α-Syn interplay, resulting in substantial functional and molecular rescue. These results support tau oligomer-selective immunotherapy as a promising disease-modifying strategy for PD and related synucleinopathies characterized by tau co-pathology.

M146-LB: Pediatric Acute-onset Neuropsychiatric Syndrome in Children With Autism Spectrum Disorder

Presenting Author(s): *Brian Gomringer, BS, Portland, OR*

Background: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) are characterized by abrupt onset of obsessive-compulsive behaviors, tics, food restriction, and other neuropsychiatric symptoms following infection or other trigger. PANS/PANDAS has overlapping clinical features with autism spectrum disorder (ASD) that may complicate diagnosis. Limited data exist regarding the co-occurrence of ASD and PANS and whether ASD modifies clinical presentation or treatment response.

Methods: ASD was present in 26.7% of patients with PANS. Patients with ASD demonstrated a later median age of PANS symptom onset (10 vs 7 years, p=0.013) and greater symptom burden (3 vs 2, p=0.005) compared to those without ASD. Median time to diagnosis was longer in the ASD group (22.5 vs 12 months), though not statistically significant (p=0.21). Among patients receiving IVIG, ASD was associated with non-significantly higher likelihood of treatment response (OR 3.37, p=0.11).

Results: In a review of PANS patients at a single institution, ASD was common and associated with later age of onset and greater number of symptoms. Physicians should consider PANS in children with autism and acute neuropsychiatric symptoms, as affected children may be severely impacted.

Conclusion: We conducted a retrospective review of patients ages 2–18 years diagnosed with PANS at Oregon Health & Science University pediatric neurology clinic between January

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2015, and October 2025. Patients with alternative primary neurologic or psychiatric diagnoses explaining acute symptom onset were excluded. Demographics, clinical features, and treatment data were abstracted. Independent variables were presence/absence of ASD. Dependent variables were number of symptoms, age of onset, time to diagnosis, and response to intravenous immunoglobulin (IVIG).

M148: Novel platform to study gut-microbiome dysbiosis in Brain Injury Associated Fatigue and Altered Cognition

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Background: Traumatic brain injury (TBI) affects millions and costs the U.S. $76.5 billion annually in lost productivity and healthcare expenses, a critical concern in brain economics. A subset of TBI patients develop Brain Injury Associated Fatigue and Altered Cognition (BIAFAC), a syndrome characterized by persistent fatigue, cognitive difficulties, and reduced quality of life. Our previous work showed that BIAFAC patients exhibit gut dysbiosis relative to healthy controls. This raises a clinically important question: can correcting dysbiosis improve

BIAFAC symptoms? Research on gut dysbiosis and microbiome-directed interventions has been limited by the lack of platforms that reproduce key features of the physiological gut microenvironment. Here, we propose a human-relevant model of the gut microenvironment to study BIAFAC-related dysbiosis and test potential treatments. This will help identify the most promising approaches to move forward into clinical trials, to determine whether correcting the microbiome improves symptoms in patients with BIAFAC.

Methods: We refined an anaerobic air–liquid interface transwell co-culture using human intestinal epithelial cell lines (Caco-2 and HT-29) to reproduce the environment colonized by gastrointestinal bacteria. Fecal samples from healthy volunteers and BIAFAC patients were analyzed using metagenomic and metatranscriptomic methods to map functional bacterial dysbiosis. Isolates of the identified bacteria successfully colonized the mature cultures, enabling 'omics analyses that are otherwise not feasible to perform directly in human subjects. Using the established model, we also tested therapeutics to restore eubiosis.

Results: The transwell cultures captured key molecular effects of the tested dysbiotic microbiota, including signatures of epithelial stress and barrier disruption. Interventions with generic prebiotics also altered intestinal epithelial function, shifting gene expression toward reduced stress signaling and recovery of barrier and metabolic programs.

Conclusion: This anaerobic transwell platform provides a physiologically relevant way to model BIAFAC-associated gut dysbiosis and a practical approach to screen microbiome-directed interventions. By enabling controlled testing of candidate therapeutics, this system will also support translational clinical trials that evaluate whether improving the gut microbiome reduces fatigue and cognitive symptoms in patients with BIAFAC, with potential benefits for millions of affected individuals.

M149: Planetary Health Diet Adherence and Domain-Specific Cognitive Function in Older Adults: Evidence from NHANES 2003–2010

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Background: The EAT–Lancet Commission's 'Planetary Health Diet' was designed to optimize human health and environmental sustainability. However, empirical evidence linking adherence to this pattern-quantified by the Planetary Health Diet Index (PHDI)-to domain-specific cognitive performance in the U.S. population remains sparse. We examined the association between PHDI adherence and performance across multiple cognitive domains, including episodic memory, semantic fluency, and executive function/processing speed, among older U.S. adults

Methods: This cross-sectional study utilized data from 2,636 participants aged ≥60 years from the National Health and Nutrition Examination Survey (2003–2010). Dietary intake was assessed via two 24-hour recalls to calculate the PHDI (range: 0–140), representing adherence to the EAT-Lancet reference diet. Cognitive outcomes included the CERAD Word Learning and Recall test, Animal Fluency, and the Digit Symbol Substitution Test (DSST).

Multivariable linear regression with survey weights was used to estimate β coefficients and standard errors, adjusting for sociodemographic characteristics, lifestyle factors, and cardiometabolic conditions (BMI, diabetes, hypertension, and dyslipidemia).

Results: Higher PHDI adherence was significantly associated with superior cognitive performance, characterized by a distinct domain-specific sensitivity. In the fully adjusted model, each 10-point higher PHDI was associated with higher scores on the DSST ($\beta = 0.9746$; $p = 0.0012$) and Animal Fluency ($\beta = 0.3811$; $p = 0.0003$). Strong dose–response patterns were observed for both executive function (p-trend = 0.0008) and semantic fluency (p-trend = 0.0001). While the PHDI was positively associated with CERAD immediate recall (Trials 1-3: $\beta = 0.1767$; $p = 0.0410$), associations with delayed recall were not statistically significant. Component-level analyses identified

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non-starchy vegetables, nuts, and unsaturated oils as the primary drivers of these associations.

Conclusion: Greater adherence to a planetary health-aligned dietary pattern was associated with significantly better executive function and processing speed in older Americans. These findings support the "co-benefit" of sustainable diets for brain health, suggesting that sustainability-aligned dietary frameworks may serve as an effective strategy for preserving cognitive resilience in an aging population.

M150: Case Report of Wernicke's Encephalopathy Mimicking Autoimmune and Psychiatric Encephalopathy in a Non-Alcoholic Female

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Background: Wernicke's encephalopathy (WE) is an acute neuropsychiatric emergency due to thiamine deficiency classically associated with alcoholism but increasingly recognized in non-alcoholic patients with malnutrition, malignancy, or psychiatric illness. Psychiatric symptoms (apathy, visual distortions, cognitive slowing) can mimic primary psychiatric or autoimmune encephalopathies, delaying diagnosis and treatment.

Methods: Case report of a 61-year-old non-alcoholic woman with major depressive disorder, recent hospitalization, and poor oral intake who presented with confusion, ophthalmoplegia, dysarthria, and malnutrition. Evaluation included neurologic exam, EEG, whole-blood thiamine level, and brain MRI. Empiric high-dose IV thiamine was administered and clinical course followed with repeat assessments and outpatient follow-up. Relevant literature reviewed to contextualize diagnosis and management.

Results: Admission findings: ophthalmoplegia, nystagmus, dysarthria, disorientation; EEG with diffuse theta–delta slowing; whole-blood thiamine markedly decreased; MRI with bilateral symmetric mammillary body enhancement consistent with metabolic/ Wernicke changes. Treatment: IV thiamine 500 mg TID × 3 days → 250 mg daily × 5 days → transitioned to 100 mg PO daily maintenance; short course corticosteroids given due to overlapping autoimmune concern. Within one week, marked improvement in ocular findings, speech, orientation, and affect; discharged with nutritional rehabilitation and outpatient neuropsychiatric follow-up. Imaging: MRI demonstrating bilateral mammillary body enhancement (pages 4–5). Relevant labs: markedly low whole-blood thiamine on admission; folate corrected during hospitalization. Medications: venlafaxine XR, buspirone; pembrolizumab for RCC. Suggested disclosure: no external funding or conflicts. Clinical takeaways: always suspect thiamine deficiency in patients with acute cognitive/ocular signs and poor intake; initiate empiric IV thiamine promptly.

Conclusion: This case underscores the need to consider WE in psychiatric patients with acute neurobehavioral changes and poor intake even without alcohol history. Prompt recognition and empiric high-dose thiamine can reverse deficits and prevent irreversible cognitive decline. Clinicians should screen for nutritional risk factors, obtain MRI and thiamine levels when indicated, and not delay treatment awaiting labs.

M151: Cognition More Closely Linked to Liver Dysfunction than Age in Cirrhosis and Liver Transplant: A Pilot Study of Cirrhosis-Associated Cognitive Impairment

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Background: Cirrhosis affects over 4 million people in the United States. Over 12,000 liver transplants were performed in the United States in 2025, 14% of which were performed on elderly patients. Cirrhosis-associated cognitive impairment (CACI), cognitive impairment distinct from hepatic encephalopathy and dementia, is seen both pre-and post-transplant, and is associated with poor outcomes. Older age is a risk factor for cognitive impairment. However, the relationship between CACI, transplant, and age is unclear. To address these questions, we implemented a pilot study of CACI at our tertiary medical center.

Methods: We conducted a pilot study (IRB#AAAV1000) at the Center for Liver Disease and Transplantation at Columbia University Irving Medical Center – NewYork Presbyterian Hospital. We enrolled 36 adult subjects between 3/11/2025 - 3/19/2026 who were listed for liver transplant or who received a liver transplant ≥ 6 months prior to enrollment, without clinical hepatic encephalopathy. Cognition was assessed using Millisecond Inquisit software with a cognitive battery including the following measures: Paired Associates Learning (immediate and delayed recall), Digit Symbol Substitution Test (executive functioning), Tower of London (visuospatial reasoning), N-back task (attention), and letter fluency (language). Correlations between variables (Spearman's rho) and multivariate regressions were performed using Stata v18.

Results: 11 subjects completed the battery. Subject demographics are: 45% female; 91% Caucasian/9% Asian; 9% Hispanic/Latino; average age 60 years; average 15 years of education; 36% pre-transplant. Liver disease etiologies are: 36% cholestatic, 18% infectious, 28% alcoholic, 9% autoimmune, 9% cryptogenic. Average Model for End-Stage Liver Disease (MELD) score, a measure of severity of liver disease, was 10 (range 6-14). Receipt of a transplant was positively associated with cognition in all domains studied (rho = 0.26 – 0.77).

MELD scores were negatively associated with cognition across all domains, meaning more severe liver disease is associated with worse cognition (rho = -0.20 – -0.60). Older age showed negative correlations with delayed recall, executive function and attention (rho = -0.4 - -0.8), but positive correlations with immediate recall, language, and visuospatial reasoning (rho = 0.6 - 0.8). Etiology of cirrhosis showed no clear pattern of correlations (rho = -0.77 - 0.26). These relationships remained despite controlling for education.

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Conclusion: In this pilot study, cognition was more closely associated with liver disease status than age. Although age is independently associated with cognitive impairment, that relationship is less clear in the context of liver disease. Further research is needed to elucidate the relationship between age, liver function, and cognition.

M152*: Plasma p-tau217/Aβ42 Ratio vs. Amyloid PET for Detecting Autopsy-Confirmed Amyloid Plaques

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Background: In the era of anti-amyloid (Aβ) therapies for Alzheimer's disease (AD), accurate detection of Aβ-pathology in the brain is critical to guide treatment initiation decisions. Plasma biomarkers, including the FDA-cleared Lumipulse p-tau217/Aβ42 ratio, offer a minimally invasive approach to indirectly assess Aβ-pathology in the brain; however, their diagnostic accuracy relative to Aβ-PET remains uncertain when benchmarked against neuropathology.

Methods: Here, we performed a head-to-head comparison of ante-mortem plasma p-tau217/Aβ42 measurements (Lumipulse G1200 system) and [18F]florbetaben PET visual reads (FBB-VR) for assessing Aβ-pathology based on post-mortem CERAD assessment in 73 participants (mean±SD age: 81.2±10.5 years) from the Phase III end-of-life study of [18F]florbetaben (NCT01020838). Aβ-pathology was present ("moderate/frequent" Aβ plaques) in 46 and absent ("none/sparse" Aβ plaques) in 27 cases. The median time from last biomarker assessment to death was 8 months (0.2-32). Plasma p-tau217/Aβ42 was classified using the FDA-cleared two-tier cut-points approach resulting in the three classifications: negative/intermediate/positive.

Results: Relative to autopsy-confirmed Aβ-positive cases, FBB-VR correctly identified 45/46 (98%) Aβ-positive cases (true positives), with one false-negative classification. Similarly, plasma p-tau217/Aβ42 was positive in 45/46 (98%) Aβ-positive cases, with one intermediate result and no false-negative classifications. Among autopsy-confirmed Aβ-negative cases, FBB-VR correctly classified 23/27 (85%) individuals (true negatives), with four false-positive classifications. In contrast, plasma p-tau217/Aβ42 correctly classified only 1/27 (4%) Aβ-negative cases as negative (true negative), while 18/27 (67%) were classified as positive (false positives) and 8/27 (30%) as intermediate. Individuals with no plaques (CERAD "no"), FBB-VR correctly identified 16/17 (94%) cases, whereas plasma p-tau217/Aβ42 correctly identified only 1/17 (6%) cases as negative, with 9/17 (53%) misclassified as positive and left 7/17 (41%) as intermediate. Discordant cases (plasma-positive/CERAD-"no") exhibited early Braak stages (8/9 Braak 0-II) and were mostly "non-demented" or "non-AD" (6/9).

Conclusion: Overall, these findings demonstrate that the plasma p tau217/Aβ42 ratio, while comparable to FBB-VR for detecting Aβ positive cases, showed frequent false-positive or intermediate classifications in Aβ-negative individuals. In contrast, FBB-VR provides substantially higher accuracy for the detection of Aβ plaques. Plasma p-tau217/Aβ42 and FBB-PET should therefore not be considered universally interchangeable.

M154: Imaging Changes Prior to Symptom Onset in Semantic Variant Primary Progressive Aphasia: A Case Report

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Background: In patients with semantic variant primary progressive aphasia (svPPA), characteristic asymmetric severe bilateral anterior temporal atrophy is often already present when functional impairment prompts initial presentation for evaluation. Acquisition of brain imaging during the preclinical stages is rare, and the timing of symptom onset has only been speculated. Here, we present the case of a patient with svPPA who presented with a five-year history of behavior changes and longitudinal progression of atrophy on annual surveillance brain imaging which began prior to his symptom onset.

Methods: This single case report will review the disease course and imaging of a 79-year-old man with history of mantle cell lymphoma (MCL) who was evaluated for behavior changes. History was gathered via semi-structured interview with family members. The evaluation included structured neurocognitive testing and review of the serial brain imaging, including MRI brain and surveillance CT head and neck scans obtained over the preceding seven years for MCL monitoring.

Results: The patient developed symptoms five years prior to presentation. Family first noticed slowed processing speed, followed by personality changes including agitation, anxiety, disinhibition, and obsessive behaviors. He developed difficulties in semantic knowledge, unable to recognize the names of items that he had commonly used (e.g. "TENS unit"). Other aspects of language such as grammar, comprehension and fluency of speech remained intact. On cognitive testing, he scored 13 out of 15 on the Boston Naming Test, had decreased verbal fluency of 18, scored 3 out of 10 on word list recall, and scored 5 out of 25 on logical memory. MMSE was 27. On imaging, atrophy of the anterior right temporal lobe was present from the time of initial imaging. Images obtained 5 years before presentation showed interval development of atrophy on the left anterior temporal lobe coinciding with patient's symptom onset. Subsequent images demonstrated the progression of bilateral anterior temporal atrophy (right greater than left).

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Conclusion: This case highlights how imaging changes predate clinical symptoms in svPPA. This suggests that bilateral involvement of the anterior temporal lobes may result in onset of clinical manifestations in svPPA.

M155: Progressive Changes in Innate Immune Responses, Post-Synaptic Dynamics, and Secretory Pathways in Virally Suppressed People with HIV

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Background: Despite effective antiretroviral therapy, people with HIV (PWH) can experience progressive neurological changes. Molecular mechanisms driving these changes remain poorly understood. We performed an exploratory proteomic analysis of cerebrospinal fluid (CSF) from PWH and people without HIV (PWoH) to explore these processes.

Methods: We analyzed 44 CSF samples from a well-characterized cohort (ClinicalTrials.gov ID: NCT01875588), including 14 virally suppressed PWH and 8 PWoH, each with two samples collected ~4 years apart with balanced demographics and age (PWH: 58.6 ± 5.1; PWoH: 57.2 ± 3.8). Protein abundance was quantified using the Olink Explore HT platform, measuring >5400 proteins via Proximity Extension Assay. Longitudinal and cross-sectional differences were assessed using linear mixed-effects models, followed by Gene Set Enrichment Analysis (Benjamini-Hochberg correction; exploratory FDR ≤ 0.25) and leading-edge analysis.

Results: Cross-sectionally, immune pathways, specifically leukocyte and lymphocyte activation, were enriched in PWH compared to PWoH, suggesting immune dysregulation despite viral suppression. MZB1 ($\beta = 2.02$; 95% CI (1.24, 2.81)), a chaperone involved in antibody secretion, was elevated in PWH, consistent with B cell dysregulation. Although amyloid beta was not measured, response to amyloid beta pathways increased longitudinally in PWH, as did CD36 ($\beta = 0.64$; 95% CI (0.30, 0.97)), a microglial scavenger receptor, and MMP-12 ($\beta = 0.60$; 95% CI (0.10, 1.11)), a matrix metalloproteinase involved in neuronal injury and inflammation; these trends potentially reflect increased microglial activity. Postsynaptic endocytosis and neurotransmitter receptor internalization pathways decreased longitudinally in PWH, as did NUMB ($\beta = -1.69$; 95% CI (-3.02, -0.37)), a clathrin adaptor involved in postsynaptic receptor endocytosis, potentially reflecting altered synaptic activity. Regulation of secretion decreased at a greater rate in PWH than PWoH, and cytokine activity was enriched among leading-edge proteins. IL-13 ($\beta = -3.01$; 95% CI (-5.40, -0.62)), secreted by resident CNS cells to promote neuroprotection, decreased over time in PWH and increased in PWoH, suggesting reduced neuroprotective effects and broader immune dysregulation in PWH.

Conclusion: Our findings suggest progressive, multifactorial involvement of immune dysregulation, altered microglial and postsynaptic activity, and decreased regulation of secretion in the CNS, despite viral suppression in PWH. Limitations include small sample size, which may reduce statistical power, and inherent limitations in applying enrichment analysis to proteomic data. Future directions include increasing the sample size, pairing CSF with plasma, and correlating findings with neuroimaging and neuropsychological assessments.

M156: Predicting Amyloid PET Positivity with Cognitive Impairment Phenotyping

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Background: Disease-modifying therapies (DMTs) for Alzheimer's disease (AD), including anti-amyloid monoclonal antibodies, require confirmation of brain amyloid pathology before initiation. Current confirmation relies on amyloid PET imaging or cerebrospinal fluid analysis – procedures that are costly, invasive, and unevenly available, creating bottlenecks in DMT eligibility workflows. Plasma biomarkers are emerging as scalable alternatives, but their positive predictive value depends critically on the patient's cognitive status and phenotype. Cognitive impairment in candidate patients is itself heterogeneous, with amnestic and dysexecutive phenotypes often reflecting different underlying pathologies that may or may not be associated with amyloid. We therefore examined whether a brief, digitally administered cognitive assessment could differentiate amyloid-PET-positive from amyloid-PET-negative patients, supporting efficient triage to confirmatory biomarker testing.

Methods: We studied 149 memory clinic patients (45.3% female; 91.1% White). All participants completed the Linus Health Digital Assessment of Cognition (DAC), a 7-minute, digitally administered, and automatically scored protocol comprising a 6-word Philadelphia (repeatable) Verbal Learning Test [P(r)VLT; verbal episodic memory], the Backward Digit Span Test (BDST; working memory), and 'animal'

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semantic fluency. Amyloid status was determined using PET/CT, with severity expressed via Brain Amyloid Plaque Load (BAPL) scores (1–3).

Results: On the P(r)VLT, groups did not differ on immediate free recall. After a delay, the amyloid-positive group showed a significant decline on P(r)VLT delayed free recall ($p< 0.001$), with no improvement on P(r)VLT delayed recognition ($p< 0.001$) and increased false-positive responses to prototypic recognition foils ($p< 0.001$). Both groups were similarly impaired on BDST and 'animal' fluency. Regression (dependent variable: BAPL) showed that delayed free recall combined with prototypic recognition responding accounted for ~25% of variance beyond age, education, and sex; 'animal' fluency and BDST models were non-significant.

Conclusion: In this cohort of patients evaluated for anti-amyloid therapy, amyloid PET positivity was characterized by a classic amnestic phenotype – rapid forgetting, impaired delayed recognition, and prototypic-foil intrusions – whereas executive and semantic-access tasks did not differ by amyloid status. Clinically, this brief, scalable digital cognitive assessment can serve as an evidence-based triage step that (1) raises the pre-test probability and positive predictive value of downstream plasma biomarkers, (2) reduces unnecessary PET and lumbar-puncture referrals, (3) accelerates identification of DMT-eligible patients, and (4) flags amyloid-negative patients with dysexecutive profiles who warrant evaluation for non-AD pathologies. Together, these findings support the integration of digital cognitive phenotyping into precision dementia care pathways.

M157*: Genetically Determined Resilience to Alzheimer's Disease Is Independent of Genetic Risk and Gated by Cardiovascular Comorbidity

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Background: PReS captures brain-protective biology in AD independent of PRS. We tested whether it predicts MCI-to-AD conversion and whether CVD suppresses this resilience. Some MCI patients progress rapidly to Alzheimer's while others remain stable or decline slowly, despite equivalent pathology and genetic risk. Polygenic risk does not explain this variation. A genomic score indexing active protective biology rather than attenuated risk has not been developed, leaving unaddressed both the biology of resilience and the conditions under which it is expressed or blocked.

Methods: PReS was developed in ADNI (N=808) using GWAS on a brain resilience signature from 247 MRI phenotypes, identifying variants linked to preserved brain structure despite pathology rather than reduced risk. Nucleotide Transformer (500M, multi-species) initialized a cross-attention model over 3,343 variants. The score was validated in Weill Cornell Medicine (WCM, N=391) and replicated in All of Us (AoU, N=26,762 WGS) AD risk cohorts. Cox models tested PReS for MCI-to-AD and cognitively normal (CN)-to-MCI conversion, stratified by APOE4, ancestry, seven cardiovascular conditions, and medications.

Results: PReS was orthogonal to DeepPRS ($r=0.041$, $p=0.28$), supporting an independent biological dimension rather than reduced genetic risk. Three variant clusters mapped to distinct pathways: synaptic integrity (cortical volume), cell adhesion (cortical thickness), and DNA repair (white matter and vascular architecture). In ADNI, higher PReS predicted delayed MCI-to-AD conversion (HR=0.872, $p=1.2\times10^{-5}$), with a 5.9-year gain in dementia-free survival (median 9.1 vs 3.2 years). Resilience preserved white matter (WMH mediation 19.2%, $p<0.001$) and reduced CSF phosphorylated tau (p-tau 181) ($\beta=-0.957$, $p=0.010$) without affecting amyloid.

Findings were consistent in WCM (HR=0.577, N=27 MCI). In AoU (3,152 AD, 3,331 MCI, 20,279 controls; median follow-up 9.7 years), PReS predicted CN-to-MCI (HR=0.961, $p=0.035$) and MCI-to-AD (HR=0.936, $p=0.0004$), with pooled HR=0.917 ($p=0.005$). CVD modulated resilience in a three-tier pattern. Treated metabolic conditions amplified PReS effects, with hyperlipidemia (HR=0.907, $p<0.001$) and hypertension (HR=0.940, $p<0.001$), consistent with statin synergy (HR=0.898 vs 0.988 in non-users). Structural vascular damage attenuated protection to non-significance, including stroke (HR=0.964, $p=0.207$) and diabetes (HR=0.980, $p=0.303$), while chronic ischemic burden from atrial fibrillation and coronary artery disease reduced but preserved significant protection (HR=0.927 and 0.936, both $p<0.01$).

Conclusion: Across 27,961 individuals including 7,682 MCI/AD cases, PReS is orthogonal to AD risk, delays conversion by 5.9 years, and is APOE4-independent. CVD accelerates conversion by blocking resilience, while statins pharmacologically restore it. This reframes AD as a trajectory shaped by genomic resilience and cardiovascular biology, positioning cardiovascular management as a genomically informed prevention strategy.

M158: Adiposity-Related Structural Brain Changes Across Midlife and Late-Life in the Dallas Heart Study

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Background: Midlife obesity is consistently associated with increased Alzheimer's disease (AD) risk in late-life, potentially through neuroinflammation in brain regions affected early in AD pathogenesis, including the hippocampus, entorhinal cortex, precuneus, and hypothalamus. However, how body adiposity affects brain structures throughout adulthood remains unclear. Therefore, we investigated associations between adiposity measures and brain macro- and microstructure across midlife and late-life in non-demented individuals.

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Methods: This study included 419 non-demented Dallas Heart Study participants who underwent 3T brain MRI. Adiposity measures included body mass index (BMI), visceral adipose tissue (VAT) volume, and hepatic proton density fat fraction (PDFFhepatic). Brain macrostructure based on normalized volumes was derived from T1-weighted MRI. For microstructural analyses, diffusion tensor imaging (fractional anisotropy [FA], mean diffusivity [MD]) and neurite orientation dispersion and density index (intracellular volume fraction [ICVF], isotropic volume fraction [ISOVF], orientation dispersion index [ODI]) parametric maps were computed. Cross-sectional regressions between adiposity and MRI measures were conducted within midlife (40-60 years, n=175) and late-life (>60 years, n=244) cohorts. Regression analyses were also performed between BMI measured 20 years prior and current MRI metrics. Models were adjusted for age, sex, race/ethnicity, APOE genotype, and cardiovascular history.

Results: Cross-sectional analyses revealed associations between higher midlife BMI and higher precuneus FA, lower entorhinal ODI, and lower hypothalamic anterior-inferior FA and tubular-superior ISOVF. For late-life participants, BMI was positively associated with hippocampal FA and ICVF and negatively with MD. Higher late-life BMI was also associated with increased precuneus ICVF and decreased entorhinal volume, ICVF, and ODI, alongside widespread hypothalamic microstructural alterations. Notably, the posterior hypothalamus showed higher ISOVF and ODI and lower FA and ICVF as BMI increased. Additionally, VAT, but not PDFFhepatic, mirrored the patterns observed in BMI across both cohorts. Finally, BMI from 20 years prior predicted a similar pattern of structural brain changes only in late-life participants.

Conclusion: Higher body adiposity was associated with hypothalamic and entorhinal structural alterations consistent with neurodegeneration, particularly in late-life. However, the hippocampus and precuneus demonstrated an opposing pattern, potentially reflecting anatomical or functional differences that highlight the importance of region-specific analyses. Furthermore, while higher midlife BMI predicted these structural changes in late-life, early adulthood BMI was not associated with midlife brain structure, supporting an age-dependent relationship. Our results also suggest that visceral, rather than hepatic, fat best reflects adiposity-related brain changes. Overall, body adiposity is associated with complex microstructural alterations in AD-vulnerable brain regions that precede macrostructural changes and may represent early neurodegenerative markers.

M159*: Wearable-Derived Physical Activity Trajectories and Incident Neurological Disease: A Prospective Cohort Study of 22,518 Adults from the NIH All of Us Research Program

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Background: Physical inactivity is a modifiable risk factor for neurological disease, yet prior evidence relies predominantly on self-reported activity at a single time point. Large-scale studies linking objectively measured, wearable-derived physical activity trajectories to incident neurological outcomes in diverse populations are lacking. We sought to identify distinct physical activity trajectory groups from 12-month wearable-derived step data and evaluate their association with incident neurological disease in a diverse real-world cohort.

Methods: We conducted a prospective cohort study using the NIH All of Us Research Program Controlled Tier (CDR 2024Q3R9). Adults aged 40 years or older with 180 or more valid Fitbit recording days within the first 12 months and no prevalent neurological disease were included (N=22,517). Monthly mean step counts were classified via K-means clustering into Low PA (n=8,956; 39.8%), Moderate PA (n=9,865; 43.8%), and High PA (n=3,697; 16.4%) trajectory groups. The primary outcome was a composite of incident dementia, Parkinson disease, and stroke or transient ischemic attack from electronic health record ICD-10 codes. Associations were estimated using sequential Cox proportional hazards models: unadjusted; adjusted for age, sex, and body mass index; and fully adjusted for demographics, cardiometabolic, and psychiatric comorbidities. Sensitivity analyses included multiple imputation, competing risk models, sex-stratified analyses, and E-value estimation.

Results: Over 114,596 person-years of follow-up, 343 composite neurological events occurred. Incidence rates demonstrated a stepwise gradient: Low PA 3.81, Moderate PA 2.71, and High PA 2.12 per 1,000 person-years (log-rank p=0.0004). In unadjusted analysis, Low PA was associated with significantly higher risk versus High PA (HR 1.80; 95% CI 1.28-2.54; p=0.0007). After adjustment for age, sex, and body mass index, this persisted (HR 1.90; 95% CI 1.16-3.12; p=0.011). In the fully adjusted model, the effect was attenuated (HR 1.53; 95% CI 0.93-2.53; p=0.094), suggesting partial mediation through cardiometabolic pathways. Depression emerged as the strongest independent predictor across all models (HR 2.47; 95% CI 1.78-3.44). E-value analysis for Low PA was 2.44, indicating substantial unmeasured confounding would be required to nullify the observed effect.

Results were consistent across competing risk, sex-stratified, and early-event exclusion sensitivity analyses.

Conclusion: In this large, diverse wearable-based cohort, sustained low physical activity demonstrated a significant dose-response gradient with incident neurological disease. Attenuation after full adjustment highlights cardiometabolic comorbidities as potential mediating pathways. These findings support wearable-derived activity monitoring for neurological risk stratification and underscore the interplay between physical inactivity, comorbidity burden, and brain health.

M160: Efficacy and Safety of Anti-Amyloid Monoclonal Antibodies in Early Alzheimer Disease: A Systematic Review of Randomized Controlled Trials

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Background: Beta-amyloid plaque accumulation is a defining pathological feature of Alzheimer disease and a primary target of disease-modifying therapy. Recent regulatory approvals of lecanemab and donanemab have intensified debate regarding the magnitude, clinical meaningfulness, and safety of anti-amyloid monoclonal antibody therapy, underscoring the need for a comprehensive, class-level evidence synthesis.

Methods: PubMed, Embase, and Cochrane Central Register of Controlled Trials were systematically searched from inception through January 2026 in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. Eligible studies were randomized placebo-controlled trials evaluating aducanumab, lecanemab, donanemab, solanezumab or bapineuzumab in adults with mild cognitive impairment due to Alzheimer disease or mild Alzheimer disease dementia with biomarker confirmation. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the Cochrane ROB 2. Primary efficacy outcomes were change from baseline in the Clinical Dementia Rating Sum of Boxes and Alzheimer Disease Assessment Scale Cognitive Subscale. Safety outcomes included incidence of amyloid-related imaging abnormalities. Given heterogeneity in enrolled populations, endpoint definitions, and assessment timepoints, findings were synthesized qualitatively with contextual reference to established thresholds of clinical meaningfulness.

Results: Ten randomized controlled trials enrolling 9,842 participants met inclusion criteria. Lecanemab and donanemab demonstrated statistically significant and consistent slowing of cognitive and functional decline in biomarker-confirmed early Alzheimer disease, with the largest and most clinically meaningful effects observed in prespecified subgroups with lower baseline tau burden. Solanezumab failed to meet primary cognitive endpoints across all three pivotal phase III trials. Aducanumab produced discordant results across two identically designed phase III trials, complicating class-level interpretation. Amyloid-related imaging abnormalities were the predominant safety signal across all active agents, with higher incidence observed at greater drug exposure and in apolipoprotein E epsilon 4 carriers. The majority of amyloid-related imaging abnormality events were radiographically detected and asymptomatic; however, symptomatic events occurred in a clinically relevant minority of treated participants. Functional, quality-of-life, and caregiver-centered outcomes were inconsistently reported across trials, substantially limiting assessment of real-world patient benefit.

Conclusion: Randomized evidence supports a disease-modifying effect of lecanemab and donanemab in narrowly defined biomarker-confirmed early Alzheimer disease populations, while earlier-generation agents failed to demonstrate convincing clinical benefit. Treatment benefit must be carefully weighed against the elevated risk of amyloid-related imaging abnormalities, necessitating apolipoprotein E epsilon 4 genotype-informed patient selection and structured neuroimaging surveillance protocols in clinical practice. Standardization of functional and patient-centered outcome measures across future trials is essential to fully define the real-world value of anti-amyloid therapy.

M161: Telehealth Music Therapy for Neuropsychiatric Symptoms in Amnestic Mild Cognitive Impairment: Exploring Behavioral and Brain Network Changes

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Background: Music therapy has demonstrated promise for enhancing neuropsychiatric symptoms, quality of life and cognitive function in individuals with dementia. In this study, we explored the impact of individualized Telehealth Music Therapy (TMT) on autobiographical memory and neuropsychiatric symptoms in individuals with amnestic mild cognitive impairment (MCI) due to Alzheimer's disease (AD). Additionally, we investigated the potential effects of TMT on functional brain network organization using functional MRI (fMRI).

Methods: Participants and caregivers completed 16 TMT sessions (2×30 minutes/week for 8 weeks) delivered by a certified music therapist. Pre- and post-intervention neuropsychiatric assessments and MRI evaluated behavioral and connectivity changes. During fMRI, participants listened to autobiographically salient, scrambled, and non-preferred song segments (1 minute each; 9 total, in pseudorandomized order). Autobiographical memory was analyzed using the autobiographical memory test (AMT) along with (1) examining correlations with MoCA-MIS scores and (2) qualitative thematic analysis.

Results: Following 16 TMT, 14 participants (3 females; age: 74.86±3.74 years; years-since-diagnosis: 1.42±1.15; MoCA: pre=23.93±4.14; post=24.07±4.57) demonstrated a reduction in anxiety (STAI: pre= 74.64±21.05; post=69.43±21.59) and depressive symptoms (GDS: pre=3.64±3.67; post=3.43±4.03), alongside a slight increase in nostalgia (pre=27.43±6.43; post=27.93±9.65). Caregivers reported a modest improvement in participants' quality of life (QoL-AD proxy: pre=38.36±6.80; post=38.71± 5.09), while participants' self-reported quality of life showed a slight decline (QoL-AD patient: pre= 39.93±6.41; post=38.86±6.53). All clinical changes were non-significant. Participant performance on the 3-digit recall task (part of the AMT set, in which participants recall three digits alongside a cue word and report a specific memory related to that word) showed a non-significant improvement in working memory accuracy (AMT: pre=0.424±0.07; post= 0.506±0.06). When participants were stratified by baseline accuracy, the lower-performing half (n=7)

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demonstrated a significant improvement (pre=0.25±0.11, post=0.42±0.18, p=.037). Spearman's rank-order correlation showed a significant positive association with pre-post MoCA-MIS scores across all participants (rs(26)=.51, p=.008). Further analysis of changes in the specificity and thematic patterns of participant memory responses is ongoing. Brain network segregation (modularity) (n=8) during music listening significantly increased (t=3.57, p=.009), while network integration (global efficiency) (n=8) showed a trending decrease (t=-2.07, p =.078).

Conclusion: These findings suggest that TMT may improve neuropsychiatric symptoms and modulate brain network dynamics in MCI and mild AD. Increased network segregation during music listening may reflect more efficient processing and a possible shift from typical MCI network patterns, potentially linked to autobiographical music engagement. Larger studies are needed to confirm these preliminary findings and inform future music-based interventions for dementia.

M162: Carboxy-terminal Blockade of Sortilin Binding Enhances Progranulin Gene Therapy, A Potential Treatment for Frontotemporal Dementia

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Background: Heterozygous loss of function mutations in the progranulin gene cause frontotemporal dementia, a devastating neurodegenerative disease characterized by deficits in social behavior, language comprehension and motor function. Of the more than seventy progranulin mutations associated with frontotemporal dementia, nearly all are loss of function. For this reason, progranulin replacement is a conceptually straightforward therapeutic strategy for frontotemporal dementia caused by progranulin mutations. Progranulin gene therapies have already entered clinical trials, along with drugs that reduce interactions between progranulin and sortilin, a transmembrane receptor responsible for progranulin uptake and intracellular degradation. In this study we investigated whether blocking the progranulin C-terminus, which harbors the sortilin binding site, improves the effectiveness of progranulin gene therapy.

Methods: We treated aged progranulin deficient mice with gene therapy vectors expressing progranulin with intact sortilin interactions, progranulin with the carboxy terminus blocked to reduce sortilin interactions, or GFP control. We used immunohistochemistry, in vivo microdialysis, qPCR, lipidomics, high resolution confocal microscopy, MATLAB and python-based imaging pipelines, unbiased machine learning, the Quanterix single molecule array platform, proximity ligation assays, immunoprecipitation, and lysosomal activity assays to generate the data in this study.

Results: We found that blocking the progranulin carboxy-terminus enhances levels of AAV-derived progranulin both at the injection site, and in more distant regions. We found that carboxy-terminal blocked progranulin was more effective at correcting microglial hyperreactivity and microglial lipofuscinosis, even in a neurotropic viral vector. Carboxy-terminally blocked progranulin was also more effective at ameliorating lipid abnormalities including ganglioside accumulation and loss of bis(monoacylglycero)phosphate lipids. Carboxy-terminally blocked progranulin was also more effective at correcting behavioral abnormalities in aged progranulin-deficient mice.

Finally, blocking the progranulin C-terminus was essential for the ability of AAV-Progranulin to reduce plasma neurofilament light chain, a biomarker of axonal damage, in aged progranulin-deficient mice.

M163: Prospective and Consecutive Evaluation of Anti-Amyloid Therapy in Patients with Alzheimer's Pathology

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Background: Background We collected prospective and consecutive information on all patients started on anti-amyloid therapy at our medical center. This was primarily for safety monitoring, in light of concerns over the potential for amyloid-related imaging abnormalities (ARIA) associated with such therapy, and also response

Methods: We assessed 112 subjects with eligibility for therapy was based on cognitive status and either cerebrospinal fluid exam or a positive cerebral beta-amyloid positron emission tomography. We followed the protocol for magnetic resonance imaging serial monitoring with additional scans for the development of ARIA or other potential complications. Data collected included age, sex, race, mini-mental status score, apolipoprotein E allele status, initial brain scan results and subsequent findings, history of stroke or incidental stroke on brain scan, anti-thrombotic therapy, significant co-morbid factors and outcome. 74 have been treated with lecanemab and 38 with donanemab.

Results: Our study includes 64 white females, 40 white males, 5 African-American females,1 African-American male,

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one Hispanic male and one female of mixed race. 97 patients have continued anti-amyloid therapy and one continued therapy but moved out of state. Three patients received only one dose of therapy related to severe headache (1), moderate ARIA (1), medical instability following the first dose (1). 12 patients (10.7%) developed ARIA in the mild to moderate category. No severe symptomatic cases of ARIA developed. Two patients are on anticoagulant therapy and 33 are on antiplatelet therapy. No major cerebral hemorrhage nor death occurred. Five patients developed seizures with one patient discontinued, one patient not treated as related to ARIA which resolved, with resumed anti-amyloid therapy, and 3 were continued on anti-amyloid therapy and levetiracetam. Significant infusion reactions were observed in 7 patients leading to discontinuation in five. 13 patients were apolipoprotein E4 allele homozygous and all have been treated with lecanemab. The vast majority of patients reported stability, if not improvement, based upon functional status reported by the patient and caregiver and desire to continue therapy.

Conclusion: Initial concern about the safety of anti-amyloid therapy has not been borne out by our collection of patients, to date, with the majority displaying cognitive stability. However, the diligence required in the safe and effective selection and monitoring of the patients must be addressed in terms of time commitment.

M164: Low-Field MRI Detects CD8-Associated White Matter Hyperintensity in Long-Treated Adults With HIV

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Background: A low CD4/CD8 ratio is a marker of immune aging and dysregulation in people with HIV (PWH). In the era of antiretroviral therapy (ART), this may reflect CD8+ T-cell (CD8+) expansion more than CD4+ T-cell (CD4+) depletion. Low-field MRI (LF-MRI) offers a scalable approach to monitor brain changes which may reflect this immune shift linked to inflammaging, vascular risk, and non-AIDS mortality. We therefore examined the association between CD8+ count and structural brain abnormalities in long-treated PWH.

Methods: Thirty PWH (10 female; median age 61.5 years) underwent 0.064-T brain MRI (Hyperfine, Inc.). Within FreeSurfer, WMH-SynthSeg automatically performed super-resolution and segmentation of subcortical regions of interest (ROIs), while cortical morphometry was performed using recon-any. Raw volume outcomes (mm^3) were adjusted for age, sex, intracranial volume, and HIV duration. Cortical ROIs were aggregated into residualized, PCA-derived summaries. Fully adjusted models included CD4+ nadir, treatment delay, viral burden, and treatment-era exposure to distinguish active from legacy HIV injury. MoCA (n=25) and CES-D (n=22) assessments were also completed. Analyses included mixed-effects models with subject random intercepts for repeated T1/T2/FLAIR sequences and BH-FDR correction. Among 23 participants with blood draws, subject-level linear regression related cross-sectional plasma cytokines quantified using a 13-plex LEGENDplex assay to longitudinal T-cell measurements (median 13.8 years; range 0.5-15.5); cumulative exposure to an elevated CD8+ count was defined as the proportion of CD8+ measurements at or above 1,000 cells/μL.

Results: Low CD4/CD8 ratio was primarily driven by CD8+ expansion (Cohen's d=1.38, AUC=0.864). After legacy HIV injury adjustment, CD8+ count remained associated with greater white matter hyperintensity (WMH) (β=908.4) and larger third ventricle volume (β=181.8; both $q<0.01$); CD4+ count and CD4/CD8 ratio associations attenuated. Higher MoCA delayed recall scores were associated with greater residualized left cingulate gray-matter volume (β=0.56, $q<0.001$) and higher CES-D scores were associated with lower residualized left limbic network gray-matter volume (β=-0.047, $q<0.001$). A higher proportion of elevated CD8+ measurements was associated with lower composite Tc1 signal (IFN-γ, TNF-α, IL-2) and higher IL-17A ($q<0.05$).

Conclusion: In long-treated PWH, CD8+ count was associated with greater WMH burden and third ventricle enlargement after adjustment for legacy HIV injury, compatible with ongoing immune-associated injury in a population with elevated vascular risk. Cumulative high-level CD8+ exposure was associated with lower Tc1 signaling and higher IL-17A, warranting further investigation of exhaustion-like biology and cardiometabolic comorbidity moderating neurovascular dysfunction. If externally validated, automated morphometry of LF-MRI offers a scalable pathway for integrating structural brain monitoring into routine HIV care.

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M165: Dual Burden of Parkinson's and Alzheimer's Disease: A CDC WONDER Analysis

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Background: Alzheimer's disease (ICD-10: G30), and Parkinson's disease (ICD-10: G20) are leading contributors to neurological morbidity and mortality in the United States. Despite advancements in geriatric care, the longitudinal mortality trends across various demographic and geographic strata remain complex. This study examines national trends and disparities in mortality involving these conditions from 1999 to 2020.

Methods: Mortality data were obtained from the CDC WONDER database for the period 1999–2020. Age-adjusted mortality rates were analyzed using Joinpoint regression software to identify significant changes in Annual Percent Change (APC) and Average Annual Percent Change (AAPC). Analyses were stratified by age, sex, race/ethnicity, census region, and urbanization status. Statistical significance was determined using 95% confidence intervals and p-values.

Results: From 1999 to 2020, the overall population experienced a significant long-term decline (AAPC: -1.47%, $p < 0.0001$). There was an initial increase from 1999 to 2005 (APC: 2.19%), a significant decline from 2005 to 2014 (APC: -6.98%), and a significant recent reversal from 2014 to 2020 (APC: 3.56%). Age-stratified analysis revealed significant declines in the 65–74 (AAPC: -2.94%) and 75–84 (AAPC: -1.96%) cohorts, while the 85+ population remained stable (AAPC: -0.67%, $p = 0.20$). Males experienced a steeper overall decline than females (AAPC: -1.85% vs. -1.38%). Regarding ethnicity, the non-Hispanic population exhibited a significant overall decline (AAPC: -1.60%), whereas the Hispanic population remained statistically stable (AAPC: -0.18%, $p = 0.72$). Regionally, the Northeast achieved the greatest improvement (AAPC: -3.08%), followed by the Midwest (AAPC: -1.79%) and the West (AAPC: -1.32%). The South showed no significant long-term trend (AAPC: -0.81%, $p = 0.21$). Both metropolitan (AAPC: -1.65%) and nonmetropolitan areas (AAPC: -1.02%) showed overall declines, though both have trended significantly upward since 2013–2014.

Conclusion: While significant progress was made in reducing AD/PD mortality in the early 21st century, these gains have been eroded by a universal increase in mortality rates over the last decade. The surge in mortality is most pronounced in the Midwest and South, highlighting an urgent need for targeted neurological care and public health support in these regions to address rising disparities.

M166: ZCCHC17 - A Novel Mechanism Of Alzheimer's Disease Pathophysiology

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Background: Alzheimer's Disease (AD) is a progressive and incurable illness with detrimental effects to one's cognition, wellbeing, and life quality. Though disease development may not be entirely understood, new studies investigating early-stage events continue to direct future treatments. A novel zinc finger protein, ZCCHC17, is a recently discovered synaptic target that suggests a new direction of potential treatment and management of AD. The ZCCHC17 protein declines in the early course of AD, and our research establishes the role of ZCCHC17 in sustaining efficient synaptic function, and maintaining the balance of excitatory and inhibitory (E/I) activity in neurons. A disruption to the E/I balance, favoring hyper-excitability, is linked to the progression and severity of AD. Understanding the mechanistic role of ZCCHC17 may provide new insight into synaptic regulators of disease, and may contribute to improvements in early-stage diagnostics and interventions.

Methods: Reductions in ZCCHC17 may play a significant role in the pathophysiology of AD. As a notable master regulator of synaptic function, it is synonymously a regulator of synaptic dysfunction when it is deficient. To further exploit this correlation, we developed an in vitro model of ZCCHC17 knockdown of ZCCHC17 in primary cortical neurons using siRNA, to evaluate the functional consequences of reduced protein expression. We employed several techniques: including immunohistochemistry, whole-cell patch clamp electrophysiology, Western Blot analysis to measure synaptic protein expression and neural activity.

Results: We show that ZCCHC17 knockdown causes overall synaptic loss, with reduced expression of PSD95 and glutamate/GABA receptors, which is commonly observed in early AD. Interestingly, we identified a shift in the balance of excitatory/inhibitory (E/I) neural activity; favoring overall hyper-excitability.

Conclusion: Our work is the first to identify ZCCHC17 as a target of AD pathophysiology - suggesting that reduced levels underlie neural hyper- excitability during the early course of AD, before hallmark gliosis and neuronal loss. These findings provide a promising avenue for exploring new diagnostic and therapeutic approaches in AD.

M169: Association of a Proteomic-based Biological Age Clock with Delirium in Older Adults with Acute Hip Fracture

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Background: Delirium is a clinical syndrome characterized by acute and fluctuating disturbances in attention associated with increased risk of mortality and adverse long-term outcomes. While advanced chronological age (CA) is a known delirium risk factor, whether biological aging captured by molecular biomarkers, independent of CA, contributes to delirium risk is unclear.

Methods: Delirium was assessed prospectively for the duration of hospitalization using the Confusion Assessment Method (CAM) with severity quantified via CAM-S. Preoperative plasma proteomics (OlinkExplore HT) were used to derive biological age (BA) estimates using a previously validated plasma proteomic aging model (Earls, John C, Journals of Gerontology Series A, 2019). Biological age acceleration (BAA) was calculated as the residual from regressing BA on chronological age. Group differences between delirious and non-delirious subjects were compared using parametric statistics.

Results: 33 subjects (mean age 76.4 years, 72.7% women, 14 with delirium) undergoing hip fracture repair were included. BA was correlated with CA ($r = 0.81$, $p < 0.001$), with residual variance reflecting individual differences in biological aging rate. Baseline BA was significantly associated with delirium occurrence, with delirious patients approximately 4 years biologically older (81.4 vs 77.3 years; $p=0.018$). Higher baseline BA was also associated with greater maximum delirium severity ($r=0.42$, $p=0.016$). No statistically significant associations were observed between BAA and delirium risk or severity.

Conclusion: In this pilot cohort, proteomic-based BA was associated with delirium occurrence and maximum delirium severity. Larger studies are needed to clarify the role of molecular aging markers in delirium risk and to determine whether proteomic aging markers change acutely in response to surgical stress.

M171: Predicting Language Recovery at 12 Months from Acute Stroke Data: Machine Learning Identifies Shared and Distinct Neural Predictors

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Background: Clinicians are routinely asked to prognosticate language recovery in the acute stroke setting, yet existing tools offer limited individualized prediction. Nearly all prior machine learning prediction studies in language disorders use chronic-phase data, where imaging captures post-reorganization neural states unavailable at the acute decision point. Moreover, recovery is multidimensional: resolution on standardized aphasia batteries and normalization of connected speech may follow distinct trajectories. No study of which we are aware has applied machine learning with model interpretability to predict long-term language outcomes from acute-phase data.

Methods: We studied 73 patients with acute left-hemisphere ischemic stroke and aphasia recruited at Johns Hopkins Hospital (2015–2023; median assessment 2.8 days post-onset; 12-month follow-up). Two outcomes were defined: aphasia resolution (Western Aphasia Battery Aphasia Quotient [WAB-AQ] ≥93.8; N=73) and discourse content normalization (Modern Cookie Theft content units ≥22.1; N=61). Four algorithms (Ridge, support vector regression, Random Forest, XGBoost) were trained on four hierarchical feature sets spanning clinical, volumetric, anatomical, and network disconnection data (5 to 45 features). Nested cross-validation (10-fold × 10 repeats) with recursive feature elimination was used. SHapley Additive exPlanations (SHAP) stability analysis across cross-validation folds provided model interpretation.

Results: Acute aphasia severity was the top-ranked predictor for both outcomes. For aphasia resolution, Random Forest using all feature sets achieved high accuracy (F1=0.874; 95% CI, 0.809–0.942; sensitivity 0.809, specificity 0.923, positive predictive value 0.950). Clinical features alone performed comparably (F1=0.851). Discourse prediction was weaker (Ridge F1=0.704; 95% CI, 0.581–0.821), and imaging did not improve prediction.

Interhemispheric supramarginal gyrus connectivity was the leading imaging predictor for both outcomes, with shared cortical contributions from pars opercularis and superior temporal gyrus. White matter contributions differed in emphasis: ventral tracts (inferior longitudinal and inferior fronto-occipital fasciculi) were weighted more heavily for aphasia resolution, whereas dorsal stream (superior longitudinal fasciculus) and uncinate fasciculus were weighted more heavily for discourse normalization. All models systematically over-predicted for patients with severe chronic aphasia (12-month WAB-AQ ≤ 50).

Conclusion: Acute-phase prediction of aphasia resolution is feasible with high accuracy, and discourse normalization is predictable with lower specificity, consistent with its reliance on distributed networks beyond the perisylvian core. Clinical features capture the most predictive variance; structural neuroimaging provides complementary mechanistic insight, revealing shared and distinct neural predictors that map dual-stream language architecture onto discrete but highly interrelated recovery dimensions. These results support both acute comprehensive communication assessment, and early identification of candidates for intensive rehabilitation and intervention trials from acute-phase data alone.

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M172: The Impact of the Trajectory of Insurance Coverage on Cognitive Function at Midlife

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Background: As the U.S. population ages, understanding how insurance shapes cognitive health has become increasingly important, particularly given the socioeconomic disparities that influence access to preventive care. This study examined how long-term insurance trajectories were associated with cognitive function and self rated memory in adulthood.

Methods: Data were drawn from the National Longitudinal Survey of Youth 1979 (NLSY79), a cohort study that followed young adults from 1979 through 2020, when respondents were 55-64 years old. Health insurance information was obtained at 7 interviews between 2008 and 2020. We calculated percentage of time spent with each insurance type (private, public, or no insurance) by dividing the number of interviews with each coverage type by the number of interviews each respondent completed between 2008 and 2020. Cognitive outcomes were obtained during the 2020 interview and included items from the modified Telephone Interview for Cognitive Status (TICS-m) and cognitive assessments adapted from the Health and Retirement Study (HRS). Additionally, respondents rated their current memory and their memory compared to two years ago using Likert scales.

Results: The study included 4,359 respondents and insurance data from 29,842 interviews, with participants having public insurance in 15% and no insurance in 11% of interviews. The median cognitive score in 2020 was 24 (IQR: 21, 27). In 2020, 15% of respondents rated their memory as fair/poor, and 17% rated their memory as worse than 2 years ago. On multivariable analysis, every 10% increase in time (years) spent with public insurance was associated with a 0.22 point decrease in cognitive score at the 2020 interview (coefficient = –0.22, 95% CI –0.29 to –0.15). Every 10% increase in time spent with public insurance was also associated with 7% lower odds of better self-rated memory (OR = 0.93, 95% CI 0.91– 0.95). More years spent uninsured were not associated with better current memory.

Conclusion: These findings suggest that long term reliance on public insurance, and to a lesser extent uninsurance, may reflect structural disadvantages that contribute to midlife cognitive disparities. Insurance trajectories therefore represent an important social determinant of cognitive health. Policies that promote stable, high quality coverage throughout adulthood may help mitigate cognitive inequities as the population ages.

M174: Efficacy and Safety of Dexmedetomidine for Prevention of Postoperative Delirium in Adult Surgical Patients - A Systematic Review and Meta-Analysis

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Background: Postoperative delirium is a common and serious complication among adult surgical patients, particularly in elderly and high-risk populations, and is associated with increased morbidity, prolonged hospitalisation, and mortality. Dexmedetomidine, a selective α2-adrenergic agonist used for perioperative and ICU sedation, has been proposed to reduce delirium; however, evidence regarding its efficacy and safety remains heterogeneous.

Methods: This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines and prospectively registered with PROSPERO (CRD420261380914). Electronic databases (PubMed, Embase, Scopus, and Cochrane CENTRAL) were searched from inception. Eligible studies included adult (≥18 years) surgical patients receiving intravenous dexmedetomidine perioperatively or postoperatively, compared with placebo or standard care. The primary outcome was the incidence of postoperative delirium diagnosed using validated tools. Secondary outcomes included duration and time to onset of delirium, ICU and hospital length of stay, and safety outcomes (bradycardia and hypotension). Random-effects meta-analysis was performed to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity was assessed using I^2. Influence diagnostics and leave-one-out sensitivity analyses were conducted.

Results: Of 68 studies assessed for eligibility, 29 were included in the systematic review, and 28 contributed to the meta-analysis. Dexmedetomidine significantly reduced postoperative delirium compared with placebo or standard care (OR 0.50, 95% CI 0.40–0.63; $p < 0.001$; $I^2 = 63.6\%$). Influence diagnostics identified Lv et al. (2022) as a highly influential study; its exclusion reduced heterogeneity but did not alter the direction or statistical significance of the effect. Dexmedetomidine was associated with an increased risk of hypotension (OR 1.36, 95% CI 1.04–1.76; $p = 0.025$; $I^2 = 59.9\%$) and bradycardia (OR 1.60, 95% CI 1.34–1.92; $p < 0.001$; $I^2 = 14.1\%$), with no significant difference in mortality (OR 0.82, 95% CI 0.50–1.34; $p = 0.407$; $I^2 = 8.1\%$).

Conclusion: Dexmedetomidine is associated with a significant reduction in postoperative delirium in adult surgical patients, although with substantial between-study heterogeneity. The findings are robust to sensitivity analyses despite the influence of an outlier study. However, the increased risk of bradycardia and hypotension highlights the need for careful patient selection and monitoring.

M175: One Year Maintenance Acoustic Neuromodulation versus Initial Neuromodulation alone for Perceived Stress in Healthcare Workers: A Randomized, Controlled Trial

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Background: Long-lasting interventions are needed to address the burden of healthcare worker stress. A prior randomized trial in healthcare workers demonstrated improved perceived stress at 6-8 weeks with closed-loop acoustic neuromodulation versus waitlist control, but longer-term outcomes were not assessed. It is unknown whether regular additional maintenance sessions would enhance long-term benefit.

Methods: An open label randomized trial was conducted to compare the effect of 8 maintenance sessions (every 6 weeks over one year) added to an initial 4-session neuromodulation intervention, versus the 4-session intervention alone. Healthcare workers with moderate perceived stress (Perceived Stress Scale, PSS ≥14) at screening were enrolled and received four 36-minute brainwave-echoing Cereset Research™ acoustic neuromodulation sessions on separate days over 2 weeks. Participants were then randomized to the maintenance intervention group or usual care control and followed every 3 months for one year. The primary outcome was perceived stress at one year (PSS), with secondary outcomes insomnia (Insomnia Severity Index) and anxiety (Generalized Anxiety Disorder-7). Exploratory outcomes included self-report symptoms (depression, quality of life) and autonomic function (heart rate variability, measured 6- and 12-months post-randomization). Linear mixed effects models were used to test between-group changes in outcomes at one year and within-group changes from baseline to one year follow-up.

Results: In total, 94 individuals enrolled, with 90 randomized after completing 4 acoustic neuromodulation sessions. The overall sample had mean age 45.1 years (SD 11.5), 17.6 years working in healthcare (SD 11.5), and were 81% female, 13% non-white, 1% Hispanic. Baseline characteristics were well balanced between groups. Maintenance acoustic neuromodulation delivery was feasible, with 78% randomized to maintenance attending all sessions and 91% meeting a prespecified adherence metric of >50% maintenance attendance. There were no significant between-group differences for change in primary, secondary, or exploratory outcomes from baseline to one year follow-up (PSS -9.8 for maintenance versus -7.6 for control, 95% CIs: maintenance -7.9 to -11.7, control -5.7 to -9.5). Compared to baseline, at one year both groups demonstrated statistically significant improvement in self-report outcomes including perceived stress, insomnia, anxiety, and depression, with one-year mean change values for these measures being in the clinically meaningful range for both groups.

Conclusion: Clinically relevant improvements in perceived stress, insomnia, and anxiety persisted through one year follow-up after a 4-session, 2-week acoustic neuromodulation intervention. The main results of this randomized trial do not suggest statistically significant benefit from adding regular maintenance sessions every 6 weeks to the initial intervention.

M177: Heart Rate Variability in Schizophrenia During Baseline Eyes-Open Resting State Compared to Healthy Controls

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Background: Schizophrenia is associated with autonomic dysregulation, which may contribute to cognitive and physiological impairments. Heart rate variability (HRV) provides a non-invasive measure of autonomic nervous system function. Objective of this study was to compare resting-state autonomic function between patients with schizophrenia and healthy controls using HRV during eyes-open (EO) baseline conditions.

Methods: Thirty patients with schizophrenia and 30 age- and gender-matched healthy controls underwent five-minute ECG recordings under EO resting conditions. Artifact-free segments were analyzed for time-domain HRV indices (SDNN, RMSSD, pNN50) and frequency-domain measures (low-frequency [LF], high-frequency [HF], and LF/HF ratio). Group differences were assessed using appropriate statistical tests.

Results: Patients with schizophrenia demonstrated significantly reduced parasympathetic-related HRV, reflected by lower pNN50 (%) ($p = 0.010$) compared to controls. No statistically significant differences were observed in RMSSD or SDNN. Frequency-domain measures, including LF, HF, LF/HF ratio, and total power, did not differ significantly between groups, although trends toward reduced HF power and total variability were observed in patients.

Conclusion: Schizophrenia is associated with reduced parasympathetic activity at rest, as indicated by decreased pNN50, suggesting impaired autonomic flexibility. HRV measures may serve as potential biomarkers for autonomic dysfunction in this population.

M178: A Novel Neuroprotective Mechanism of Hexaraphane (6 MSITC) Derived from Wasabi

Presenting Author(s): *Isao Okunishi, Dr, Nagoya, Aichi*

Background: Hexaraphane (HXN; 6-methylsulfinylhexyl isothiocyanate) is a bioactive isothiocyanate derived from wasabi (Eutrema japonicum) that exhibits antioxidant, anti-inflammatory, and neuroprotective properties. Accumulating evidence suggests that HXN activates the Nrf2 pathway and modulates molecular processes relevant to neurodegenerative diseases. However, its direct impact on pathological tau phosphorylation and related neurodegenerative mechanisms remains incompletely understood. This study aimed to

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elucidate the neuroprotective potential of HXN with a focus on tauopathy-related mechanisms and translational relevance.
Methods: Mechanistic evaluations integrated previously reported in vivo and in vitro experimental frameworks with complementary pharmacokinetic analyses. Published murine studies employed primary neurons and APP/TAU transgenic mouse models treated with orally administered HXN, followed by biochemical, histological, and behavioral assessments including tau phosphorylation status, phosphatase activity, synaptic plasticity, and cognitive performance. Pharmacokinetic profiling using HPLC-based methods confirmed systemic absorption, brain penetration, and region-specific distribution. In parallel, human evidence was drawn from randomized clinical studies assessing cognitive outcomes following daily intake of HXN-containing wasabi-derived supplements.
Results: HXN consistently reduced pathological tau phosphorylation at disease-relevant epitopes across cellular and animal models. Mechanistic analyses demonstrated that this effect occurred independently of canonical tau kinases and Nrf2 signaling, and was instead associated with enhanced phosphatase activity, particularly protein phosphatase 2A. Oral administration achieved measurable brain concentrations and was accompanied by reduced neuroinflammatory markers, preservation of neuronal integrity, and improvements in synaptic plasticity and cognitive function in mice. Translationally, human intervention studies showed significant improvements in attention, judgment, and memory, as well as reductions in neurological symptoms such as brain fog, supporting the clinical relevance of HXN.
Conclusion: Collectively, mechanistic, pharmacokinetic, and clinical findings identify HXN as a promising neuroprotective compound that modulates tau-associated pathology through phosphatase-dependent mechanisms while maintaining favorable brain bioavailability. These results highlight HXN's potential as a disease-modifying agent for tau-related neurodegenerative disorders and support further clinical development targeting cognitive resilience across different life stages.

M181-LB: The Cognitive Effects of Creatine Supplementation in Older Adults and Preclinical Models of Dementia: A Scoping Review

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Background: Dementia represents a growing global health crisis, yet disease-modifying therapies remain limited. Impaired brain energy metabolism, neuroinflammation, and synaptic dysfunction are some shared pathological features across dementia subtypes that may be amenable to metabolic intervention. Creatine supplementation, through its role in the phosphocreatine/ATP buffering system and proposed neuroprotective properties, has attracted growing scientific and public interest as a candidate intervention for dementia. This scoping review maps the existing evidence on creatine supplementation and dementia-related cognitive outcomes, with attention to intervention characteristics including dose, duration, formulation, route of administration as well as the characteristics of preclinical models.
Methods: Following the Joanna Briggs Institute (JBI) methodology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines, a systematic search of PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted. No date or language restrictions were applied. Studies were eligible if they evaluated creatine supplementation in older adults or preclinical animal models with dementia and reported at least one cognitive outcome.
Results: From 8,318 records identified and screened, six studies reported across seven publications, met eligibility criteria comprising one in vitro study, four in vivo animal model studies, and one human pilot trial resulting in two publications. Evidence was heterogeneous across study design, population, and intervention characteristics.
Preclinical studies demonstrated predominantly neuroprotective effects through bioenergetic support and neuroinflammatory modulation, though one rodent study reported worsening spatial memory. A single human pilot trial (n=20) found that high-dose supplementation (20g/day for 8 weeks) increased brain total creatine by 11% and was associated with improved fluid cognition. Sex-specific effects were identified in one rodent study, with female animals demonstrating cognitive benefit and males showing a trend toward harm and were paralleled by sex-divergent bioenergetic responses in the human trial.
Conclusion: Current evidence for creatine supplementation in dementia is limited, heterogeneous, and predominantly preclinical. Preliminary human data suggest biological plausibility and feasibility, supporting the need for adequately powered, sex-stratified randomized controlled trials in adults with dementia. While preclinical data support a mechanistic rationale for its use, this review identifies critical gaps including the absence of any controlled clinical trials, limited understanding of optimal dosing for brain penetrance, and the need to prospectively examine sex as a biological moderator of treatment response.

M182: Frontline Perspectives on the Real-World Use of Blood-Based Biomarkers in Alzheimer's Disease

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Background: Blood-based biomarkers (BBMs) are increasingly used in suspected Alzheimer's disease (AD), with some assays showing strong concordance with amyloid PET and CSF. However, real-world perspectives on BBM use for confirming amyloid pathology without follow-up PET or CSF are limited. We surveyed clinicians and staff already experienced in using BBMs for confirmation of pathology to assess appropriateness, acceptability, and feasibility.

Methods: Nineteen participants from three geographically and structurally diverse U.S. clinical settings completed validated implementation surveys. Participants included clinicians (n=12; neurologists, physician assistants, nurse practitioners) and non-clinicians (n=7; including neuropsychology, nursing, research and care coordination roles), with representation across genders, educational backgrounds, and racial/ethnic groups. All sites selected had experience using BBMs in routine clinical practice to confirm amyloid pathology without additional PET or CSF testing. Surveys assessed participant characteristics, contextual determinants aligned to the Consolidated Framework for Implementation Research (CFIR), and responses to the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM), each scored on a 1–5 agreement scale. Descriptive statistics were used to summarize responses.

Results: Respondents expressed highly positive perceptions of confirmatory BBMs, with unanimous agreement (19/19; 100%) across several domains and roles: confirmatory BBMs meet diagnostic needs in high- and intermediate-suspicion AD, organizations were successful in implementing BBMs, use would be sustained and should be diffused nationally (agreement defined as "agree" or "strongly agree" responses). Agreement was also near-universal (18/19; 95%) for positive attitudes, perceived effectiveness, organizational receptivity, self-efficacy, and ease of use. Views were more varied for use in low-suspicion AD cases (12/19; 63%), and financial incentives showed the lowest alignment (8/19; 42%). Implementation outcome scores were uniformly strong – AIM 4.49 (SD 0.49), IAM 4.51 (SD 0.50), FIM 4.46 (SD 0.53) – with low SDs demonstrating strong consistency across sites and roles.

Conclusion: Participants across geographically and structurally diverse settings reported positive views of confirmatory BBMs as alternative options to CSF and amyloid PET in high- and intermediate-suspicion AD, with strong perceived acceptability, appropriateness, and feasibility. Perspectives differed for low-suspicion cases, aligning with published recommendations which limit confirmatory BBM use to higher-suspicion evaluations. Despite differences in geography, resources, and workflows, respondents showed notable alignment in their attitudes toward confirmatory BBMs in routine clinic use, with BBMs viewed as compatible with existing workflows. These findings demonstrate the feasibility of confirmatory BBMs and support scalable, evidence-aligned real-world implementation.

M184: Sex-Based Outcomes of Lecanemab in Early Alzheimer's Disease: A Comprehensive Multicenter, Real-World, Retrospective Study (LEADER)

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Background: As women represent two-thirds of patients with AD and face higher lifetime risks, evaluating their real-world treatment outcomes is important. This subgroup analysis of LEADER describes effectiveness and safety of lecanemab, reported by sex.

Methods: LEADER, a multicenter, retrospective, real-world study, used deidentified chart data from 15 US neurology clinics for individuals treated with ≥7 lecanemab doses. This interim subgroup analysis compared safety and clinical outcomes by sex (data cutoff: March 26, 2026). Clinical status (improved, stable, progressed) was determined by judgment of the practicing clinician, informed by cognitive, functional, and other routine practice data.

Results: Of 309 participants, mean (SD) age was 74.1 (6.7) years, and 55.7% were female. Characteristics (age, race, ethnicity, and APOE ε4 status) were balanced between sexes. At baseline, 61.6% of females and 62.8% of males had MCI, and 38.4% of females and 37.2% of males had mild AD dementia. Mean (SD) treatment duration and doses were similar between sexes (females: 450.4 [233.5] days, 23.5 [13.0] doses; males: 450.9 [236.7] days, 21.7 [12.3] doses). During the observation period, 83.3% of females and 90.4% of males remained on therapy. Clinicians reported that patients were stable or had perceived improvement in 85.1% of females and 89.0% of males (78.0% and 85.7% stable; 7.1% and 2.3% perceived improvement, respectively); there were no statistically significant differences between outcomes by sex (chi-square test). ARIA occurred in 11.6% (n=20) of females and 14.6% (n=20) of males. Distribution by type was similar: ARIA-E (8.1% [n=14] vs 5.8% [n=8]),

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ARIA-H (6.4% [n=11] vs 10.2% [n=14]), including concurrent ARIA-E and ARIA-H (2.9% [n=5] vs 1.5% [n=2]) for females and males, respectively. All ARIA-E events in both males and females were radiographically mild to moderate, with 1.2% of cases symptomatic in females and 0% in males. Adverse events leading to discontinuation or dose modification occurred in 6.4% of females and 3.6% of males, with 3.5% of females and 2.9% of males discontinuing treatment due to ARIA. No macrohemorrhages or treatment-related deaths occurred.

Conclusion: In this large real-world cohort, lecanemab demonstrated comparable clinical outcomes, safety, and durability across sexes. Most female and male patients were reported as either clinically stable or improved over a mean observation period of 15 months, with similar ARIA incidence and severity. These data suggest that the effectiveness and safety of lecanemab in females is similar to that in males in clinical practice.

M185: GWAS Identifies Single-Nucleotide Polymorphisms in the SRPK1 Gene Linked To Diverse Neurological Traits

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Background: SRPK1, a member of the SRK protein family, plays a role in neuronal survival, cell cycle sequel, as well as memory formation in individuals with neurological disorders. The objective of this study was to explore the genetic association, including single-nucleotide polymorphisms of neurological diseases with SRPK1 by using the GWAS catalog.

Methods: Methods: We utilised a large GWAS catalogue dataset comprising 7,725,243 persons, including cases and controls from 15 studies and 15 associations with 15 traits across African, Asian, European, and Hispanic populations, up to 31st January 2026. The collected data were meta-analyzed and the combined P-values were measured using Fisher's Combined Probability Test in RStudio, and the results were adjusted for genetic controls and tabulated.

Results: Results: Using case-only analysis, we found no correlation between sex or age, and antidepressant treatment resistance (> 2 drugs prescribed) was significantly associated with SNP rs111968111, with an odds ratio (OR) of 3.00 (95% CI: 2.58–3.42; $p = 4 \times 10^{-7}$). This association was observed for the C/T alleles on the forward strand, with the minor allele T having a frequency of 0.01198. In addition, SNP rs12210988 was significantly associated with increased serum levels of the protein CLPS in Alzheimer's disease (AD), with an OR of 0.311 (95% CI: 0.27–0.35; $p = 4 \times 10^{-46}$). This association was observed for the G/A alleles on the forward strand, with the minor allele A having a frequency of 0.1833.

Conclusion: Conclusions: This study provides evidence that SRPK1 gene expressions with associated risk loci are linked to a spectrum of neurological and neuro-psychiatric disorders, as indicated by GWAS-derived data.

M186: The Montreal Cognitive Assessment (MoCA) Memory Index Score (MIS) Classification Accuracy for Delayed Memory Performance Across Neuropsychological Measures

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Background: The MoCA MIS was developed to provide a more diagnostically informative index of memory functioning, particularly for detecting deficits in encoding versus storage/retrieval. However, its classification accuracy for identifying clinically meaningful memory impairment remains incompletely characterized. We examined the extent to which the MIS identifies memory impairment using receiver operating characteristic (ROC) analysis and explored a sample-derived cutoff to inform potential clinical utility.

Methods: A mixed clinical sample ($N = 119$; mean age = 67.6 years, SD = 14.9; mean education = 16.0 years, SD = 2.8), completed the MoCA and at least one memory measure including the Rey Auditory Verbal Learning Test (RAVLT) and Wechsler Memory Scale Fourth Edition (WMS-IV) Logical Memory (younger and older adult norms) as part of a larger battery. A composite delayed memory score was derived. Participants were drawn from the Neurocognitive Outcomes and Variables Archive (NOVA) project from two outpatient clinics located in a Southern California academic medical center. 114 participants had complete MoCA and delayed memory data. Receiver operating characteristic (ROC) analysis was conducted in participants with complete data ($n = 85$), with a memory impairment defined as performance < -1.0 standard deviations on the composite memory score. Regression analyses were also conducted.

Results: The MIS was a significant predictor of delayed memory performance, with the strongest association observed for list-learning memory. MIS predicted performance on the RAVLT ($1 = .67$, $p < .001$) and the WMS-IV Logical Memory II in older adults ($1 = .61$, $p < .001$) and younger adults ($1 = .46$, $p = .006$). ROC analysis demonstrated very good discrimination (AUC = .874). An optimal cutoff of MIS 1 8.5 yielded high sensitivity (.944) with moderate specificity (.687).

Conclusion: The MIS demonstrates strong criterion validity, particularly for list-learning, and shows good accuracy for identifying memory impairment. Its high sensitivity supports utility as a screening and triage tool in clinical settings; however, given only moderate specificity, in addition to non-uniform ability across all memory domains, it should not be used in isolation for diagnostic determination and does not replace comprehensive neuropsychological evaluation.

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M187: A Three-year Update of Lecanemab Use in Early Alzheimer's Disease: A Comprehensive Multicenter, Real-World, Retrospective Study (LEADER)

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Background: Lecanemab is indicated for patients with AD at the MCI or mild dementia stage. Real-world evidence describing treatment outcomes across initiation and beyond, including during maintenance dosing, remains limited. This updated analysis from LEADER expands prior reporting with five additional sites (15 total), a larger patient cohort, and follow-up beyond 18 months. LEADER is among the first real-world datasets to characterize maintenance-phase lecanemab utilization, including both intravenous (IV) and at-home subcutaneous (SC) regimens.

Methods: LEADER is a multicenter, retrospective, real-world cohort study conducted across 15 geographically diverse US neurology practices. Sites abstracted deidentified medical chart data for patients who received ≥7 IV biweekly infusions. Maintenance cases were defined as patients with ≥3 months of maintenance therapy following initiation, including monthly-IV or weekly-SC dosing. Safety and treatment outcomes included change in disease stage from baseline to last follow-up visit based on clinician-reported observations. Descriptive statistics were generated using data collected through March 26, 2026.

Results: Of 309 patients included, 270 received IV-initiation only and 39 transitioned to monthly-IV maintenance, of whom 7 switched to weekly SC maintenance. Mean age was 74.1 years; 55.7% were female; 91.2% of patients were White, and 13.3% were Hispanic or Latino origin. At baseline, 62.1% of patients had MCI due to AD and 37.9% had mild dementia due to AD; 79.0% currently or had previously received approved AD medications (e.g., donepezil and/or memantine). 63.8% of patients were APOE ε4 carriers (n=197), and 13.6% were homozygotes (n=42), with 11 unknowns. Clinicians reported that 86.4% of patients were either stable (81.4%) or perceived as improved (5.0%; from mild AD dementia to MCI due to AD) over the observation period (mean treatment duration: 450.6 days; mean number of lecanemab doses: 28.0). ARIA occurred in 12.9% (n=40) of patients, including 7.1% of ARIA-E (n=22) and 8.1% of ARIA-H (n=25); 7 events were concurrent ARIA-E and ARIA-H. Adverse events leading to treatment discontinuation or dose modification occurred in 5.2% of patients (n=16), of which, 3.3% were related to ARIA (n=10; ARIA-E: n=3; ARIA-H: n=4; ARIA-E and ARIA-H: n=3). No macrohemorrhages or treatment-related deaths occurred.

Conclusion: In routine clinical practice, most patients treated with lecanemab remained clinically stable over the observation period, with a mean treatment duration of 15 months. Safety outcomes, including ARIA, were consistent with the known risk profile of lecanemab. Ongoing analyses of the full LEADER dataset (data cutoff: June 2026) will further characterize longer-term outcomes and safety in routine clinical practice.

M188-LB: Altered Resting-State Connectivity of the Auditory Cortex in Alzheimer's Disease

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Background: Alzheimer's disease (AD) is marked by reduced resting-state functional connectivity (RSFC), reflecting synaptic loss and disrupted neural communication (Sheline, Biological Psychiatry, 2013). Structural MRI studies have reported decreased cortical volumes in auditory cortical (AC) regions including the Planum Polare (PP), Planum Temporale (PT), and Heschl's Gyrus (HG) in AD (Sousa Menezes, Hearing Research, 2025). However, the relationship between connectivity of specific AC subregions and cognitive performance remains poorly understood. This study examined AC subregion connectivity differences between AD patients and healthy controls and evaluated how these connectivity patterns relate to cognitive measures that rely on auditory processing.

Methods: AD patients had reduced RSFC of the right PP with the lateral and medial cortical regions, with clusters located in frontal and parietal lobes. Reduced clusters in the medial cortices involved were the bilateral anterior cingulate and right paracingulate gyri, while lateral reductions included bilateral insula, left inferior frontal gyrus, and left inferior temporal gyrus. Within the AD group, stronger right PP connectivity positively correlated with letter fluency, with clusters in left prefrontal, parietal, putamen, and thalamic regions. Greater right PP connectivity was also linked to better RAVLT performance, with clusters in the posterior cingulate cortex, precuneus, and medial frontal areas. Trail Making

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Test Part B control analysis showed connectivity primarily within the parietofrontal (visuospatial) network.

Results: In our group of AD patients, we found reduced connectivity between PP and lateral/medial frontoparietal and cingulate regions. Reduced AC connectivity with left lateral cortical and subcortical regions contributes to impaired letter fluency, while decreased connectivity with medial limbic structures is known to underlie episodic memory deficits. The Trail Making Test Part B control analysis further supports the relative specificity of right PP connectivity to auditory-verbal cognitive performance. These findings suggest the involvement of central auditory cortical processing in cognitive decline in AD.

Conclusion: Structural and RSFC data were obtained from 51 healthy controls and 33 AD patients (84.8% mild, 15.2% moderate) per ADNI protocol. Seed-based connectivity analyses were performed for bilateral PP, PT, and HG. Group differences were assessed using two-sample t-tests (AD

M189: Utility of CSF Biomarkers in Patients with Suspected Alzheimer's Disease : A Tertiary Care Center Experience from India

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Background: Cerebrospinal fluid (CSF) biomarkers, namely amyloid-beta 42 (Aβ-42), phosphorylated tau (pTau), and their ratio, offer a highly reliable marker of underlying Alzheimer's disease (AD) pathology. Yet evidence for their utility in lower income countries remains inadequate. Clinical diagnosis alone often lacks specificity, particularly in mild cognitive impairment (MCI), potentially leading to misclassification and impacting clinical management and eligibility for disease modifying therapy. This study evaluated the role of CSF biomarkers in patients with suspected AD at a high-volume tertiary care center in India, with relevance to diagnostic challenges in low- and middle-income countries, where access to advanced diagnostic resources is often limited.

Methods: We conducted a retrospective observational study of 52 consecutive patients presenting to our outpatient department with progressive memory impairment between March 2023 and February 2025. Patients received initial clinical diagnoses (AD, amnestic MCI, non-AD dementia, or subjective cognitive impairment) based on standard clinical criteria. CSF samples were analyzed using Roche's Elecsys machine for Aβ1-42 and pTau concentrations. Amyloid positivity was defined as pTau/Aβ1-42 ratio >0.023. Descriptive statistics were used to summarize patient demographic details. Diagnostic accuracy was assessed by comparing pre-CSF diagnoses against biomarker-confirmed diagnosis, and changes were quantified.

Results: The cohort had a mean age of 67.5±6.8 years and mean MMSE score of 21.5±3.8. Initial clinical diagnoses included amnestic MCI (46.1%), AD (38.5%), and non-AD dementia (13.5%). CSF analysis revealed amyloid positivity in 32 patients (61.5%). Overall clinical diagnostic accuracy was 68% (32/47 cases). Accuracy varied substantially by diagnosis: 95% for clinically diagnosed AD (19/20) but only 50% for MCI-AD (12/24). Non-AD dementia diagnoses showed 83% accuracy in confirming absence of amyloid pathology. Notably, 29.4% (15/51) of patients had their diagnosis changed following CSF biomarker analysis, including reclassifications from AD to non-AD dementia and from MCI to biomarker-confirmed AD pathology. Biomarker profiles showed 67.3% with abnormal Aβ1-42, 27% with elevated pTau, and 19% with both markers abnormal.

Conclusion: CSF biomarker analysis improved diagnostic accuracy in this Indian cohort, with nearly one-third of patients reclassified. Clinical diagnosis was reliable in established AD but less accurate in MCI, where biomarkers added clarity. In low income settings, reducing misclassification could guide more appropriate treatment decisions and resource stewardship. Our findings support targeted use of CSF biomarkers to enhance diagnostic precision, guide patient counseling, and inform eligibility for disease-modifying therapies, especially in lower income countries. Further multi center prospective studies are needed to assess the cost-effectiveness and scalability in resource-limited settings.

M190: Age at Onset Influences the Frequency and Etiology of Rapidly Progressive Alzheimer Disease and Related Dementias

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Background: Background: Individuals with symptomatic Alzheimer disease (AD) with onset before age 65 decline faster than those with later onset. However, it is not known whether younger individuals with AD and AD-related dementias (ADRD) are also more likely to experience rapidly progressive dementia. The answer to this question may inform the potential contributors to rapidly progressive AD/ADRD (rpAD/ADRD). Objective: To compare the frequency, demographics, clinical features, and causes of rpAD/ADRD in individuals with early (<65-years) vs late-onset (≥65-years) AD/ADRD.

Methods: Methods: Established definitions of rapidly progressive dementia were applied to individuals assessed across Alzheimer's Disease Research Centers (ADRC; 2005-2023) and Longitudinal Early-Onset Alzheimer's Disease Study sites (LEADS; 2018-2025). Rapidly progressive dementia was diagnosed in participants who developed dementia (Clinical Dementia Rating® [CDR] ≥1) within 1 year or incapacitation (CDR ≥2) within 2 years of symptom onset. Participant demographics, clinical features, and etiologic diagnoses recorded in ADRC and LEADS databases were compared

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using Mann-Whitney U (continuous) and Chi-Square tests (categorical variables).

Results: Results: 675/20,992 participants (3.2%) met criteria for rpAD/ADRD, including 178/3868 (4.6%) participants with early-onset AD/ADRD and 497/17124 (2.9%) participants with late-onset AD/ADRD (p<0.001).

Individuals with late- versus early-onset rpAD/ADRD were more likely to be female (OR 1.6, 95%CI: 1.1, 2.2) and Black (OR 4.0, 95%CI: 2.1, 7.7). Cases with rapidly progressive frontotemporal lobar degeneration were overrepresented in younger individuals (early: 76/178, 42.7%; late: 43/497, 8.7%; p<0.001), whereas rpAD was more common in older individuals (early: 92/178, 51.7%; late: 401/497, 80.7%; p<0.001). A clinically relevant association between rapidly progressive Lewy body disease and age at symptomatic onset could not be excluded (early: 53/497, 10.7%; late: 10/178, 5.6%; p=0.066).

Conclusion: Conclusion: rpAD/ADRD occurred more frequently in individuals with symptomatic onset <65-years, who were more likely to experience rapidly progressive frontotemporal lobar degeneration and less likely to experience rapidly progressive AD, than individuals ≥65-years. Differences in the frequency of rpAD/ADRD may reflect age-specific vulnerability to specific neuropathologies associated with rapid decline.

M191: Same Tau, Different Story: The Effect of Assay Choice on Prion Disease Detection

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Background: Background: Cerebrospinal fluid (CSF) total tau (t-tau) levels are elevated in patients with Alzheimer disease (AD) and markedly elevated in patients with prion disease. Assays optimized to detect disease-specific t-tau levels are available; however, whether AD-optimized assays can be reasonably applied to identify patients with prion disease is unclear. Objective: Assess the diagnostic applications of CSF t-tau assays optimized for AD and prion disease.

Methods: Methods: Diagnostic lumbar punctures were performed in patients undergoing evaluation for possible prion disease (n = 34), rapidly progressive dementia (n = 67), or typically progressive dementia (n = 409) at Mayo Clinic Jacksonville from 2013 to 2024. T-tau levels were measured in contemporaneously sampled CSF aliquots at the National Prion Disease Pathology and Surveillance Center (Cleveland, OH) using enzyme-linked immunosorbent assay (ELISA; Invitrogen) and at Mayo Clinic Laboratories (Rochester, MN) using electrochemiluminescence immunoassay (ECLIA; Roche Elecsys). Assay bias was assessed using Passing-Bablok regression and correlation coefficient. Youden's method was used to determine the optimal diagnostic threshold.

Results: Results: Patients were an average of 69.1±8.9 years-old; 53.1% were female; 93.3% were non-Hispanic White. Cognitive impairment was attributed to symptomatic AD (55.1%), AD-related dementias (10.0%), prion disease (10.2%), normal pressure hydrocephalus (8.3%), or other diagnoses (16.5%). Median t-tau levels were 505.5 pg/mL (IQR, 256.5–819.8) by ELISA and 267.5 pg/mL (IQR, 175.5–379.0) by ECLIA (p<0.001). As expected, patients with prion disease exhibited the greatest assay specific differences (median difference: 1321 pg/mL, 95%CI: 829-2215). Passing–Bablok regression showed both proportional and constant bias between measures (ECLIA = 0.335 x ELISA + 93.9; slope 95%CI: 0.309–0.342; intercept 95%CI: 91.7–109.4) with a concordance correlation coefficient of 0.451 (95%CI: 0.260–0.620). T-tau levels were above established ELISA-based cutoffs for prion disease (>1150 pg/mL) in 43/52 patients (sensitivity 82.7%) with and 21/458 without prion disease (specificity 95.4%), and above ELICA-based cutoffs (>393 pg/mL) in 40/52 patients with (sensitivity 76.9%) and 81/458 without prion disease (specificity 82.3%). Youden's method affirmed that optimized thresholds were nearly identical to published ELISA-based cutpoints (>1134 pg/mL: sensitivity 84.6%, specificity 95.0%) but higher than currently recommended ECLIA cutpoints (>493 pg/mL: sensitivity 73.1%, specificity 92.8%).

Conclusion: Conclusion: The ability to detect a breadth of CSF t-tau levels, and their corresponding disease-specific diagnostic cutoffs, vary substantially by assay. When prion disease is suspected, testing should be performed using assays and cutpoints optimized to measure higher ranges of t-tau to maximize detection.

M192: A Novel Neurological Divide: IgG Subclass-Dependent CNS Safety, Neuropsychiatric Outcomes, and Survival Across PCSK9 Inhibitors, A Real-World Propensity-Matched Analysis

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Background: PCSK9 inhibitors (PCSK9i) achieve LDL-cholesterol reductions unattainable with statins, yet their net neurological impact remains uncertain. Structural differences may be biologically relevant; IgG1 alirocumab carries greater Fc-gamma receptors (FcγR) binding and microglial activation than IgG2 evolocumab, raising a plausible differential CNS effect between subclasses.

Methods: Retrospective cohort study using the TriNetX US Collaborative Network. Three mutually exclusive cohorts:

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alirocumab (n=13,552), evolocumab (n=90,860), and statins (n=6,843,215). Patients with dyslipidemia or established atherosclerotic cardiovascular disease were included; those with prior dementia, neurodegenerative disease, intracranial hemorrhage, or brain malignancy at baseline were excluded, with 1:1 propensity-score matching adjusting for diabetes, hypertension, tobacco use, myocardial infarction, cerebral infarction, obesity, and antithrombotic use. Outcomes were assessed at 1, 3, 5, and 20 years (full follow-up) using hazard ratios (HR) and risk ratios (RR) with 95% confidence intervals.

Results: Both evolocumab and alirocumab reduced mortality versus statins at 1-year mortality by 65.5% (HR 0.345 [0.321-0.372]) and 43.5% (HR 0.565 [0.490-0.653]), respectively. Evolocumab sustained superiority at 5 years (HR 0.646 [0.571-0.731], p<0.001). Neuropsychiatric morbidity was reduced by both versus statins at 5 years (alirocumab: RR 0.830 [0.718-0.960]; evolocumab: RR 0.822 [0.777-0.869], p<0.001). Neither agent increased dementia risk (alirocumab: RR 0.956 [0.526-1.738] to 0.801 [0.593-1.082]; evolocumab: RR 0.770 [0.598-0.991] to 0.624 [0.543-0.717], 1 to 20 years), with evolocumab maintaining superiority. Encephalopathy demonstrated a biphasic, time-dependent pattern, with evolocumab conferring protection versus statins at 1 year (HR 0.878 [0.773-0.998], p=0.046; RR 0.818 [0.720-0.928], p=0.002), reversing from 3 years onward with elevation (HR 1.401 [1.289-1.523], p<0.001 at 5 years) and (HR 1.495 [1.384-1.615], p<0.001 at 20 years). Alirocumab showed no elevation versus statins through 3 years, with late hazard at 5 years (HR 1.252 [1.029-1.524], p=0.024) and full follow-up (HR 1.265 [1.058-1.513], p=0.010). Evolocumab versus alirocumab demonstrated sustained encephalopathy protection at 3, 5, and 20 years (RR 0.766, 0.732, 0.733; all p<0.01), despite evolocumab risk versus statins at those horizons. Both agents significantly elevated delirium risk versus statins at 5 years (alirocumab: HR 1.759 [1.140-2.714], p=0.010; evolocumab: HR 1.624 [1.371-1.924], p<0.001), warranting prospective surveillance.

Conclusion: In the largest real-world analysis of PCSK9i neurological outcomes, both PCSK9i were associated with substantial mortality reduction and neuropsychiatric protection without independent dementia risk. A consistent, class-wide delirium signal and a biphasic encephalopathy pattern with subclass-dependent temporal heterogeneity warrant prospective surveillance. IgG antibody subclass, particularly the relative CNS selectivity of IgG2, may represent a novel determinant of neurological safety, offering a biologically plausible mechanistic hypothesis for future investigation.

M193*: Circulating Microbial DNA Signatures Associated with Cognitive Impairment in People with HIV

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Background: Cognitive impairment remains common among people with HIV (PWH) despite antiretroviral therapy (ART) and may be influenced by host–microbial and inflammatory pathways. Circulating microbial DNA signatures in plasma are poorly characterized, particularly in relation to neurocognitive outcomes. We examined whether plasma 16S microbial features were associated with global deficit score (GDS)–defined cognitive impairment among PWH.

Methods: We performed plasma 16S rRNA gene amplicon sequencing data from 480 PWH enrolled through the HIV Neurobehavioral Research Program at UC San Diego. Cognitive impairment was defined as GDS ≥ 0.5, derived from a comprehensive neuropsychological battery with age-, sex-, ethnicity-, and education-corrected T-scores. Alpha diversity (Faith's phylogenetic diversity, PD) was compared using Mann–Whitney U tests, and beta diversity (UniFrac distances) was evaluated by PERMANOVA. Genus-level differential abundance was assessed using BIRDMAn negative-binomial regression models adjusted for ART and hepatitis C virus (HCV) coinfection status.

Results: Participants had a mean age of 42.6 ± 8.8 years; 388 (80.8%) were male. Overall, 320 (66.7%) were receiving ART, 137 (28.5%) had concurrent HCV coinfection, and 158 (32.9%) met criteria for cognitive impairment. Faith's PD was lower among participants receiving ART (Mann–Whitney U, $p = 0.02$) and higher among those with HIV/HCV coinfection ($p = 0.04$). Alpha diversity did not differ by cognitive status in the full cohort.

However, beta diversity assessed by unweighted UniFrac differed between cognitively impaired and unimpaired participants (pseudo-$F = 1.53$, $p = 0.04$) and was also associated with ART and HCV status (both $p < 0.01$). In stratified analyses, ART-naïve participants with HIV/HCV coinfection showed differences by cognitive status in both alpha (Mann–Whitney U, $p = 0.03$) and beta diversity (PERMANOVA pseudo-$F = 1.30$, $p = 0.04$). In adjusted BIRDMAn models, cognitively impaired participants showed lower abundance of an unclassified Micrococcaceae genus and Methylotenera_A_557105, and higher abundance of Cloacibacterium and Chishuiella.

Conclusion: Among PWH, cognitive impairment was associated with distinct plasma microbial community structure and specific genus-level taxonomic shifts, with effects modified by ART exposure and HCV coinfection. These findings identify the circulating microbial DNA compartment as a measurable correlate of neurocognitive status in PWH and support its further evaluation as a potential biomarker, while underscoring the methodological considerations inherent to low-biomass plasma microbiome analyses.

M194: Clinical and Comorbidity Correlates of Discordant Plasma p-tau217

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Background: Discordance between plasma p-tau217 and other biomarkers of amyloid pathology (CSF, amyloid-PET) occurs in clinical practice. As blood-based biomarkers are increasingly used to guide treatment decisions in patients with symptomatic Alzheimer's disease (AD), such discordance has important implications: false-positive (FP) results may lead to overtreatment and false-negative (FN) results to missed or delayed use of disease-modifying therapies.

Methods: Participants from longitudinal Mayo Clinic studies with "positive" (>0.324 pg/mL) or "negative" (<0.186 pg/mL) plasma p-tau217 concentrations and available confirmatory AD biomarkers (CSF p- tau181/Aβ42 or amyloid-PET) were included. Plasma results were classified as true positive (TP), true negative (TN), FP, or FN, referencing amyloid PET and CSF ptau181/Aβ42 markers. Demographic, clinical, comorbidity, and laboratory variables were compared using univariate analyses. Multivariable logistic regression models were used to identify independent predictors of discordance.

Results: Among 706 participants (median age 70.0 [IQR 15.8] years; 54% male), most were in early symptomatic stages (CDR 0-0.5, 80.4%); median MMSE 25). Plasma p-tau217 was discordant with established AD biomarkers in 60 individuals (9%), with FN results more frequent than FP (6% vs 3%; p=0.0067). Discordant participants were older than concordant individuals (OR 1.05 per year, 95% CI 1.02–1.08; p<0.001), and more likely to have obstructive sleep apnea (OR 1.94, 95% CI 1.08–3.49). When stratified by amyloid status, FN results were associated with milder clinical stage (CDR, p<0.001) and higher MMSE scores (OR 1.20 per point, 95% CI 1.05–1.36) compared with TP participants. FN participants also demonstrated higher BMI (OR 1.11 per kg/m^2, 95% CI 1.03–1.20) and better renal function (higher eGFR, OR 1.03 per mL/min/1.73 m^2, 95% CI 1.01–1.05). In multivariable models, higher BMI (OR 1.14, 95% CI 1.03–1.25), higher eGFR (OR 1.05, 95% CI 1.02–1.08), and clinical stage remained independently associated with FN classification. FP results were associated with older age (OR 1.09 per year, 95% CI 1.03–1.15), thyroid disease (OR 4.41, 95% CI 1.36–14.3), lower eGFR (OR 0.93 per mL/min/1.73 m^2 increase, 95% CI 0.89–0.96) and more advanced disease stage (p=0.004). In multivariable models, lower eGFR remained independently associated with FP classification.

Conclusion: Plasma p-tau217 discordance with established AD biomarkers occurred in ∼9% of participants. Clinical stage and physiologic factors related to brain amyloid clearance, systemic clearance, and volume of distribution contributed to discordant results, highlighting patient subgroups in whom confirmatory testing may be important.

M194-B: Eligibility for Anti-Amyloid Therapies in Biomarker-Confirmed Atypical Alzheimer's Disease Phenotypes

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Background: Clinical trials of anti-amyloid therapies (AAT) for Alzheimer's disease (AD) primarily enrolled patients with mildly symptomatic, amnestic predominant presentations. The applicability of eligibility criteria to atypical AD phenotypes, including posterior cortical atrophy (PCA), logopenic variant primary progressive aphasia (lvPPA), dysexecutive AD (dAD) and corticobasal syndrome (CBS-AD), is unknown.

Methods: We conducted a retrospective eligibility analysis of suspected atypical AD patients evaluated at Mayo Clinic. Theoretical eligibility for AAT was assessed by applying inclusion criteria from landmark clinical trials (CLARITY-AD and TRAILBLAZER-ALZ2) and appropriate use criteria for lecanemab and donanemab, referencing clinical data available at initial assessment. Eligibility percentages and reasons for exclusion were compared across phenotypes.

Results: The cohort included 184 patients with biomarker-confirmed atypical AD: PCA (n=98, 53.3%), lvPPA (n=42, 22.8%), dAD (n=37, 20.1%) and CBS-AD (n=7, 3.8%). Functional impairment differed by phenotype ($p = 0.005$), with lvPPA more often diagnosed at the MCI/very mild stage (CDR 0.5; 71.4%), whereas PCA and dAD more frequently presented with mild dementia, although time from symptom onset to diagnosis did not differ ($p = 0.634$). Age at onset (p=0.039) and presentation (p<0.001) also differed, with lvPPA patients oldest (median age at onset, presentation: 63.1, 66.9 years) and dAD patients youngest (onset, presentation: 55.1, 57.3). MMSE scores differed (p=0.036), with lower scores in PCA and lvPPA (median 21 and 21, respectively) compared to CBS-AD (median 27). Depending on the eligibility framework applied, 70–85% of patients would not meet treatment criteria. Bedside cognitive thresholds were the primary drivers of ineligibility (50–67% of exclusions), despite most patients having early symptomatic disease (global CDR 0.5-1; 82%). Imaging-based exclusions (22–27%) and severity thresholds (moderate or severe dementia, 19-23%) were also frequent. Reasons for ineligibility were similar across phenotypes.

Conclusion: Most patients with atypical AD would not meet eligibility criteria for AAT, typically due to MMSE-based exclusion rather than measures of cognitive function. Eligibility rates are broadly similar across atypical phenotypes. These findings highlight the need to develop measures that accurately capture disease severity across phenotypes and reliably detect patients with early symptomatic presentations of atypical AD who may benefit from AAT.

M195: National Trends in Alzheimer's Disease and Arrhythmia Mortality Among Older Adults in the United States, 1999–2025

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Background: Alzheimer's disease (AD) is a leading cause of death among older adults and frequently coexists with cardiovascular conditions. Arrhythmia is frequently recorded as a contributing condition but remains underexplored in this population. National trends and demographic disparities in AD-arrhythmia co-mortality remain poorly characterized.

Methods: We analysed death certificate data from the CDC WONDER database (1999–2025) for adults aged 65 years and older. AD (ICD-10: G30) was designated the underlying cause of death and arrhythmia (ICD-10: I44–I49) as a contributing multiple cause of death. Age-adjusted mortality rates (AAMR) per 100,000 were calculated and stratified by sex, age group (65–74, 75–84, 85+ years), census region, urbanization status, race, and Hispanic ethnicity. Joinpoint regression was used to estimate annual percent change (APC) and average annual percent change (AAPC) with 95% confidence intervals.

Results: A total of 303,213 deaths were identified over the study period. AAMR approximately doubled from 14.63 (1999) to 28.65 (2025), with an overall AAPC of 2.35 (95% CI: 2.03–2.77; p<0.000001) and a significant post-2020 decline (APC: −3.14; p=0.023). Females accounted for 68.3% of deaths (n=207,166) and demonstrated a higher AAPC than males (2.49 vs 2.20; both p<0.000001). The 85+ age group exhibited the steepest rise (AAPC: 2.99; 95% CI: 2.64–3.43), with two significant surges in 1999–2005 (APC: +7.36) and 2013–2016 (APC: +10.32). Regionally, the West recorded the highest AAPC (3.72; 95% CI: 3.32–4.18) and the South the lowest (0.50; 95% CI: 0.12–1.00). Metro and non-metro areas showed comparable trends (AAPC: 3.72 vs 3.73). Among racial groups, Asian/Pacific Islander individuals had the steepest AAPC (3.84; 95% CI: 3.36–4.56), while Black individuals showed the sharpest post-2020 decline (APC: −4.79; p=0.021). Hispanic/Latino individuals demonstrated a higher AAPC than non-Hispanic individuals (3.57 vs 2.24; p<0.000001).

Conclusion: AD-arrhythmia co-mortality nearly doubled over 26 years, reflecting a growing and underrecognized cardiovascular burden in dementia-related death. Disproportionate rises among females, adults aged 85 and older, western regions, and Asian/Pacific Islander and Hispanic populations suggest structural inequities in cardiovascular monitoring beyond population aging alone. The post-2020 deceleration may reflect competing COVID-19 mortality, coding changes, or care disruptions, and should not be prematurely interpreted as clinical improvement. These findings support embedding routine arrhythmia surveillance within AD care frameworks and call for research into whether disparities stem from biological, access-related, or diagnostic factors.

M196: Differences in Functional Connectivity of the Basal Ganglia between Parkinson's Disease and Dementia with Lewy Bodies

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Background: Parkinson's Disease and Dementia with Lewy Bodies share α-synuclein pathology and a common prodromal sleep disorder, REM Sleep Behavior Disorder (RBD), yet they develop into distinct clinical diseases. Parkinson's Disease (PD) is primarily characterized by earlier, asymmetric, and more pronounced motor symptoms, while Dementia with Lewy Bodies (DLB) is characterized by milder parkinsonian symptoms along with cognitive and psychiatric impairment. The neural underpinnings of these diverging disease pathways remain poorly understood. This study investigates whether these diseases differ in basal ganglia functional connectivity. We assessed connectivity of the putamen, caudate, globus pallidus interna (GPi), and substantia nigra pars compacta (SNc) because of their central roles in both motor and cognition in PD and DLB.

Methods: MRI data were collected and preprocessed for 12 early-stage PD and 6 early-stage DLB participants. Using the CONN toolbox in MATLAB, seed-based functional connectivity analyses were performed on the four right-hemisphere basal ganglia seeds. For each seed, the mean BOLD time series across all voxels within the seeds were extracted and correlated with the rest of the brain to generate whole-brain functional connectivity maps. Functional connectivity analyses were conducted using a voxel-level threshold of $p < 0.05$ and a cluster-level threshold of $p < 0.01$.

Results: Results showed significantly greater connectivity in DLB vs PD between the putamen and frontal, temporal, parietal, and cerebellar regions. No connectivity differences were observed in the caudate or GPI. For the SNc, at a more relaxed cluster threshold ($p < 0.05$), results showed greater connectivity in PD compared to DLB between the SNc and posterior cortical regions.

Conclusion: These findings in a small pilot cohort suggest region-specific differences between PD and DLB, particularly in connectivity of the putamen. While preliminary, they suggest that functional connectivity differences in early-stage disease may contribute to the divergence in motor and cognitive symptoms observed as both diseases progress. Future studies with larger sample sizes are needed to further validate these findings and assess their utility in clinical settings.

M197: Young Cerebrospinal Fluid Induces Oligodendrocyte-Associated Transcriptomic Remodeling with Relevance to Alzheimer's Disease

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Background: Young cerebrospinal fluid (CSF) has been shown to enhance oligodendrogenesis and cognitive function in aged mice via Fgf17 (Iram et al., 2022). However, the broader transcriptomic effects of young CSF on the central nervous system and their relationship to neurodegenerative diseases such as Alzheimer's disease (AD) remain unclear. This study aimed to define transcriptional changes induced by young CSF and evaluate their relationship to AD-associated gene expression profiles, particularly whether

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young CSF induces programs that oppose disease-associated transcriptional states.

Methods: Bulk RNA-seq data from hippocampal tissue of aged mice treated with young CSF (n=7) and controls (n=8) were obtained from the NCBI SRA. Reads were processed using fastp and quantified with Salmon through Galaxy Bioinformatics. Gene-level counts were analyzed in R using DESeq2, with principal component analysis confirming group separation. Cell-type composition was estimated using BisqueRNA with Tabula Muris Senis reference data. Functional enrichment was assessed via Gene Set Enrichment Analysis (GSEA). For disease comparison, differential expression from a 5xFAD AD model (GSE161848) was generated using limma and intersected with the young CSF expression profile.

Results: Young CSF treatment resulted in a significant increase in oligodendrocyte proportions ($p = 0.02$) and produced targeted transcriptional remodeling, with 56 upregulated and 35 downregulated genes ($|log2FC| > 0.5$, $padj < 0.05$). The most significantly upregulated gene, Fgfbp3 ($log2FC = 1.04$, $padj = 2.24 \times 10^{-5}$), supports activation of FGF-associated signaling beyond previously described mechanisms. Pathway analysis revealed activation of programs associated with extracellular matrix remodeling, development, and myelination. Strikingly, cross-model comparison revealed a strong inverse alignment between young CSF and AD transcriptional signatures (Pearson $r = -0.90$, $p = 0.016$), suggesting that young CSF induces a system-level shift opposing disease-associated states. Within this, S1pr5 was significantly upregulated following young CSF treatment ($log2FC = 1.12$, $padj = 0.0157$) but downregulated in AD, implicating it as a potential mediator of oligodendrocyte-associated response. Protein kinase A-related genes exhibited opposing directional trends, further supporting pathway-level divergence.

Conclusion: These findings provide evidence that young CSF induces system-level transcriptional reprogramming toward a state opposing neurodegenerative pathology, rather than isolated gene-level changes. The identification of an inverse disease signature suggests that microenvironmental modulation may represent a viable strategy for shifting pathological states at the network level. S1pr5 emerges as a candidate regulator within this framework.

More broadly, this work reframes young CSF as a driver of coordinated transcriptional state transitions, offering a systems-level basis for developing multi-target therapeutic modalities in neurodegeneration.

M198: Interim Results from a Phase I Clinical Trial of AAV2-BDNF Gene Therapy in Alzheimer's Disease and Mild Cognitive Impairment

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Background: Brain Derived Neurotrophic Factor (BDNF) prevents neuronal death, activates neuronal function, restores synapses and improves learning and memory in animal models of Alzheimer's disease. Improved learning and memory after BDNF gene delivery to entorhinal/hippocampal circuits are observed in APP transgenic mice, aged rats and aged non-human primates. Based on the preceding evidence, we advanced AAV2-BDNF gene delivery to a Phase 1 clinical trial in patients with mild Alzheimer's disease dementia (AD) and Mild Cognitive Impairment due to AD (MCI).

Methods: 6 patients with mild AD and 6 patients with MCI have been recruited. Patients undergo MRI-guided injection of AAV2-BDNF into the entorhinal cortex and are monitored over 2 years with serial cognitive testing and FDG and Tau PET scans. As of this writing, 6 patients with mild AD have been treated and 3 patients with MCI.

Results: AD Cohort: At least 12 months of post-treatment data are available for 6 patients in the mild AD cohort. 1. PET Scans: All 6 subjects exhibit preservation or improvement in glucose metabolism on FDG PET in the entorhinal cortex. This persisted for 24 months in two subjects reaching two years. 2. Cognition: The first two AD subjects were treated in the Right entorhinal cortex only; the remaining 4 subjects were treated bilaterally. Among all 6 patients, the mean Delayed Memory score on the MMSE declined by 0.71 points over 12 months. Among the 4 patients treated bilaterally, there was no mean decline in the Delayed Memory component of the MMSE. One of the 4 bilaterally treated patients sustained a medical problem unrelated to gene therapy, and was the only bilaterally treated subject to exhibit cognitive decline; if this patient is excluded, the remaining 3 bilateral patients exhibited a mean 0.7 point improvement in memory over 12 months. The 4 bilaterally treated patients were ApoE 4/4, 2/4, 4/4 and 3/4. 3. Safety: One patient sustained an SAE due to study treatment: a small striatal infarct that rapidly resolved. MCI Cohort: Post-treatment followup for the MCI cohort is under 6 months. There have been no serious adverse events attributable to the treatment.

Conclusion: AAV2-BDNF gene therapy to the entorhinal cortex in mild AD has been safe to date, restores FDG-PET in the treated brain region, and appears to improve memory in some patients. BDNF gene therapy offers the potential to prevent neuronal loss, activate neuronal function and restore synapses, representing a possible neuro-restorative treatment for AD and MCI.

M199: Targeting Menopause Hormone Treatment (MHT) for the Brain

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California, Los Angeles, Los Angeles, CA, Christi Till, RN, University of California, Los Angeles, Los Angeles, CA

Background: Estrogens are neuroprotective, and menopause may contribute to neurodegeneration. Estriol preferentially binds estrogen receptor beta (ERβ) in brain to induce neuroprotection. Previously, oral estriol improved cognitive processing speed and reduced cerebral cortex atrophy at treatment month twelve in women with multiple sclerosis (MS).

Methods: Treatment with a blisterpack designed for healthy menopausal women which contains estriol (not estradiol) was assessed for its effect on cognitive domain-specific symptoms in a case series of twenty menopausal women (mean age 53.5 years). A preclinical model of cognitive deficits of menopause was then used to determine mechanisms of estriol mediated neuroprotection.

Results: In menopausal women at treatment month twelve, there were significant improvements in cognitive domains affected by menopause, namely brain fog, concentration, working memory, processing speed, verbal memory, and problem solving. In the preclinical model of cognitive deficits of menopause, ovariectomized midlife female mice had cognitive deficits, glial activation, and synaptic loss in dorsal hippocampus. Transcriptomics of astrocytes showed glucose utilization pathways as the most differentially expressed when comparing normal versus estrogen-deficient astrocytes in hippocampi of midlife female mice. Transcriptomics of hippocampi of menopausal women showed increased Enolase 1, a key protein in glucose utilization. At the protein level, astrocytes from estrogen-deficient midlife female mice had increased Enolase 1, and this increased Enolase 1 correlated with worse cognitive performance. Deletion of ERβ in astrocytes in midlife females recapitulated effects of ovariectomy at midlife. Conversely, treatment with either ERβ ligand or estriol reduced Enolase 1 expression in hippocampal astrocytes and improved cognitive performance.

Conclusion: This study suggests estriol treatment for cognitive symptoms of menopause. This warrants further investigation given the safe use of estriol in Europe and Asia for decades to reduce other menopausal symptoms.

M200: COVID-19 and Socioeconomic Disparities in Developmental Abnormalities Among US Children: Changes in Preexisting Trends

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Background: Childhood cognitive development is influenced by multiple social determinants, particularly socioeconomic status. The extent to which the COVID-19 pandemic altered preexisting socioeconomic disparities in cognitive developmental abnormalities in the United States remains unclear.

Methods: Using cross-sectional data from the National Survey of Children's Health from 2016 to 2024, based on parent-reported information, we evaluated temporal changes in rates of developmental diagnoses. Building age-aligned cohorts enabled comparisons across time. Children were grouped into age-range brackets across paired years (e.g., 2016 and 2020: ages 2-5; 2017 and 2021: ages 3-6). We compared 2016-2019 diagnosis rates (pre-COVID) to 2020-2024 diagnosis rates (post-COVID) to evaluate for potential changes. Developmental issue composite indexes, including Attention Deficit Disorders, Autism Spectrum Disorder, intellectual disability, developmental delay, and speech delays. Variables including sex, race/ethnicity, insurance status, parent education, primary household language, family structure, and federal poverty level were included in the survey weighted regression analyses.

Results: Adjusted analyses demonstrated that developmental issues maintained a higher prevalence among lower-income children. Children in households under 200% of the federal poverty level had approximately twice the chance of being diagnosed with cognitive developmental issues compared to children in households ≧400% of the federal poverty level. Relatively lower parental education level and non-traditional family structures were associated with higher odds of diagnoses; however, race and ethnicity, when evaluated independently, were not associated with higher rates of diagnoses post adjustment. Comparing pre- and post-2020 analyses, there were no significant overall differences in population-level trends. However, when comparing children in households ≧at 400% of the federal poverty level to those in households at 100% of the federal poverty level, those in households ≦at 100% of the federal poverty level had a significantly slower rate of increase in developmental disorder diagnoses post-2020 (OR 0.47, 95% CI 0.28–0.81, p=0.006). Children in single-mother households experienced significantly increased rates of diagnoses compared to children in two-parent households (OR 2.59, 95% CI 1.41–4.77, p=0.002).

Conclusion: Developmental issues persisted in both the pre- and post-2020 periods regarding income-based disparities. Although population-level trends post-2020 were not associated with significant changes, the relative trajectory varied by income group. These findings indicate that post-2020 changes may have shifted developmental risk, recognition, diagnosis, or access to healthcare without eliminating socioeconomic disparities.

M201*: 12-Month Results of a Randomized, Blinded Placebo-Controlled Trial of Shunting for Idiopathic NPH (PENS Trial)

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Background: Idiopathic normal pressure hydrocephalus (iNPH) is a disorder of neurologic gait impairment, urinary incontinence, cognitive impairment, and ventriculomegaly in individuals ≥60 years. The PENS trial, a double-blind, randomized, placebo-controlled study of shunting in iNPH, showed that gait velocity was significantly improved at 3 months in the Open shunt group and unchanged in the Placebo group (NEJM 2025; 393:2198-2209). We present 12-month outcomes of all symptom domains with open shunt condition for all participants.

Methods: 99 participants selected for surgery according to the International iNPH Guidelines were randomized to Open or Placebo setting with a shunt valve that permits blinded non-invasive setting adjustment. The Placebo and Open shunt groups were combined for analysis. The primary outcome is gait velocity. Secondary outcomes include: 1) Gait: Tinetti Gait and Balance Assessment, % of participants reporting falls; 2) Cognition and Funtional: MoCA, SDMT, NIH Toolbox Flanker, and Dimensional Change Card Sort, Beck Depression Inventory II, quality of life (EQ-5D-5L-VAS), Lawton ADL/IADL, Modified Rankin Scale (mRS); 3) Bladder Control: Overactive Bladder Questionnaire Short Form (OABQsf); and 4) Complications. Evaluations occurred at Baseline, 3, 6, and 12 months of open shunt condition for outcomes, or from time of surgery for complications.

Results: Gait velocity showed sustained improvement: Baseline=0.85 ± 0.28 m/s; 12 Months=1.09 ± 0.33 m/s. Compared to Baseline, at 12 months improvement was seen in: Gait velocity by 0.26 ± 0.24 m/s; Tinetti Total by 1.76 ± 2.99; MoCA by 1.88 ± 3.16; OABQsf by -3.13 ± 6.25; and EQ-5D-5L-VAS by 10.37 ± 21.36 ($p<0.001$ for all). 92% of participants responded they would have shunt surgery again. Participants reporting falls declined by nearly half: 3 months=35.3%; 12 months=18.2%. All other gait, cognitive and functional outcomes were significantly improved at 12 months. Subdural hematoma (SDH) requiring surgery: 0-3 months post-op=3 (3%); 4-12 months post op=0. SDH requiring no action or only a shunt setting change: 0-3 months post op=4 (4%); 4-12 months post op=4 (4%).

Conclusion: The 12-month results of the PENS trial of shunting for iNPH suggest sustained, clinically meaningful improvements in all symptom domains: 1) gait velocity, measures of gait and balance, and % of participants reporting falls; 2) measures of cognition, functional status, and quality of life; and 3) bladder control. The rate of serious complications was low, and over 90% of participants would have surgery again, suggesting a favorable 12-month risk/benefit profile for shunting in iNPH. NIH

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M202: Secondary Progression in Alzheimer Dementia after Achieving Treatment-Related Amyloid Clearance - a Case Report

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Background: After 2023 when the FDA-approved drugs (lecanemab and donanemab) are available for clinical application, many patients with early-stage Alzheimer's disease have achieved treatment-related amyloid clearance (TRAC) by completion of 18-month treatment protocol. Yet, long-term benefits of these drugs are not adequately investigated. For this report, detailed clinico-neuropathological study regarding a case of phase 2 drug trial of Donanemab is presented to explain secondary progression after receiving the anti-amyloid therapy.

Methods: The clinical data of the subject were reviewed in the electronic medical record system. A post-mortem brain autopsy report and amyloid tracer brain PET scans were studied for this case report.

Results: A 77-year-old R-handed woman with16-year education sought for consultation regarding 2-year history of short-term memory loss and difficulty driving. The diagnostic work-up concluded diagnosis of mild cognitive impairment (MCI). she started on donepezil for treatment. In 2 years, her cognitive symptoms deteriorated with MMSE scores declining from 24 to 19. Her diagnosis converted from MCI to mild dementia. She then received add-on drug memantine and was enrolled into the phase 2 drug study of donanemab (2019-2021). Her clinical dementia rating scale global score was 1 and MMSE score was 22 when study ended. Her amyloid tracer - florbetapir brain PET scan revealed positive results before she received of scheduled donanemab infusions. Two follow-up amyloid brain PET scans (12 months apart) were obtained; both demonstrated complete clearance of amyloid signals. Later on, her daily cognitive function was stable and independent for two years. Subsequently she developed cognitive deterioration into advanced dementia in 3 years. The post-mortem neuropathological examination demonstrated only few neuritic amyloid plagues in hippocampus, entorhinal cortex, amygdala and in occipital cortices. Tau-positive neurofibrillary tangles and neuropil threads were abundantly found in hippocampus, entorhinal cortex, amygdala, thalamus, basal ganglia and nucleus basalis. Surprisingly, alpha-synuclein-positive Lewy bodes were detected brain stem nuclei, amygdala, hippocampus and prefrontal cortices. TDP-43 positive cytoplasmic inclusions and neurites were discovered in amygdala and hippocampus; the distribution of TDP-43 pathology can fulfill diagnostic criteria of limbic-predominant age-related TDP-43 encephalopathy (LATE-NC) stage 2. Finally, the tau-positive granular structures with ballooned neurons were found in amygdala and hippocampus; these features fit diagnostic criteria of argyrophilic grand disease.

Conclusion: This case illustrates the complexities of age-related neurodegenerative changes even after receiving anti-

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amyloid immunotherapy and achieving TRAC. Amygdala is the critical center of developing multiple neurodegenerative pathologies.

HEADACHE AND PAIN

M203-K: Clinical and Network Predictors of Response to Motor Cortex repetitive Transcranial Magnetic Stimulation (rTMS) for Trigeminal Neuropathic Pain: A Randomized Controlled Trial

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Background: Trigeminal neuropathic pain (TNP) is notoriously severe, debilitating, and often refractory to conventional treatments. Repetitive transcranial magnetic stimulation (rTMS) is a promising non-invasive treatment modality that uses focused magnetic pulses to modulate brain activity. Although rTMS is FDA approved for depression and obsessive-compulsive disorder and is widely used in Europe for neuropathic pain, its role in pain management remains experimental in the United States. Prior studies indicate that high frequency (≥10 Hz) rTMS (HF-rTMS) targeting the primary motor cortex (M1) contralateral to pain is effective for neuropathic pain, but treatment responses are variable and analgesic mechanisms remain poorly understood. To evaluate the efficacy of HF-rTMS and identify predictors of treatment response, we conducted a pilot randomized controlled trial comparing HF-rTMS to active-control low-frequency (1 Hz) rTMS (LF-rTMS) in patients with TNP.

Methods: We conducted a randomized parallel-group trial in adults aged 18–80 years with unilateral neuropathic facial pain. Single-pulse TMS was used to identify the abductor pollicis brevis motor hotspot contralateral to pain and determine resting motor threshold (RMT). Neuronavigation software was used to identify and register the individualized M1 treatment target for precise stimulation and extraction of neural data. Participants were randomized 1:1 to HF-rTMS (10 Hz, 3,000 pulses/session, 30,000 pulses total) or LF-rTMS (1 Hz, 300 pulses/session, 3,000 pulses total) delivered at 90% RMT for 10 consecutive weekdays. Participants underwent magnetic resonance imaging (MRI) before treatment and after the final stimulation session, including structural imaging and resting-state functional MRI (rs-fMRI). The primary endpoint was change in visual analog scale (VAS) pain intensity after 10 treatment days. Secondary endpoints included validated measures of pain, mood, disability, and sleep, collected through 6-month follow-up. Group differences were evaluated using constrained longitudinal mixed-effects models. Functional connectivity and graph-theoretical measures were derived from preprocessed and denoised rs-fMRI data using subject-specific whole-brain network parcellations. Electric-field modeling was performed using SimNIBS to identify the stimulated M1 target for each participant.

Results: Thirty participants completed all study procedures (HF-rTMS n=16; LF-rTMS n=14). Groups were comparable at baseline with respect to demographic, clinical, and TMS-related variables. Blinding integrity was preserved, with 54.5% of participants receiving HF-rTMS and 75.0% receiving LF-rTMS believing they had received active stimulation. HF-rTMS produced significantly greater reductions in pain intensity than LF-rTMS at the primary endpoint after 10 treatment days (mean difference = -1.57/10 VAS points, t=-2.66, p=0.008). Significant between-group differences were also observed at 1-week follow-up (mean difference = - 2.29/10, t=-3.93, p<0.001) and 1-month follow-up (mean difference = -1.65/10, t=-2.50, p=0.012). At 1 week, 50% of HF-rTMS participants achieved responder status (≥30% pain reduction) compared with 8% of LF-rTMS participants, while 38% of HF-rTMS participants achieved very meaningful relief (>50% pain reduction) compared with 0% of LF-rTMS participants. Similar trends were observed for pain disability measures. Adverse effects were mild and included transient scalp discomfort, fatigue, and lightheadedness. Multiple regression analyses identified several predictors of treatment response. A significant interaction between stimulation intensity and treatment group indicated that higher stimulation intensities predicted greater pain relief following HF-rTMS but not LF-rTMS (β=4.18, t=3.00, p=0.007). Current gabapentinoid use was associated with reduced treatment benefit, with a significant frequency-by-gabapentinoid interaction demonstrating lower likelihood of response among patients taking gabapentin or pregabalin (β=-54, t=-2.20, p=0.038). Baseline graph-theoretical analyses revealed a significant interaction between M1 node strength and treatment group (β=0.83, t=2.60, p=0.017), such that HF-rTMS targeting highly connected M1 regions predicted greater improvement whereas LF-rTMS targeting highly connected M1 regions predicted worse outcomes.

Incorporating M1 node strength into a multivariate model containing age, sex, baseline pain, stimulation intensity, and gabapentinoid use increased explained variance in pain relief from 49% to 62% (ΔR^2=13%, p=0.049).

Conclusions: Ten days of HF-rTMS targeting M1 was safe, well tolerated, and produced clinically meaningful reductions in pain relative to active-control LF-rTMS in patients with trigeminal neuropathic pain. Both treatment-related factors (stimulation intensity, medication use) and network-level characteristics of the stimulated M1 target predicted clinical outcomes. These findings support a network-based mechanism of analgesia and suggest that individualized targeting strategies based on brain connectivity, perhaps combined with optimized TMS dosing and concomitant medication strategies, may improve the

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efficacy of rTMS for neuropathic pain. Ongoing analyses are evaluating longitudinal effects of rTMS on whole-brain network organization and their relationship to clinical outcomes.

M204: Prevalence and Clinical Correlates of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in Adults with Celiac Disease: A Cross-Sectional Study

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Background: Celiac Disease is an immune-mediated disorder characterized by a wide range of gastrointestinal and extraintestinal manifestations. Neurological symptoms are considered common in celiac disease patients and unexplained fatigue is a frequently reported complaint. Chronic fatigue syndrome is also known as Myalgic encephalomyelitis; it is a chronic neurological disorder that is characterized by chronic unexplained fatigue. The aim of our study was to estimate the prevalence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), among adults with clinician-confirmed celiac disease, and to identify associated clinical factors including fatigue severity, quality of life, and adherence to a gluten-free diet.

Methods: A cross-sectional study was conducted between July and August 2025, including 629 adults with biopsy- and/or serology reports provided by Jordanian board-certified gastroenterologists. Participants were recruited from gastroenterology clinics at Jordan University of Science and Technology and five other celiac disease organizations in Jordan. ME/CFS classification was performed according to the IOM/NAM (2015) and NICE (NG206) criteria using a structured, validated questionnaire. Fatigue severity was assessed using the Fatigue Assessment Scale (FAS), and quality of life was evaluated using the SF-36 Health Survey. Multivariable regression and comparative analyses were performed to identify factors associated with fatigue burden and reduced quality of life.

Results: Among 629 adults with celiac disease (72.5% female; predominantly aged 30–44 years), over 60% reported persistent physical or mental fatigue. The mean Fatigue Assessment Scale score was 29.31 $\pm$ 8.91, indicating a high fatigue burden. Severe fatigue manifestations were common, including persistent tiredness (63.8%) and rapid fatigability (61.0%). Quality of life was markedly reduced, with low physical (25.34 $\pm$ 6.88) and mental (18.73 $\pm$ 7.26) component scores. In multivariable analysis, female sex was significantly associated with severe fatigue (OR 3.20, 95% CI 1.75–5.82, $p < 0.001$). Younger age groups also showed higher odds of severe fatigue, particularly those aged 18–29 years (OR 5.22, 95% CI 1.18–23.06, $p = 0.029$) and 30–44 years (OR 6.31, 95% CI 1.22–32.62, $p = 0.028$). No other variables showed consistent independent associations.

Conclusion: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome is highly prevalent in adults with celiac disease and is associated with significant functional impairment, suggesting a potential shared neuroimmune and inflammatory basis. Further studies are needed to better elucidate the relationship between ME/CFS and systemic inflammatory diseases, possibly including the role of anti-inflammatory therapies, which may help guide more targeted and mechanism-based management strategies.

M205: Burden of Migraine and Its Impact on Quality of Life in Adults with Celiac Disease: A Cross-Sectional Study

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Background: Celiac disease is a common immune-mediated enteropathy that usually has several non-gastroenterological manifestations. Neurological manifestations, including migraine, are increasingly recognized among patients with celiac disease. This study aimed to assess the prevalence and clinical characteristics of migraine and its impact on quality of life among adults with celiac disease in Jordan.

Methods: This cross-sectional study included 629 adults with celiac disease whose diagnoses were confirmed by biopsy and/or serology reports provided by Jordanian board-certified gastroenterologists. Patients were recruited from gastroenterology clinics at Jordan University of Science and Technology-affiliated hospitals and the Celiac Care Providers Society between July and August 2025. Participants completed a structured questionnaire that assessed the demographic data, disease history, comorbidities, and headache characteristics. Migraine screening was performed using the ID-Migraine™ tool, and headache-related disability was assessed using the Migraine Disability Assessment (MIDAS). Multivariable analyses were performed to identify factors associated with headache burden.

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Results: Among 629 adults with Celiac Disease (72.5% female; predominantly aged 30–44 years), the prevalence of clinically diagnosed migraine was 8.6% (n=54). Headache phenotypes were predominantly throbbing (74.2%) and bilateral (72.1%), with frequent associated features including photophobia (71.4%) and nausea (68.8%). Aura was reported in 5.9% of participants. Significant headache-related disability was observed in 78.6% of affected individuals. On HIT-6 classification, 70.4% demonstrated severe impact, with a mean score of 62.0 ± 9.02. Strict adherence to a gluten-free diet was reported in 57.7%, while 5.9% reported headache episodes temporally associated with gluten exposure. In multivariable logistic regression, female sex was independently associated with higher headache impact scores (OR 1.78, 95% CI 1.22–2.61, p = 0.003), and younger age showed a significant inverse association with headache burden (OR 0.64 per increasing age category, 95% CI 0.48–0.85, p = 0.002). No other variables retained independent significance in the final model.

Conclusion: Migraine and migraine-like headache disorders are common in adults with Celiac Disease and are associated with significant functional burden. These findings support a potential neuroinflammatory basis for migraine, possibly driven by gluten-related immune activation and systemic inflammation. Further studies are needed to clarify inflammatory mechanisms and evaluate the effects of dietary and immune-targeted interventions on headache outcomes.

M206: Safety and Efficacy of Atogepant for Migraine Prophylaxis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Migraines affect approximately 15% of the global population and rank among the leading causes of disability worldwide. Atogepant, an oral CGRP receptor antagonist approved for both episodic and chronic migraine prevention, has an expanding evidence base across doses and migraine subtypes. Comparative efficacy by dosing regimen and migraine type remains incompletely characterized across trials.

Methods: A PRISMA-compliant systematic search of PubMed, Cochrane Library, and Google Scholar (through December 2024) identified RCTs evaluating atogepant for migraine prevention. Eight RCTs comprising 5,906 participants (atogepant n=2,836; placebo n=3,070) were included. Doses of 10 mg, 30 mg, and 60 mg once daily or twice daily were evaluated over 12 weeks using RevMan 5.4 random-effects models. Risk of bias was assessed using the Cochrane RoB 2 tool. The primary outcome was change from baseline in monthly migraine days (MMDs); secondary outcomes included monthly headache days (MHDs), acute medication use days, ≥50% responder rates, and patient-reported outcomes (HIT-6, MSQ Role Function–Restrictive, AIM-D).

Results: Chronic migraine showed consistently greater benefit than episodic migraine across MMDs (MD −2.00 vs. −1.24 days; p=0.0003), MHDs (MD −2.23 vs. −1.47; p=0.0004), and acute medication use (MD −2.30 vs. −1.37; p<0.00001). Overall, atogepant significantly reduced MMDs (MD −1.53; 95% CI −1.79 to −1.27; p<0.00001; I^2=46%), MHDs (MD −1.73; 95% CI −1.96 to −1.51; p<0.00001), and acute medication use (MD −1.74; 95% CI −1.99 to −1.48; p<0.00001), and increased the likelihood of ≥50% MMD reduction by 76% (RR 1.76; 95% CI 1.57–1.98). MSQ and AIM-D domains improved significantly across groups; HIT-6 benefit was confined to chronic migraine (MD −3.12; p<0.00001). No dose-response gradient was identified. Total and treatment-related adverse events were modestly elevated (RR 1.10 and 1.66, respectively); serious adverse events were not significantly increased (RR 1.32; p=0.30). Elevated total adverse events were observed only with the 30 mg twice-daily regimen.

Conclusion: Atogepant is efficacious for both episodic and chronic migraine prevention, with consistently greater benefit in chronic migraine. The absence of a dose-response gradient and the favorable safety profile of once-daily regimens (30 mg or 60 mg) support their use as the preferred dosing strategy. These findings provide a synthesis of the current evidence base to guide clinical decision-making and future trial design.

M207-LB: Neuralgia due to Bifid Mandibular Condyle: a Rare Condition Caused by an Extremely Rare Disorder

Presenting Author(s): *Hossein Ansari, La Jolla, CA*

Background: Bifid mandibular condyle (BMC) is an exceedingly rare anatomical anomaly that is often asymptomatic, although it may occasionally present with pain, clicking, or restricted mandibular movement due to temporomandibular joint (TMJ) ankylosis. To our knowledge, no prior cases of neuralgic facial pain associated with BMC have been reported. We present the first case of trigeminal neuralgia (TN) associated with BMC.

Methods: Brain MRI, dedicated trigeminal protocol MRI, and an extensive autoimmune workup were unremarkable. A trial of indomethacin up to 225 mg daily, undertaken to exclude hemicrania continua, was ineffective. Physical examination revealed marked tenderness over the right mandibular condyle that reproducibly triggered pain attacks. Subsequent facial bone CT demonstrated a right-sided BMC.

Results: The patient's symptoms fulfilled diagnostic criteria for trigeminal neuralgia with concomitant continuous pain based on the International Classification of Headache Disorders, 3rd edition (ICHD-3). The presence of an ipsilateral BMC corresponding to the side of symptom provocation on examination suggests the finding was unlikely to be incidental. BMC is not currently recognized as a cause of trigeminal neuralgia in the ICHD-3. Our literature review identified no

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previous reports of TN associated with BMC. Given the neuralgic characteristics and classic TN triggers, the pain could not be fully explained by TMJ-related pathology alone. This case, therefore, represents the first reported association between TN and BMC. It is possible that some cases currently classified as "idiopathic" TN may be related to this rare anatomical anomaly; however, additional cases are needed to establish a causal relationship.

Conclusion: 26 years old woman with a history of chronic migraine for over 9 years, controlled with a botulinum toxin treatment, presented with right-sided facial pain, which started about 18 months ago. Her pain is sharp and electric shock-like, which localizes to the right mandibular nerve (V3) distribution. Each pain attack lasts for a few seconds. In addition, she reports constant dull pain in the same distribution. The pain attacks trigger by touching, chewing, brushing teeth, talking, wind, and barometric pressure. She denies numbness or tingling in the face and no associated autonomic features.

M208-LB*: Patient-Similarity Graph Neural Networks Stratify Treatment Escalation in Pediatric Headache

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Background: Pediatric headache encompass overlapping clinical phenotypes in which diagnostic labels may not fully capture symptom burden or management complexity. In real-world practice, some patients require escalation beyond simple analgesic or supportive therapy, yet the symptom relationships associated with higher-intensity pharmacological management remain poorly defined. Graph neural networks (GNN) may provide a clinically relevant framework to model relational symptom structure and identify phenotypes associated with treatment escalation.

Methods: A total of 321 patients were included, 58.5% were females with a mean (SD) age 12.41(3.39). Treatment escalation was observed in 70 patients (21.8%). The patient-similarity graph model classified treatment escalation with an AUC of 0.78 (95%CI: 0.62–0.91), balanced accuracy of 0.73 (95%CI: 0.61–0.84), F1-score of 0.53 (95%CI: 0.31–0.70), and recall of 0.91 (95%CI: 0.70–1.00). Precision was modest at 0.37 (95%CI: 0.19–0.56), indicating a sensitivity-oriented classification pattern. The confusion matrix showed that the model identified 10 of 11 patients who received treatment escalation in the test set, while generating false positives among non-escalated patients. SHAP-based interpretability of the baseline model highlighted cervicalgia, nausea, photophobia, cervical contracture, and phonophobia as the most influential symptom-level contributors. Treatment-related features included both classical migraine-associated symptoms and cervical/sensory manifestations, supporting phenotypic heterogeneity beyond diagnostic labels.

Results: Patient-similarity GNN identified treatment-escalation phenotypes in pediatric headache, suggesting that relational symptom structure may capture clinically meaningful management complexity beyond diagnostic labels. This exploratory framework may support phenotype-informed risk stratification in pediatric headache, although external validation in larger, multicenter cohorts is required before clinical implementation.

Conclusion: We conducted a retrospective study of 321 pediatric patients evaluated for headache between 2023 and 2024 at a hospital in Amazonas, Peru. Binary headache-related symptoms were used to construct a patient-similarity graph using Jaccard similarity, with patients represented as nodes and edges reflecting shared symptom profiles above a predefined threshold. Node features encoded symptom presence or absence. The primary outcome was treatment escalation, defined as prescription of any of the following: ergotamine, propranolol, valproate, prednisone, dexamethasone, or tramadol, compared with simple analgesic, supportive, or no pharmacological treatment. A graph convolutional network (GCN) was trained using a stratified train/validation/test split with class weighting to account for outcome imbalance. Performance was evaluated on a held-out test set using AUC, balanced accuracy, F1-score, recall, precision, and bootstrap-derived 95% confidence intervals. SHAP analysis of a logistic regression baseline was performed to explore symptom-level contributions to treatment classification.

M209: Systematic Review of Post-Surgical Opioid-Induced Hyperalgesia: Neurological Consequences of Persistent Opioid Prescriptions

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Background: Opioid-induced hyperalgesia (OIH) is a paradoxical phenomenon where opioid exposure increases pain sensitivity. Existing reviews emphasize intraoperative opioid strategies, leaving limited synthesis on whether opioid prescribing at hospital discharge relates to OIH or downstream opioid harms. We aim to evaluate whether higher opioid prescribing at discharge versus lower exposure or opioid-sparing regimens is associated with (1) OIH or (2) clinically relevant downstream outcomes, including pain control efficacy, refill/unplanned care for pain, patient-reported outcomes, and new persistent opioid use 90−180 days post-operation.

Methods: We conducted a systematic literature review that included peer-reviewed, U.S.-based English-language quantitative studies (published in 2020−2025; data collected ≥2015) of adults discharged after surgery with documented opioid prescribing at discharge. The primary comparison was higher versus lower/limited opioid exposure at discharge, defined by total prescribed MME, days' supply, or dose intensity; opioid-sparing/zero-opioid discharge pathways were included when available. Given heterogeneity in exposure

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definitions and study designs, findings were synthesized using a structured narrative, direction-of-effect approach.

Results: Results were summarized overall and within prespecified strata: Open Surgery versus Minimally Invasive Surgery, organ system categories, and an OB/GYN-only sensitivity analysis. A total of eighteen studies met the inclusion criteria; however, only one study with a sample size of 22 presented direct clinical measurement of OIH. In contrast, the most consistent signals were observed for downstream outcomes: higher discharge opioid exposure was not associated with better pain control (three studies, sample size 20,985) and was more often associated with increased refills/unplanned care for pain (four studies, sample size 5,325), worse patient-reported outcomes (two studies, sample size 20,431), and increased new persistent opioid use 90−180 days post-operation (six studies, sample size 88,125) among opioid-naïve and previously exposed patients.

Conclusion: Direct evidence linking discharge opioid prescribing to clinically measured OIH remains limited. However, higher opioid prescribing at discharge was not associated with better pain outcomes and was more often associated with adverse downstream outcomes, including persistent opioid use. These findings support individualized opioid stewardship at hospital discharge and highlight the need for future research clarifying the relationship between discharge prescribing and OIH.

M210: Psychiatric and Functional Burden of Neuropathic Pain Components in Chronic Low Back Pain: A Registry-Based Analysis

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Background: Low back pain (LBP) is the leading cause of disability worldwide and is frequently accompanied by psychological distress. Among individuals with CLBP, those with neuropathic pain often experience greater symptom severity and poorer treatment outcomes. PainDETECT is a validated screening tool (0–38) for identifying neuropathic pain while the Patient-Reported Outcomes Measurement Information System (PROMIS) quantifies psychosocial and functional domains using standardized T-scores in a referent population (mean = 50, SD = 10).

Methods: This retrospective analysis utilized patient-reported outcomes from the University of Pittsburgh's Patient Outcomes Repository for Treatment (PORT) registry, collected via the Collaborative Health Outcomes Information Registry (CHOIR). The cohort included 16,783 adults reporting LBP at an initial or standalone visit with valid PainDETECT scores. Participants were categorized as likely neuropathic (PainDETECT ≥ 19), intermediate (12< PainDETECT <19), and unlikely neuropathic (PainDETECT ≤ 12). Groups were compared across PROMIS domains of anxiety, depression, sleep disturbance, physical function, and positive outlook using ANOVA with post-hoc Tukey HSD. These results were then adjusted for social and demographic covariates known in literature to have associations with neuropathic pain using ANCOVA (age, sex, race, marital status, education, insurance, tobacco, alcohol, drug use, and BMI).

Results: Patients with likely neuropathic pain (vs intermediate vs unlikely neuropathic pain) reported higher mean PROMIS scores for depression (59.1 vs 54.8 vs 51.6), anxiety (60.4 vs 56.2 vs 52.7), and sleep disturbance (64.1 vs 59.4 vs 55.8), and lower scores for physical function (32.4 vs 35.4 vs 36.9) and positive outlook (46.5 vs 48.6 vs 50.5; all $p < 0.001$). In multivariable linear regression models adjusting for demographic, clinical, and psychosocial covariates, neuropathic pain status remained an independent predictor of greater psychological distress (β range = +2.6 to +6.6) and poorer functioning (β range = −3.2 to −5.8).

Conclusion: Individuals with CLBP with neuropathic pain components exhibit significantly greater psychological distress, sleep disruption, and functional impairment compared to those without neuropathic pain components, even after adjusting for demographics, socioeconomic factors, substance use, and BMI. These findings highlight the need for integrated treatment targeting both CLBP with neuropathic pain components as well as their psychosocial comorbidities.

M211: Safety and Efficacy of Atogepant for Migraine Prophylaxis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Migraines affect approximately 15% of the global population and are a leading cause of disability worldwide. Atogepant, an oral CGRP receptor antagonist, has emerged as a promising preventive option. This meta-analysis evaluates its efficacy and safety stratified by migraine type and dosing regimen.

Methods: A PRISMA-compliant systematic search of PubMed, Cochrane Library, and Google Scholar identified RCTs evaluating atogepant for migraine prevention. Eight RCTs comprising 5,906 participants (atogepant n=2,836; placebo n=3,070) were included. Doses of 10 mg, 30 mg, and 60 mg once daily (OD) or twice daily (BD) were evaluated over 12 weeks using RevMan 5.4 random-effects models. The primary outcome was change from baseline in monthly migraine days (MMDs). Secondary outcomes included monthly headache days (MHDs), acute medication use days, ≥50% responder rates, and patient-reported outcomes (HIT-6, MSQ Role Function–Restrictive, AIM-D Performance of Daily Activities and Physical Impairment domains). Safety outcomes included total, treatment-related, and serious treatment-emergent adverse events (AEs), as well as AEs leading to discontinuation.

Results: Atogepant significantly reduced MMDs (MD −1.53, 95% CI −1.79 to −1.27; p<0.00001; I^2=46%), MHDs (MD −1.73, 95% CI −1.96 to −1.51; p<0.00001; I^2=14%), and acute medication use (MD −1.74, 95% CI −1.99 to −1.48; p<0.00001) versus placebo, and increased the likelihood of ≥50% MMD reduction by 76% (RR 1.76, 95% CI 1.57–1.98; p<0.00001). Chronic migraine showed greater reductions than episodic migraine in MMDs (2.00 vs 1.24 days; p=0.0003), MHDs (2.23 vs 1.47 days; p=0.0004), and acute medication use (2.30 vs 1.37 days; p<0.00001). MSQ and both AIM-D domains improved significantly (p<0.00001); HIT-6 benefit was confined to chronic migraine (MD −3.12; p<0.00001). No dose-response gradient was identified. Total AEs (RR 1.10; p=0.01) and treatment-related AEs (RR 1.66; p<0.00001) were modestly elevated; serious AEs were not significantly increased (RR 1.32; p=0.30). Only the 30 mg BD regimen showed a statistically significant rise in total AEs.

Conclusion: Atogepant is an efficacious oral preventive for both episodic and chronic migraine, with consistently greater benefit in chronic migraine. Once-daily dosing (30 mg or 60 mg OD) offers comparable efficacy with a more favorable safety profile, reinforcing atogepant's role as a first-line preventive option.

M212: Crisugabalin for Neuropathic Pain in Neuromyelitis Optica Spectrum Disorders: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial (TERMINATOR)

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Background: NMOSD is an autoimmune demyelinating disease with high relapse and disability rates. yet no unified recommendation exists for managing its common complications, including chronic neuropathic pain, paresthesia, and painful spasms. Crisugabalin is a China-developed innovative drug that reduces neuronal excitability to achieve analgesia and improve sleep. It has obtained indications for diabetic peripheral neuropathic pain (DPNP) and postherpetic neuralgia (PHN) in China, with central neuropathic pain under review. This study aims to provide preliminary clinical data to address the therapeutic gap in NMOSD-related neuropathic pain.

Methods: This prospective, randomized, double-blind, placebo-controlled exploratory trial enrolls adult NMOSD patients with neuropathic pain (Douleur Neuropathique 4 Questions [DN4] ≥ 4, Numeric Rating Scale [NRS] ≥ 4). Patients are randomized 1:1 to receive Crisugabalin 20 mg twice daily (BID) or placebo for 2 weeks (double-blind period), followed by an 8-week open-label extension period (Crisugabalin 20–40 mg BID). For Phase 1 (2-week), the primary endpoint is change from baseline in NRS pain score at week 2; secondary endpoints
include NRS responder rates (≥30% and ≥50% reduction), change in Short-Form McGill Pain Questionnaire (SF-MPQ) score, and improvements in sleep quality (Daily Sleep Interference Scale [DSIS]), spasm frequency (Penn Spasm Frequency Scale [PSFS]), anxiety (Hamilton Anxiety Rating Scale [HAMA]), and depression (Hamilton Depression Rating Scale [HAMD]). For Phase 2 (10-week), the primary endpoint is change from baseline in NRS pain score at week 10, and secondary endpoints include all Phase 1 secondary endpoints plus Patient Global Impression of Change (PGIC) (numbness/paresthesia) and quality of life using the EuroQol 5-Dimension 5-Level (EQ-5D-5L). Safety endpoints include treatment-emergent adverse events (TEAEs) and incidence. A total of 110 patients are planned (80% power, $\alpha = 0.025$, one-sided). Rescue medication (acetaminophen) is permitted.

Results: The study is ongoing (planned period: November 2025 – December 2027). Outcomes will compare Crisugabalin versus placebo at week 2 and week 10. Safety endpoints include TEAEs.

Conclusion: This first randomized controlled trial of Crisugabalin in NMOSD-related neuropathic pain will provide preliminary evidence on its efficacy and safety, addressing a critical unmet need for symptomatic management in this population.

M214: GLP-1 Receptor Agonists in Migraine: Differential Clinical Response in an Expanded Single-Center Retrospective Cohort

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Background: Migraine is a disabling neurologic disorder characterized by severe, unilateral, throbbing pain lasting 4-72 hours accompanied by nausea, vomiting, and/or sensitivity to light, sound or movement (IHS, 2018), and a leading cause of Emergency Department visits in the United States (Cortel-LeBlanc et al., 2023). Affecting an estimated 40 million Americans (Cohen et al., 2024), migraine disease causes significant disability across work, family, and social domains (Buse et al., 2019). While the complete pathophysiology of migraine remains elusive (Zanandrea and Colombo, 2025), growing evidence implicates systemic inflammation and metabolic dysregulation as key contributors, with obesity-related cytokines and adipokines promoting trigeminal nociceptor sensitization and central nervous system hyperexcitability. Obesity, particularly abdominal obesity, is a state of chronic low-grade inflammation that may amplify migraine through overlapping neuroimmune and neuroendocrine pathways (Peterlin et al., 2010; Winter et al., 2012). Adipose tissue functions as an active endocrine organ, releasing cytokines and adipokines such as leptin and adiponectin, which interact with serotonergic (Spekker and Nagy-Grócz, 2023) and hypothalamic (Stanyer et al., 2024) signaling systems implicated in migraine generation (Cavestro, 2025). Migraine prevalence, frequency, and severity is linked to obesity in adults (Ornello et al., 2015), and approximately 70% of the US adult population is classified as overweight or obese (Ogden et al., 2014). Weight loss is associated with reductions in migraine frequency and severity (Agbetou and Adoukonou, 2022). GLP-1 receptor agonists offer a new opportunity to achieve sustainable weight loss and metabolic improvement in this population (Popoviciu et al., 2023). We hypothesized that GLP-1 agonist therapy may reduce headache burden in high-frequency migraineurs with obesity.

Methods: This retrospective review of electronic medical records included 26* migraine patients prescribed GLP-1 receptor agonists for metabolic indications. Patients were selected if they had received GLP-1 therapy for ≥1 year, with Migraine Disability Assessment (MIDAS) scores extracted from visits one year before and after prescription.

Results: Mean reductions in headache days (7.0 ± 25.7/3 months) and MIDAS scores (3.3 ± 30.1) were not statistically significant (p=0.599, p=0.493). Outcomes varied markedly (−83 to +39 days; −73 to +55 MIDAS). Six patients (23%, N=26) achieved ≥30-day reductions, and 13 patients (50%) showed MIDAS improvement. Note: 12 additional patients enrolled, pending analysis: results to be presented@ANA.

Conclusion: GLP-1 therapy did not significantly reduce migraine outcomes overall, but responses varied widely, including dramatic improvements in some patients. This variability suggests potential migraine subtypes with differential GLP-1 responsiveness. Larger prospective studies are needed to identify responder characteristics and guide targeted therapy.

M215: Enlarged Virchow-Robin Spaces and Lacunar Pathology: Mechanistic Insights into Neurovascular Dysfunction

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Background: Virchow-Robin (VR) spaces are perivascular compartments visible on MRI, often considered incidental. However, their enlargement may collectively reflect impaired glymphatic clearance, microvascular stasis, and early cerebral small vessel disease (cSVD). Comprehending these mechanistic pathways simultaneously positions VR space prominence as a potential imaging marker of neurovascular pathology rather than a mere benign finding.

Methods: A 72-year-old female presented with a one-month history of throbbing parieto-temporal headache, without any prior history of migraine or tension-type headache. Neurological examination was unremarkable. MRI revealed prominent VR spaces with a possible lacunar infarct of the basal ganglia.

Results: MRI demonstrated a significant cSVD burden, including bilateral fronto-parieto-occipital periventricular white matter hyperintensities on T2W/FLAIR. A well-defined ovoid lesion in the left basal ganglia appeared hypointense on T1W/FLAIR and hyperintense on T2W sequences. Although morphologically compatible with a prominent ePVS, its adjacency to ischemic white matter changes and the patient's progressive headache raised concern for a high-probability lacunar infarct or significant microvascular flow impairment. The radiological pattern supports interpreting ePVS as a potential marker of pathological small-vessel dysfunction rather than incidental or physiological perivascular dilatation.

Conclusion: This case illustrates how enlarged VR spaces may serve as sentinel markers of neurovascular pathology. Their prominence suggests mechanistic links to a compendium of glymphatic failure, microvascular compromise, and lacunar stroke risk. Incorporating VR space assessment into routine MRI interpretation could enhance early detection of cSVD and refine risk stratification for neurovascular disease. Larger studies are needed to validate their role as mechanistic biomarkers in neuroimaging.

M217: Hydrocephalus as a Delayed Complication of Post-Transpedicular Fixation Meningitis: A Diagnostic & Therapeutic Challenge

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Background: Communicating hydrocephalus is an exceptionally rare complication following lumbar spinal fixation,

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particularly when preceded by postoperative meningitis secondary to an incidental durotomy. Incidental durotomies occur in 1.7–17.4% of spinal fixation surgeries (SI Tafazal, European Spine Journal, 2005; S Wolff, Orthopaedics & Traumatology, 2012), with CNS infections arising in approximately 9.7% of affected patients (S Liang, World Neurosurgery, 2023). Early recognition of this uncommon progression is critical, as delayed diagnosis may result in rapid neurological deterioration.

Methods: We present a detailed case report of a 38-year-old female who developed delayed-onset meningitis and subsequent communicating hydrocephalus following L5–S1 transpedicular fixation complicated by an intraoperative dural tear. Clinical presentation, imaging, laboratory findings, management, and outcomes were analyzed in the context of existing literature.

Results: The patient initially recovered well postoperatively but returned on post-operative day 23 with fever, severe headache, photophobia, and meningeal signs including neck stiffness, confusion, and a positive Brudzinski's sign. Laboratory investigations revealed leukocytosis ($\sim$13,000/mm^3) and markedly elevated inflammatory markers. CSF analysis demonstrated semi-turbid fluid with a cell count of 1,304/mcL (65% neutrophils), elevated protein (224 mg/dL), and reduced glucose (12 mg/dL), highly suggestive of bacterial meningitis despite negative cultures - likely attributable to prior antibiotic exposure, which has been shown to reduce CSF culture sensitivity from 88% to 59% (LE Nigrovic, Pediatrics, 2008). CT brain confirmed meningeal enhancement consistent with Fazeka Grade II changes. Despite 14 days of broad-spectrum intravenous antibiotic therapy (vancomycin, ceftriaxone, meropenem), the patient's GCS deteriorated to 13/15 on day five of admission, with repeat CT brain revealing communicating hydrocephalus. Urgent ventriculoperitoneal shunt placement resulted in rapid clinical improvement, with full neurological recovery and resolution of symptoms at three-week follow-up.

Conclusion: This case underscores the need for heightened vigilance in patients with repaired dural tears, as postoperative meningitis and secondary hydrocephalus may evolve insidiously and unpredictably. The inflammatory impairment of CSF absorption at the arachnoid granulations, rather than direct bacterial burden alone, is proposed as the primary pathophysiological mechanism (SM Robert, Cell, 2023). Culture-negative meningitis remains a diagnostic challenge, often influenced by prior antibiotic exposure. Early neuroimaging, prompt antimicrobial therapy, and timely CSF diversion are critical to prevent long-term morbidity. Standardized postoperative surveillance protocols may aid in earlier detection of similar complications in future cases.

M218: AI-Driven Closed-Loop Neuromodulation for Chronic Pain: A Pilot Evaluation of a Digital Self-Management Platform

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Background: Pain is a complex experience involving emotional, cognitive, and physiological pathways. Neuroadaptive strategies have been shown to reduce self-reported pain and improve movement by reinforcing adaptive neural pathways. Repetitive engagement plays a key role in strengthening beneficial pathways while reducing pain-related signaling. However, adherence to rehabilitation programs ranges from 63–82% in the hospital and declines to 21–47% after discharge, often due to lack of routine and forgetfulness. To address these barriers, a closed-loop, AI-driven digital platform was developed to deliver multimodal strategies through personalized suggestions, daily check-ins, and adaptive feedback.

Methods: This is a study that primarily focused on identifying domains that may support the development of a closed-loop, AI-driven platform for chronic pain self-management. The findings highlight symptom awareness, integration into daily routines, and engagement in self-management as priority domains for future evaluation. This study provides a conceptual framework to guide the next phase of research involving prospective surveys of platform users. Future studies evaluating usability, acceptability, engagement, and long-term impact in larger patient populations will provide greater generalizability and help define clinical effectiveness.

Results: A structured review of the literature was conducted to identify domains related to chronic pain self-management, rehabilitation adherence, usability, engagement, and behavioral consistency. Published literature describing barriers and facilitators to chronic pain self-management and digital health engagement was reviewed, and recurring concepts were grouped into major domains. These domains were then mapped to platform features, including personalized suggestions, daily check-ins, symptom trend tracking, and adaptive feedback. The identified domains were used to guide the development of a future 10-item survey focused on usability, ease of use, control, perceived impact, and likelihood of continued use.

Conclusion: The literature-informed analysis identified three major domains: (1) increased awareness of symptom patterns, (2) ease of integration into daily routines, and (3) improved engagement in self-management. Daily check-ins and trend tracking were identified as potential approaches to helping users better recognize changes in symptoms over time and generate actionable insights. The platform was designed to be simple to incorporate into daily routines, while personalized suggestions were intended to remain relevant and responsive to individual needs. The literature also highlighted the importance of greater involvement in care, intentional behavior, and improved behavioral consistency in self-management strategies. These domains were used to identify key domains for future prospective evaluation, including usability, continued engagement, perceived relevance, and integration into daily routines.

M219: Interventional Pain Exposure in Neurology Residents: A Observational Cohort Study

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Background: Several neurologic disease result in chronic pain, including stroke, nerve compression radiculopathy, and headache (Lalani et. al, 2006). Neurologists frequently interact with patients who suffer from chronic pain but have a limited ability to offer interventional treatments without formal fellowship training. We sought to assess the impact of an educational intervention designed to improve exposure of neurologists to interventional pain medicine.
Methods: This is an ongoing single-site observational cohort education study of neurology residents rotating at the Mount Sinai Hospital on their elective pain medicine rotation. The study team developed 1) a clinic schedule that provides shadowing experiences with a neurology-trained pain medicine physician 2) pre- and post- rotation knowledge and confidence questionnaires. The confidence survey uses a 3-point Likert scale for all responses, ranging from "not at all confident" to "very confident" to describe provider comfort in identifying the correct interventional treatment for common pain management complaints. The 10-question multiple-choice knowledge questionnaire is informed by literature review and neurology board examination content, covering common physical exam maneuvers used to diagnose pain complaints as well as interventional treatment options. A neurology resident spends two days of the week in the pain clinic, one day observing diagnostic maneuvers and one day observing interventional treatment techniques. Participants complete the voluntary and anonymous surveys electronically via Redcap after the session. In this interim analysis, we summarized pre- and post-rotation surveys responses using descriptive statistics. We scored pre- and post- knowledge questionnaires as a percentage correct. We assessed pre- and post- confidence knowledge difference with paired t-tests.
Results: From October 2025 – December 2025, ten residents completed the rotation. Fifty percent (n=5) completed the pre-and post- rotation assessments. Average knowledge scores increased from 28% pre-test to 68% post-test (paired t-test p-value <0.001). Eighty percent (n=4) reported feeling not at all confident in their pre-rotation general knowledge of common pain medicine diagnoses and treatment options. Post-rotation, 80% (n=4) reported feeling somewhat or very confident in their knowledge of common pain medicine diagnoses and treatment options.
Conclusion: Preliminary results from the first cohort of neurology residents completing the pain medicine rotation demonstrated improved knowledge and confidence in diagnosis and treatment of common pain management complaints. Resident involvement is ongoing, and we hope to increase response rate and better understand the impact of the rotation on management of pain in patients with neurologic illness.

M220: Chronic Pain in Ehlers-Danlos Syndrome Patients: Prevalence, Pathophysiology, and Management

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Background: Chronic pain is one of the most prevalent symptoms reported in individuals with Ehlers-Danlos Syndrome (EDS), particularly the hypermobile subtype (hEDS). While pain in EDS has been attributed to musculoskeletal instability, joint hypermobility, and tissue fragility, recent research suggests that central sensitization and altered pain processing potentially play a key role. The mechanisms underlying chronic pain in EDS remain obscure, and the variable presentations complicate diagnosis and management. Only a small number of studies systematically investigate the underlying pathophysiology relating chronic pain syndromes, such as fibromyalgia, to EDS. Our objective was to investigate the existing literature on the relationship between EDS and chronic pain syndromes, focusing on prevalence, proposed pathophysiologic mechanisms, clinical features, and management.
Methods: A comprehensive search was performed in PubMed for studies published between January 2020 and October 2025. Studies were included if they examined both EDS and pain disorders. S.R, S.J.H. and S.N. screened the texts to determine if they were in scope. Studies excluded were those that did not discuss both pain disorders and EDS, systematic reviews, review articles, and meta-analyses. Study selection was guided by PRISMA guidelines.
Results: After identifying 61 articles without duplicates, screening was preformed, leaving 31 articles that fit the criteria for our search. 20 articles were ultimately included, encompassing 2,373 participants. Four (20%) were case reports, 7 (35%) were cross sectional in design, and three (15%) were case-control. 15 (75%) of the included studies reported data on chronic pain and EDS. Three (15%) of these studies specifically reported data on fibromyalgia, with two of them also providing prevalence data on EDS patients who have fibromyalgia. Four (20%) studies discussed the role of neuropathic pain in EDS patients, with three of these reporting data on neuropathic pain. Pathophysiologic mechanisms were described in 14 studies (70%). Central sensitization was the most frequently reported underlying mechanism (50%), followed by altered nociceptive processing (43%), joint instability (21%), autonomic dysfunction (21%), and recurrent microtrauma (7%). Management strategies were heterogeneous with six (30%) of the included articles discussing pharmacologic treatments and eight (40%) highlighting physical and rehabilitation therapies. Overall, treatment outcomes were variable.
Conclusion: Our review explores central sensitization, altered nociceptive processing, and autonomic dysfunction as emerging contributors to pain in EDS patients, particularly in patients with overlapping fibromyalgia features. It is important to recognize the significance of neurologic mechanisms to comprehend the multifactorial nature of pain in EDS patients.

M222: Treatment Of Chronic Nausea with Proposed Left Vagal Afferent Nerve Blocks

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Background: To observe and describe the clinical improvement of patients with chronic nausea with nerve blocks over the proposed left vagal afferent nerve. Background: Chronic nausea is a common occurrence with suffering that may affect all realms of daily life, including negative behavioral aspects, i.e. mood disorders. The remedies in treating nausea are mostly pharmacological and chronic in nature with potential long term and, in some cases, permanent side effects.

Methods: Consecutive patients with chronic nausea of various etiologies presented to the neurology clinic. Clinical features were chronic sustained nausea in the epigastric and the anterior periumbilical areas. Nerve blocks consist of 8-10, 27 gauge 1 & 1/4 inch needles inserted approximately 2 cm in the epigastric and anterior periumbilical area, with bupivacaine 0.25%, 0.2 cc injected in each needle.

Results: Thirty-two consecutive patients with chronic nausea for 1 week to over 15 years presented from June 2024 through August 2026, with age range from 20 years to 82 years, 94 percent female, for nerve blocks. Twenty-five patients had immediate relief and 19 patients had long-term relief (over 6-8 weeks or longer) initially post-procedure with no nausea or much less nausea and with serial procedures (1 to 3 trials).

Conclusion: Nerve blocks in the abdomen over the left vagal afferent nerve may be an alternative in treatment for patients with chronic nausea.

M223: Safety, Efficacy and Impact of Patient-Specific Moderators on CGRP Monoclonal Antibodies for Migraine Prevention: A Systematic Review and Meta-Analysis with Meta-Regression

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Background: CGRP monoclonal antibodies (mAbs) are effective for migraine prevention, yet are often used as class-based therapies despite variability in individual response. Existing evidence is largely agent-specific, with limited integration of comparative effectiveness and patient-level moderators. Addressing this gap is essential for developing clinically actionable, individualized treatment strategies.

Methods: A systematic review of randomized, placebo-controlled trials in episodic and chronic migraine was conducted. Random-effects meta-analysis estimated ≥50% and ≥75% responder rates and monthly migraine day (MMD) reduction. Meta-regression was used to identify clinically actionable moderators, including age, sex, cumulative dose, chronic migraine proportion, and follow-up duration. Safety was assessed using odds ratios (OR) with 95% confidence intervals (CI).

Results: All CGRP mAbs demonstrated significant efficacy versus placebo. For ≥50% responder rate, fremanezumab showed the highest effect (OR 3.46, 95% CI 0.97–12.43), followed by erenumab (OR 2.99, 95% CI 2.46–3.64), galcanezumab (OR 2.45, 95% CI 1.63–3.67), and eptinezumab (OR 2.04, 95% CI 1.11–3.73). Eptinezumab improved ≥75% response (OR 2.08, 95% CI 1.05–4.09) and reduced MMD (−1.73 days), while galcanezumab significantly reduced MMD (−1.71 days, 95% CI −2.03 to −1.38). Fremanezumab showed a non-significant MMD reduction (−1.48 days). Meta-regression identified a significant dose–response relationship for eptinezumab ($p=0.006$), representing a clinically actionable finding. Trends suggested demographic modulation of response for galcanezumab (age and sex, $p\approx0.06$) and time-dependent efficacy effects for erenumab ($p=0.055$), while fremanezumab demonstrated consistent efficacy across subgroups. Safety analysis revealed agent-specific profiles. Nasopharyngitis was reported across all groups, with eptinezumab showing the highest point estimate (OR: 1.30, 95% CI: 0.93–1.82), followed by erenumab (OR: 1.00, 95% CI: 0.73–1.38), fremanezumab (OR: 0.96, 95% CI: 0.74–1.25), and galcanezumab (OR: 0.91, 95% CI: 0.70–1.17). Regarding injection site reactions, erenumab showed the highest risk for pain (OR: 1.55, 95% CI: 0.94–2.56), followed by galcanezumab (OR:1.16, 95% CI:1.42-0.94), and fremanezumab (OR:1.13, 95% CI:1.35-0.95). Fremanezumab demonstrated significant risk for injection site induration (OR: 1.30, 95% CI: 1.07–1.59) and erythema (OR: 1.40, 95% CI: 1.14–1.72). Nausea risk was low for both eptinezumab (OR: 1.09) and fremanezumab (OR: 0.64). Erenumab also had higher propensity for URTI (OR:1.4, 95% CI: 2.07-0.95).

Conclusion: CGRP mAbs demonstrate robust but clinically heterogeneous efficacy across agents. The identification of dose-dependent effects and emerging moderator-driven response patterns highlights meaningful variability beyond a uniform class effect. These findings provide a comparative, data-driven framework for individualized therapy selection, supporting a shift toward precision-guided use of CGRP-targeted treatments in migraine prevention.

M224: Opioid Deprescribing in Neurology: Trends Among U.S. Neurologists From 2013 to 2023

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Background: Neurologists often manage chronic pain conditions including neuropathy, migraine, multiple sclerosis, and post-stroke pain, for which opioid use remains controversial. While national opioid prescription trends are well-documented, neurology-specific prescribing trends are poorly characterized despite neurologists being the 14th most frequent opioid-prescribing specialty in the United States. As

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such, we aimed to characterize Medicare Part D opioid prescribing by neurologists from 2013 to 2023.

Methods: Medicare Part D Prescriber Public Use Files from 2013 to 2023 were queried for providers with the "Neurology" specialty taxonomy. Opioid-containing filled claims were identified by generic drug name and grouped by primary agent. Claims, day supply, prescriber counts, gross drug cost, opioid type, Health and Human Services (HHS) region, and provider state were tabulated annually. Gross drug cost per claim was inflation-adjusted to 2023 U.S. dollars using annual average Consumer Price Index for All Urban Consumers (CPI-U).

Results: Opioid claims declined 56.5%, from 924,754 in 2013 to 402,723 in 2023, while opioid-prescribing neurologists fell 43.2%, from 5,520 to 3,137. Mean day supply per claim remained stable between 26.5 and 27.6 days.

Median claims per prescriber declined from 53 to 34, though prescribing became more concentrated, with the top decile accounting for 60.8% of claims in 2013 and 66.0% in 2023. Among 2,069 neurologists present in both years, median claims declined from 89 to 49. Drug composition shifted as hydrocodone fell from 42.3% to 31.4%, oxycodone increased from 24.2% to 32.7%, and tramadol increased from 17.1% to 23.5%. Fentanyl saw the sharpest decline, decreasing 81.9%. Inflation-adjusted gross drug cost per opioid claim declined from $93.57 to $53.09. Claims declined across all Health and Human Services regions, although the Southeast remained the largest contributor.

Conclusion: Medicare Part D opioid claims by neurologists declined substantially from 2013 to 2023, reflecting fewer opioid-prescribing neurologists, lower same-prescriber intensity, and greater concentration among high-volume prescribers. Stable claim duration suggests a chronic pain prescribing pattern. Drug mix shifted away from hydrocodone toward oxycodone and tramadol, while fentanyl and inflation-adjusted gross cost per claim declined. These trends likely reflect a combination of guideline-driven reductions in overall opioid prescribing, substitution to non-opioid therapies, or changes in opioid access among patients with chronic pain, and warrant further investigation into patient-level indications and outcomes.

M226-LB: Insurance-Mandated Delays in OnabotulinumtoxinA Treatment for Chronic Migraine: Functional Consequences of Administrative Barriers

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Background: Chronic migraine is a disabling neurologic disorder associated with substantial impairment in academic, occupational, and social functioning. Although onabotulinumtoxinA is an evidence-based preventive therapy for chronic migraine, insurance authorization barriers and inflexible treatment interval requirements may delay access to effective care and contribute to preventable morbidity.

Methods: Prior to initiation of onabotulinumtoxinA therapy, the patient experienced approximately 10 migraine days per month despite trials of multiple preventive and abortive therapies, several of which were ineffective or poorly tolerated. Following treatment initiation, migraine frequency improved to approximately 4–6 days per month with substantial improvement in daily functioning and academic performance. After interstate relocation, the patient experienced a six-month interruption in care due to insurance denials, referral requirements, and delays in neurology authorization, resulting in recurrent weekly migraines and increased reliance on rescue medications.

Following re-establishment of care, insurance-mandated 12-week treatment intervals were associated with clinically significant wearing-off effects beginning approximately 10 weeks after injection, resulting in severe breakthrough migraines during the final weeks of each treatment cycle.

Results: Insurance-related delays and inflexible authorization policies may significantly worsen disease burden in patients with chronic migraine by limiting timely access to evidence-based preventive therapy. Greater flexibility in treatment authorization and individualized dosing interval approvals may improve neurologic outcomes, functional status, and quality of life.

Conclusion: A single-patient case study was developed to characterize the functional impact of insurance-related barriers to onabotulinumtoxinA treatment for chronic migraine. Patient-reported migraine frequency, treatment history, interruption in care, rescue medication use, and academic and social functioning were summarized before treatment initiation, during insurance-related treatment delay, and after treatment re-establishment.

M227-LB*: The Endometriosis-Migraine Visibility Gap: A 13-Million Patient Meta-Analysis of Shared Neuro-Gynecological Biology

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Background: Endometriosis and migraine are classic Chronic Overlapping Pain Conditions (COPCs) linked by an integrated shared biological blueprint involving neurovascular cross-talk, estrogen-dependent central sensitization, and synergistic neuro-inflammatory pathways, most notably Calcitonin Gene-Related Peptide (CGRP) signaling. Discrepancies between clinical presentation and administrative logging obscure this relationship. This systematic meta-analysis quantifies the global pooled odds ratio (OR) of this specific comorbidity to evaluate how diagnostic filters and hospital billing networks mask its true underlying biological reality.

Methods: The final dataset synthesized 207,675 endometriosis cases and 12,963,120 non-endometriosis controls spanning a 50-year publication lifespan (1975–2026). Pooling all cohorts confirmed a robust, significantly elevated overall odds of migraine in the endometriosis population (OR = 2.30, 95% CI, 1.75 - 3.05, $p < 0.0001$). Crucially, prevalence and association strengths demonstrated a tri-modal distribution tied directly to data-capture

Methods: - Administrative Floor: Restrictive, 1-year ICD billing coding demonstrated the lowest prevalence (4.5% to 4.7%). - Chronic Cumulative Net: Claims data utilizing longitudinal, lifetime look-back windows captured intermediate

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tracking (17.8% to 42.8%). - Biological Ceiling: Specialized, clinic-based cohorts employing direct patient interviews revealed a massive biological signal ceiling, with migraine prevalence consistently reaching 54% to 78%. Sensitivity analysis confirmed that widespread combined oral contraceptive (COC) utilization acts as a powerful confounding filter due to screening-by-contraindication bias. While cohorts dominated by high hormonal usage demonstrated depressed, non-significant odds ratios flirting close to 1.0, dropping these heavily medicated samples unmasked the true biological signal, yielding a highly significant 2.41-fold overall increased odds of migraine in women with endometriosis (OR = 2.41, 95% CI: 1.91–3.04).

Results: A standard macro-average of endometriosis-migraine comorbidity is fundamentally flawed due to profound methodological heterogeneity ($I^{\cdots}2 > 80\%$). This variance maps a predictable visibility gap where administrative networks miss an 11x-to-14x under-reporting gap, hiding up to 90% of the active biological burden.

Characterizing this shared neuro-gynecological biology validates the clinical reality of this co-occurring syndrome and provides a direct, highly innovative pathway for therapeutic translation, supporting the clinical repurposing of established migraine therapies (such as CGRP blockers) as non-hormonal, non-opioid strategies for gynecological pain management.

Conclusion: We systematically reviewed 35 global cohorts reporting raw case-control cross-tabulations of migraine status in patients with and without endometriosis. Data extraction captured exact event counts and denominator profiles across clinical trials, population surveys, and insurance databases. Studies were stratified by data-capture style to evaluate the visibility gap between administrative billing registries and formalized clinical phenotyping (ICHD-3 criteria). A random-effects model completely pooled the individual effect sizes.

M229: Identification of Acute Pain Signatures in Healthy Adults Using Time-Domain Near-Infrared Spectroscopy

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Background: There are currently no established, clinically validated monitoring instruments for the objective measurement of pain in humans. Vulnerable populations, such as patients who cannot communicate effectively due to their clinical condition, are at risk for suboptimal pain management. Studies using near-infrared spectroscopy (NIRS) have shown that pain can cause changes in cerebral oxygenation. Time-domain NIRS (TD-NIRS) is a next-generation optical system capable of monitoring cerebral oxy-/deoxy-/total-hemoglobin (O2Hb, HHb, Hbtot) concentrations and oxygen saturation (StO2). In this pilot study, we investigated whether TD-NIRS can capture consistent prefrontal cortex oxygenation responses and serve as candidate biomarkers of acute pain.

Methods: This IRB-approved study included nineteen healthy adults undergoing the cold pressor test (CPT) while being recorded with two-channel TD-NIRS until subjective pain was reported as zero via the Numeric Analog Scale. For each subject, the CPT-baseline was computed for each parameter and averaged between channels. Optical TD-NIRS measurements were obtained from the right and left forehead. The primary tests assessed change per-subject and ipsilateral versus contralateral lateralization. Exploratory tests also included within-day adaptation and test-retest reliability across recordings. Wilcoxon signed-rank statistics were Benjamini-Hochberg corrected across the four parameters.

Results: Three of four parameters increased significantly during CPT (n=19): O2Hb (median +2.36 μM, p=0.002), tHb (+2.27 μM, p=0.007), and StO2 (+0.57%, p=0.002). ΔHHb demonstrated a non-significant decrease (-0.21 μM, p=0.095). Oxygenation responses ipsilateral to the side of CPT were approximately twice the magnitude of the contralateral side for O2Hb (p=0.0006), tHb (p=0.0009), and StO2 (p=0.0008) but not HHb (p=0.581). Test-retest reliability between days (n=6) was observed for O2Hb (Spearman rho=+0.886, p=0.033) and tHb (rho=+0.886, p=0.035). Exploratory analyses demonstrated within-day adaptation for O2Hb (n=5 subjects, one-sided, p=0.031).

Conclusion: In 19 healthy adults, CPT produced a robust and significant oxygenation response over the prefrontal cortex. Ipsilateral O2Hb, tHb, and StO2 were more pronounced compared to the contralateral side, while HHb showed no significant differences. Strong test-retest reliability between days and within-day adaptation was observed. To our knowledge, this is the first TD-NIRS demonstration of a quantifiable optical signature during the cold pressor test-evoked pain. Future large-scale validation and mechanistic studies may explore the possibility of using TD-NIRS-recorded response as a non-invasive, continuous biomarker of pain.

MOVEMENT DISORDERS

M231: Plasma proteomics profile in atypical parkinsonism syndromes reveals shared and unique molecular signatures

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Background: Atypical parkinsonism syndromes frequently exhibit overlapping clinical features. However, they have distinct neuropathologies, ranging from alpha-synuclein aggregation in Lewy body dementia (LBD) and multiple system atrophy (MSA) to tau accumulation in corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). Previous studies have demonstrated the potential utility of plasma proteins as biomarkers of neurodegenerative disorders. This study aimed to leverage high-throughput plasma proteomics to identify putative disease signatures in the plasma that are uniquely and jointly enriched in atypical parkinsonism syndromes.

Methods: Our study cohort consisted of healthy controls ($n = 65$) and participants diagnosed with CBS ($n = 8$), LBD ($n = 7$), MSA ($n = 5$), and PSP ($n = 17$). We obtained plasma proteomic profiles of all study participants using the Olink Explore 3072 assay to determine the relative abundance of 2,868 unique plasma proteins. In performing differential protein abundance analyses, we identified proteins that were enriched in atypical parkinsonism syndromes by comparing each disease (CBS, LBD, MSA, and PSP) to healthy controls, while controlling for age and sex. Proteins were considered enriched for a disease if the p-value was < 0.05. We defined the shared set of proteins as proteins enriched in at least three of the four diseases included in this study. Finally, we evaluated biological pathways of enriched proteins using the Reactome and Gene Ontology databases.

Results: Differential abundance analyses identified proteins enriched for CBS ($n = 89$ proteins), LBD ($n = 303$ proteins), MSA ($n = 110$ proteins), and PSP ($n = 386$ proteins). A total of 9 enriched proteins were determined to be shared across atypical parkinsonism syndromes. Integrin signaling pathways ($p = 1.2 \times 10^{-3}$) were enriched in CBS; proteoglycans ($p = 3.8 \times 10^{-5}$) in LBD; and autophagy/mitophagy ($p = 2.4 \times 10^{-6}$) in PSP. The shared set of proteins was enriched for glial cell differentiation, intermediate filament organization, and lipid metabolism.

Conclusion: Plasma proteins enriched in atypical parkinsonism syndromes reflect known biological pathways associated with neurodegeneration. Our findings also suggest that cytoskeletal organization, gliogenesis, and lipid metabolism are shared pathways in atypical parkinsonism syndromes, potentially revealing common risk factors for these neurodegenerative disorders. Further expanding our study cohort will help establish the validity of our findings and potentially reveal novel mechanisms.

M232: Expanding the Therapeutic Window in DBS: A Comparison of Pseudomonopolar and Monopolar Configurations

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Background: Deep brain stimulation (DBS) is an established therapy for motor symptoms from Parkinson's disease and other movement disorders. However, benefits are sometimes limited by stimulation-induced adverse effects, particularly when current spreads to adjacent corticobulbar or corticospinal fibers. When significant, these capsular side effects constrain the therapeutic window, limit efficacy, and sometimes introduce unwanted speech or gait symptoms. Novel technological paradigms such as independent current control, directional lead architectures, and anodic stimulation increase programming flexibility, but whether and how these advances improve outcomes versus legacy systems is unclear.

Methods: Here we compare stimulation side effect profiles with traditional monopolar versus pseudomonopolar stimulation with the Boston Scientific DBS platform. Pseudomonopolar stimulation utilizes distributed current return across multiple electrode contacts to shape the electric field while maintaining a monopolar-like configuration, potentially improving the spatial selectivity of stimulation. We examined capsular side effect thresholds across stimulation configurations and contrasted their neurophysiological manifestations with stimulus-evoked electroencephalography (EEG) potentials.

Results: Within a given participant, pseudomonopolar stimulation fields elicit capsular side effects at higher amplitude thresholds than traditional monopolar configurations (4.94 ± 0.53 versus 2.79 ± 0.25 mA, $p<0.001$, paired t-test, mean $\pm$ standard error, $n=13$ participants). Additionally, ongoing studies suggest that stimulus-evoked scalp EEG potentials differ within individuals between clinically effective stimulation settings versus those that elicit unwanted capsular side effects.

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Conclusion: Our findings suggest that pseudomonopolar stimulation alters the spatial distribution of stimulation, improves side effect thresholds, and produces distinct electrophysiologic signatures. Pseudomonopolar stimulation could serve as an alternative stimulation paradigm for patients with dose-limiting side effects from conventional DBS parameters. Greater knowledge on stimulation-evoked neurophysiology could also provide mechanistic insights to inform future open- and closed-loop neuromodulation strategies that utilize cortical feedback.

M233: Suspected Lifelong POLR3A-Related Disorder with Late-Emerging Levodopa-Responsive Parkinsonism and Pyramidal Signs: A Video Case Report

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Background: POLR3A-related disorders are rare neurologic diseases caused by pathogenic variants in POLR3A, which encodes the largest subunit of RNA polymerase III. Their phenotypic spectrum ranges from childhood-onset 4H leukodystrophy, classically characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism, to milder adult-onset spastic ataxia. Childhood-onset cases typically present with variable combinations of cerebellar ataxia, tremor, spasticity, and dystonia. Although cerebellar, pyramidal, and extrapyramidal manifestations such as ataxia, spasticity, tremor, and dystonia are well recognized, adult-onset levodopa-responsive parkinsonism has only rarely been reported.

Methods: We report the case of a 70-year-old man with a past medical history of hypothyroidism and anosmia who presented with a 3-year history of progressive cervical dystonia, gait instability, dysphonia, and dysphagia. Despite living independently and having completed high school without special assistance, he had lifelong speech difficulties. Family history was significant for three nieces and nephews with POLR3A-related leukodystrophy and one nephew with mitochondrial complex IV deficiency.

Results: Examination showed hypomimia, bilateral bradykinesia and rigidity, cervical dystonia, diffuse hyperreflexia involving the upper and lower extremities, bilateral palmomental reflexes, and a scissoring, shuffling gait. Brain MRI showed mild periventricular and subcortical T2/FLAIR hyperintensities with relative U-fiber sparing. A trial of carbidopa/levodopa produced subjective improvement, with objective improvement in parkinsonian features on follow-up examination. For cervical dystonia, he was treated with botulinum toxin injections. Given the suspected POLR3A-related disorder, we recommended referral to Genetics for diagnostic clarification, comprehensive phenotypic assessment, and genetic counseling.

Conclusion: This case highlights a suspected POLR3A-related phenotype presenting with lifelong speech difficulties followed by late-emerging levodopa-responsive parkinsonism, cervical dystonia, and pyramidal features. Although anosmia may suggest prodromal synucleinopathy-associated parkinsonism, the patient's strong family history, lifelong speech difficulties, upper motor neuron signs, and suggestive neuroimaging raise concern for a broader genetic leukodystrophy phenotype, including a possible POLR3A-related disorder. Recognition of these associations may prompt earlier genetic evaluation.

M234: Integrated Multi-omics Identifies Convergent Dysregulation of Fam107b and Tph2 as Potential Therapeutic Targets in SCA7

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Background: Spinocerebellar ataxia type 7 (SCA7) is a polyglutamine neurodegenerative disorder characterized by progressive cerebellar ataxia and retinal degeneration. While transcriptional and epigenetic dysregulation have been implicated, their integration with downstream proteomic alterations remains incompletely understood.

Methods: We performed integrative multi-omics analysis using whole-brain tissue from symptomatic SCA7266Q/5Q mice at 12 weeks. Bulk tissue RNA sequencing, DNA methylation analysis, and quantitative proteomic analyses were conducted. Differentially expressed genes (DEGs) and proteins (DEPs) were integrated to identify concordant molecular alterations. Key candidates were validated by RT-qPCR and cross-referenced with public datasets from other polyglutamine ataxia models.

Results: SCA7 mice demonstrated progressive motor impairment, with reduced stride length and decreased latency to fall, compared to wildtype littermates ($p<0.05$). Transcriptomic analysis identified 491 DEGs (220 upregulated, 271 downregulated), of which 58 were hypomethylated-upregulated and 62 hypermethylated-downregulated (FDR<0.05, Δmethylation >0.2). Gene ontology analysis revealed these genes to be enriched in axonogenesis, channel activity, and monoaminergic signaling pathways. Proteomic analysis identified 492 DEPs (211 upregulated, 281 downregulated; FDR<0.05), with enrichment in immune response and cellular motility pathways. Integrated analysis across all three omics layers identified three candidate genes (Fam107b, Tph2, Gpr88). Fam107b (RNA logFC −1.541, protein log2FC −0.602, $p=1.92\times10^{-7}$) and Tph2 (RNA logFC −3.554, protein log2FC −0.276, $p=4.69\times10^{-6}$) showed consistent hypermethylation and downregulation across all platforms. RT-qPCR confirmed significant downregulation (Fam107b relative FC 0.461, $p<0.001$; Tph2 0.058, $p<0.001$). Tph2 dysregulation was also observed in SCA1 models (log2FC −2.594, $p<0.001$).

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Conclusion: This integrative multi-omics study identifies Fam107b and Tph2 as convergently dysregulated core genes in SCA7, linking epigenetic, transcriptional, and proteomic alterations. These findings provide mechanistic insight and highlight potential therapeutic targets for polyglutamine ataxias.

M235*: Developmental Failure of Cortical Inhibition in Huntington's Disease: Implications for Early Therapeutic Intervention

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Background: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by CAG repeat expansion in the HTT gene. Increasing evidence suggests that HD is not solely degenerative but also involves early neurodevelopmental abnormalities, particularly affecting cortical circuit formation. GABAergic interneurons, especially somatostatin (SST) subtypes, play a critical role in establishing excitatory-inhibitory (E/I) balance and may represent a key site of vulnerability. Here, we investigate cortical interneuron alterations in HD and define their contribution to circuit dysfunction using complementary immunohistochemistry (IHC) and single-nucleus RNA sequencing (snRNA-seq), with the goal of identifying developmental windows and circuit mechanisms that may inform therapeutic intervention.
Methods: Postmortem cortical tissue from HD patients and controls (n=155 samples) was analyzed using IHC to quantify interneuron subtypes across cortical layers. snRNA-seq was performed on 139,833 nuclei to identify cell-type specific transcriptional changes. Differential expression and pathway enrichment analyses were conducted, and cell–cell communication was further interrogated using CellPhoneDB.
Results: IHC revealed a robust, age-independent reduction of SST+/CR- interneurons across cortical regions and layers, with no correlation to disease duration, CAG repeat length, or neuropathological grade. snRNA-seq demonstrated that SST interneurons retain lineage identity but exhibit transcriptional signatures of developmental arrest, including upregulation of guidance cues such as RELN, NTRK3, SLIT1 and downregulation of mature synaptic adhesion molecules. Concurrently, upper-layer pyramidal neurons displayed increased expression of excitatory receptor subunits and synaptic scaffolds alongside loss of inhibitory input markers, consistent with compensatory hyperexcitability and dendritic remodeling. CellPhoneDB analysis confirmed disrupted inhibitory signaling networks, revealing altered ligand–receptor interactions between SST interneurons and pyramidal neurons that support impaired dendritic inhibition and circuit instability.
Conclusion: These findings support a model in which HD cortical dysfunction arises from early developmental miswiring rather than purely degenerative processes affecting medium spiny neurons. SST interneurons exhibit persistent immaturity and impaired synaptic targeting, while pyramidal neurons undergo maladaptive excitatory scaling, together driving E/I imbalance and cortico-striatal hyperexcitability. Targeting interneuron maturation and restoring dendritic inhibition may represent a promising strategy for early therapeutic intervention in HD.

M236: Severe Holmes Tremor Associated with Autosomal Recessive Spinocerebellar Ataxia Type 16 (SCAR16)

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Background: Autosomal recessive spinocerebellar ataxia type 16 (SCAR16) is a genetic disorder associated with progressive cerebellar ataxia and cognitive dysfunction. Knowledge of the natural history and neurological signs associated with this disorder is limited.
Methods: We provide a detailed case description of a patient with SCAR16, including video evidence of the patient's examination demonstrating a severe Holmes tremor. We compare the patient's presentation to all previously reported cases of SCAR16, and identify unique characteristics of this case that expand current knowledge of SCAR16.
Results: At 39 years, the patient first noticed symptoms of progressive difficulty with balance, eventually requiring the use of a wheelchair, followed later on by cognitive decline. Examination in our clinic at the age of 73 showed a constant, slow, proximal, and very large amplitude (>15cm) rest tremor that worsened with posture and action, consistent with a severe Holmes tremor (video images available). There was also severe cerebellar dysarthria and appendicular dysmetria, gaze-evoked horizontal nystagmus in lateral gaze, and appendicular and axial hypotonia. She required the assistance of two people to stand and walk. She was able to name single items and follow single-step but not multi-step commands. There was no family history of similar neurological phenomena. CT imaging revealed prominent cerebellar atrophy. Whole Exome Sequencing (GeneDx) identified one variant in exon 3 of the STUB1 gene ((c.433 A>C p.(K145Q)), and one variant in intron 4 of the STUB1 gene (c.613-2 A>G p.?) (phase unknown). Both variants were classified as likely pathogenic, most consistent with a diagnosis of SCAR16.
Conclusion: Establishing a differential diagnosis for patients with chronically progressive cerebellar ataxia with a suspected genetic etiology often presents a clinical challenge. While some forms of genetic cerebellar ataxia are associated with highly specific clinical signs that point to a genetic diagnosis, many forms exist where this is not the case. The differential diagnosis of genetic cerebellar ataxia associated with severe tremor is narrow, including most notably SCA12 and FXTAS. Case reports have noted moderate or severe tremor in patients with SCA1, SCA2, SCA3, SCA6, SCA27, and SCA48, but video exams are not available in most cases, and distinctions between severe and moderate tremors are not reported. Our case description adds SCAR16 to the list of genetic ataxias to be considered in patients presenting with a severe Holmes tremor, and expands our knowledge of the phenotypic spectrum of SCAR16.

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M237*: In Vivo Screen of Parkinson's Disease GWAS Risk Genes Identifies ARIH2 as a Novel Regulator of α-synuclein Toxicity in Dopaminergic Neurons

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Background: Parkinson's disease is a late onset neurodegenerative disease characterized by preferential degeneration of midbrain dopaminergic neurons and α-synuclein containing Lewy bodies that are found in both familial and sporadic forms. Genome wide association studies (GWAS) have identified many loci associated with risk of sporadic PD, but their role in PD pathogenesis remains largely unknown.

Methods: We screened a subset of GWAS genes in Caenorhabditis elegans (C.elegans) as potential modulators of α-synuclein-mediated degeneration of dopaminergic neurons. Loss of ari-2 (human ARIH2), an E3 ubiquitin ligase was identified as the strongest suppressor of dopaminergic neurodegeneration in C.elegans. Using iPSC derived DA neurons, we performed mass spectrometry to identify putative substrates of the human ortholog, ARIH2.

Results: Unbiased proteomics analysis in human iPSC-derived dopaminergic neurons revealed novel substrates of ARIH2 including TPPP3, a regulator of microtubule dynamics. Importantly, TPPP3 was required for ARIH2's effects on α-synuclein induced dopaminergic neurodegeneration.

Conclusion: Our studies reveal an unexpected genetic interaction between two PD-linked genes α-synuclein and ARIH2, and suggest that inhibition of ARIH2's enzymatic activity may serve as a potential therapeutic approach in PD.

M238: The Rising Burden of Alzheimer's Disease and Respiratory Failure Mortality among Older Adults (1999-2025): a CDC WONDER Analysis

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a leading cause of mortality amongst older adults with concurrent respiratory failure. Complications such as dysphagia, aspiration and reduced pulmonary reserve overwhelmingly lead to fatalities. This study is a systemic evaluation of long-term trends and disparities due to Alzheimer's disease and respiratory failure amongst older adults in the United States.

Methods: Data were extracted from the CDC WONDER Multiple Cause of Death database from 1999-2025 using ICD-10 codes G30.0, G30.1, G30.8, and G30.9 for AD and J96.0, J96.1, and J96.9 for respiratory failure in older adults (≥65 years). Age-Adjusted Mortality Rates (AAMRs) per 100,000 population were analyzed to assess long-term mortality trends. Join point regression analysis was used to estimate Annual Percent Changes (APC) and Average Annual Percent Changes (AAPC), with $p < 0.05$ considered significant, denoted by an asterisk (*).

Results: From 1999-2025, a total of 150,857 deaths were recorded. The AAMR rose from 9.12 in 1999 to 14.4 in 2025 per 100,000 population (AAPC: 1.34*; 95% CI: 0.64 to 1.90). There was sharp rise in mortality from 2014-2020 (APC: 8.45*; 95% CI: 4.81 to 17.6), followed by a recent decline from 2020-2025 (APC: -5.04*; 95% CI: -10.5 to -2.04). A significant rising trend was observed in females (AAPC: 1.72*; 95% CI: 1.02 to 2.29) as compared to males (AAPC: 0.70; 95% CI: -0.02 to 1.26). The 85+ age group showed a substantial rise throughout the study span (AAPC: 1.71*; 95% CI: 0.91 to 2.34). Race analysis demonstrated that Hispanics (AAPC: 1.91*; 95% CI: 1.00 to 2.84) had greater mortality rates than Non-Hispanics (AAPC: 1.19*; 95% CI: 0.50 to 1.74). Amongst non-Hispanics, the most pronounced increase was seen in Asian and Pacific Islander (AAPC: 2.35*) followed by Blacks and African Americans (AAPC: 1.38*). Regionally, The Midwest showed the highest mortality trend (AAPC: 2.53*) followed by the West (AAPC: 1.81*). Non-metropolitan areas had greater mortality (AAPC: 3.63*) than metropolitan areas (AAPC: 2.85*).

Conclusion: From 1999-2025, mortality in AD coexisting with respiratory failure showed a rising trend among older adults with significant disparities across demographic groups and regions. These findings highlight the need for targeted geriatric care and public health interventions to address persisting inequities.

M239: Late-Onset Ataxia-Telangiectasia in a 75-Year-Old Woman: A Rare Diagnostic Insight from Whole Exome Sequencing

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Background: Ataxia-telangiectasia (A-T) is a rare autosomal recessive disorder typically presenting in early childhood with progressive cerebellar ataxia, immunodeficiency, and telangiectasias. Adult-onset cases are exceedingly rare and often underrecognized.

Methods: A 75-year-old retired teacher presented with a 10-year history of slowly progressive gait instability and dysarthria. She denied vertigo, diplopia, or sensory changes. Examination revealed pure cerebellar signs, including limb and gait ataxia more prominent on the left, dysarthria, and impaired tandem walking. There were no signs of peripheral neuropathy, parkinsonism, or telangiectasias. Her mother had a history of gait unsteadiness and recurrent falls in advanced age, raising suspicion for a hereditary ataxia. Workup for

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treatable causes of ataxia including serum vitamin E, anti-GAD65 antibodies, gliadin antibodies, and paraneoplastic panel was unremarkable. A repeat expansion panel for spinocerebellar ataxias (Fulgent) was negative. Whole exome sequencing revealed two pathogenic variants in the ATM gene. Although phase could not be confirmed, the recessive inheritance pattern and clinical phenotype suggest the variants are likely in trans and causative. The patient's age at onset and diagnosis is highly atypical, representing one of the oldest reported cases of A-T.

Results: This case expands the phenotypic spectrum of A-T, demonstrating that biallelic ATM mutations may present with isolated cerebellar ataxia in late adulthood. The absence of telangiectasias, immunodeficiency, or malignancy at diagnosis underscores the variability in clinical expression and the importance of genetic testing in atypical cases. The ATM gene plays a central role in DNA repair and cell cycle regulation. Haploinsufficiency and compound heterozygosity have been implicated in a range of phenotypes, including adult-onset ataxia, breast cancer susceptibility, and neurodegeneration. While most A-T cases present in childhood, milder or atypical forms may remain undiagnosed until later in life.

Conclusion: This case illustrates the diagnostic utility of WES in adult-onset cerebellar syndromes and highlights a rare presentation of A-T in late life. WES can uncover rare genetic aetiologies in adult-onset cerebellar syndromes, prompting reconsideration of age-based diagnostic assumptions and enabling targeted management. The scientific relevance of this abstract lies in its contribution to expanding the diagnostic and phenotypic understanding of ataxia-telangiectasia (A-T), particularly in late-onset presentations. Traditionally considered a paediatric neurodegenerative disorder, A-T is rarely recognized in older adults due to its early onset and multisystem involvement. This case challenges that paradigm by documenting a 75-year-old woman with isolated cerebellar signs and pathogenic ATM variants making her one of the oldest reported individuals with a likely A-T diagnosis.

M240: When Dopa-Responsive Dystonia Is Not So Dopa-Responsive: An Atypical G

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Background: Dopa-responsive dystonia (DRD) is classically associated with childhood- or adolescent-onset lower limb dystonia with diurnal fluctuations and a sustained, dramatic response to low-dose levodopa, without long-term complications. It is most commonly caused by pathogenic variants in the GCH1 gene, which encodes guanosine triphosphate cyclohydrolase 1, a key enzyme involved in the pterin pathway. Consistent with its autosomal dominant inheritance pattern, a positive family history is frequently present.

Methods: We report a genetically confirmed case of GCH1-related dystonia presenting with atypical clinical features.

Results: A 47-year-old man presented with a 7-year history of spasms involving the neck and right-sided extremities, along with prominent jerky movements of the head and shoulders. The family history was unremarkable.

Neurological examination revealed a cervical dystonia with jerky head tremor, which improved with a tactile sensory trick. During gait, right foot dragging and torsional trunk dystonia were evident. Levodopa-associated dyskinesias were also observed, an uncommon finding in GCH1-related DRD. Genetic testing confirmed heterozygous variant in the GCH1 gene. However, the phenotype was atypical for classic DRD. In contrast to the usual childhood onset, and predominant lower-limb involvement, our patient presented with an adult-onset cervical dystonia. Moreover, he showed only a mild response to levodopa despite a relatively high daily dose of 800 mg and no diurnal fluctuations were reported. Treatment was optimized with levodopa (800 mg/day) and clonazepam (3 mg/day), in combination with botulinum toxin injections for his cervical dystonia.

Conclusion: This case illustrates that genetically confirmed GCH1-related dystonia may present outside the classic Segawa phenotype. Absence of diurnal fluctuation, family history, or dramatic levodopa responsiveness should not exclude the diagnosis. Recognition of atypical DRD presentations is essential to avoid missing this treatable condition.

M241-K: Mechanistic Cross-talk Between LRRK2 and GBA1 in Regulating Lysosomal Function and Inflammatory Activity in Microglia

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Background: Examination of genetic etiologies of Parkinson's disease has revealed multiple genes involved in regulation of lysosomal function. This includes the two genes most commonly linked to Parkinson's disease, GBA1 and LRRK2. GBA1 encodes the lysosomal enzyme GCase and LRRK2 has been shown to regulate lysosomal function by multiple mechanisms. The goal of this study is to evaluate the mechanistic interaction between LRRK2 and GBA1 in regulating lysosomal function in microglia and to examine the impact of these genes on inflammatory responses of microglia to CNS substrates.

Methods: To address the mechanistic cross-talk between LRRK2 and GBA1 we generated induced pluripotent stem cells (iPSCs) from fibroblasts obtained from PD patients harboring both the GBA1 N370S and LRRK2 G2019S variants. Isogenic control iPSCs were produced using CRISPR/Cas9 technology to correct the LRRK2 variant, GBA1 variant, or

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both. These iPSCs were differentiated into microglia (iMGs) and the impact of the LRRK2 and GBA1 variants on lysosomal activity was assessed by measurement of lysosomal protease expression and activity, immunocytochemical analysis of lysosomal morphology, and analysis of phagocytic uptake of exogenous myelin and alpha-synuclein. In addition, the effects of myelin and alpha-synuclein on inflammatory profiles was assessed via measurement of secreted cytokines.

Results: iMGs generated from PD patients harboring both the GBA1 N370S and the LRRK2 G2019S variants displayed aberrant lysosomal morphology with enlarged lysosomes, as well as reduced lysosomal protease activity as measured by DQ-BSA. However, preliminary analysis showed that iMGs harboring both the GBA1 N370S and LRRK2 G2019S variants displayed higher lysosomal GCase enzymatic activity compared to isogenic single GBA1 mutant iMGs. Evaluation of a panel of secreted cytokine demonstrated no genotype-specific differences in cytokine levels in iMGs treated with alpha-synuclein or myelin.

Conclusions: Examination of iPSC-derived microglia harboring dual pathogenic mutations in the GBA1 and LRRK2 genes revealed that double mutant iMGs display multiple defects in lysosomal function. However, lysosomal GCase activity appears to be higher in double mutant iMGs compared to GBA1 single mutant iMGs, suggesting that LRRK2 G2019S may mediate a possible compensatory increase in lysosomal GCase activity in microglia.

M242: Machine Learning Identifies GBA1 and LRRK2 Molecular signatures in Sporadic Parkinson's Disease Patients Beyond Clinical Phenotypes

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Background: Clinical trials in Parkinson's disease (PD) have been unsuccessful, in part due to patient molecular heterogeneity. We hypothesized that blood transcriptomic classifiers trained on the two most common genetic forms of PD - GBA1 p.N370S and LRRK2 p.G2019S - could identify homogeneous molecular subtypes within sporadic PD that are missed by clinical phenotyping.

Methods: In the PPMI cohort (AMP-PD baseline RNA-seq, n=671), we trained elastic-net models for GBA1-PD (n=89) vs sporadic PD (n=394) and LRRK2-PD (n=188) vs sporadic PD across 100 held-out splits to identify enriched patients. We performed pathway and module analyses on model-driving genes, baseline clinical phenotyping, and orthogonal CSF proteomic follow-up (n=405).

Results: GBA1 and LRRK2 models showed median held-out AUCs of 0.728 and 0.723, respectively, against sporadic PD cases, identifying 15 GBA1-like, 32 LRRK2-like, and 11 dual-enriched patients. GBA1-vs-LRRK2 discrimination was near chance (AUC 0.565), suggesting overlapping rather than independent pathways. Shared stable genes driving the two models revealed significant enrichment in ATP-synthesis / chemiosmotic-coupling pathways (FDR = 0.0103). Genes for the LRRK2 model revealed a glycogen-metabolism / oxidative-phosphorylation enrichment signature (FDR = 0.0044 / 0.0318). Genes for the GBA1 model showed enrichment for ATP-synthesis / aerobic-respiration (Reactome FDR=0.033). Gene expression module analysis revealed that GBA1 model genes overlapping with the respiratory pathways strongly separated GBA1-like from remaining sporadic PD (FDR=7.5×10^{-6}) and from LRRK2-like sporadic PD (FDR=0.002), while not separating LRRK2-like from remaining sporadic PD (FDR=0.70). Enriched sporadic subgroups showed limited clinical separation, although LRRK2-enriched patients had lower disease progression and higher RBD burden, and GBA1-enriched patients had worse olfaction versus remaining sporadic PD. CSF proteomics showed small overlap with the respiratory module, with one protein showing same-direction and nominal support for separating GBA1-like vs remaining sporadic PD (NDUFB8, p=0.022; FDR=0.066).

Conclusion: Blood transcriptomics identifies reproducible GBA1 and LRRK2 enriched molecular signatures in sporadic PD that are not captured by baseline clinical phenotypes. These results support molecular trial enrichment and prioritizing bioenergetic pathways for functional follow-up.

M243: Patients Taking Once-Daily Valbenazine Report Improved Quality of Life/Functionality and Experience Remission of Tardive Dyskinesia Symptoms: Findings From the KINECT-PRO™ Trial

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Background: Valbenazine is approved for tardive dyskinesia (TD), a persistent drug-induced movement disorder associated with physical, social, and emotional impacts. KINECT-PRO™ (NCT05859698) is the first and only clinical trial to assess and report the effects of an approved TD medication (valbenazine) on quality of life (QoL) and functionality using multiple validated patient-reported outcomes (PROs).

Methods: Participants received once-daily valbenazine (40, 60, or 80 mg) for 24 weeks. Participants had at least mild TD movement severity (per Abnormal Involuntary Movement Scale [AIMS] item 8) and awareness of their TD with at least mild associated distress (per AIMS item 10). Primary endpoints included changes from baseline to Week 24 in 3 PROs: Tardive Dyskinesia Impact Scale (TDIS, the only psychometrically validated PRO developed for TD);

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Sheehan Disability Scale (SDS); and EuroQoL Group's EQ Visual Analog Scale (EQ-VAS). The mean change at Week 24 in AIMS total score (sum of items 1-7, secondary endpoint) and the percentage of participants reaching TD symptomatic remission (score ≤1 on all AIMS items 1-7) (post hoc analysis) were also evaluated.

Results: Mean TDIS scores at baseline (n=54) indicated QoL/functional impacts, even in participants with mild TD severity per clinician assessment. Robust and continued improvements were observed across all outcomes, with mean changes from baseline to Week 24 as follows: TDIS (-8.0), SDS Work/School (-1.2), SDS Social/Leisure (-2.3), SDS Family/Home (-1.6), EQ-VAS (+13.1), AIMS (-6.8); n=45 except for all outcomes except SDS Work/School (n=10). Mean improvements that exceeded minimal clinically important differences for TDIS (-4 points) and AIMS (-2 points) were observed in participants regardless of TD severity at baseline: mild (AIMS item 8 score=2: TDIS -6.8, AIMS -5.6 [n=20]); moderate or severe (AIMS item 8 score=3 or 4: TDIS -8.9, AIMS -7.8 [n=25]). Overall, 57.8% (26/45) of participants met the threshold for TD symptom remission at Week 24.

Conclusion: These results highlight valbenazine as the only VMAT2 inhibitor with robust datasets that demonstrate improvements in QoL/functionality, along with high rates of symptomatic remission, regardless of primary psychiatric condition or movement severity.

M244: Once-Daily Valbenazine Demonstrates Greater and More Predictable Pharmacokinetic Exposure and VMAT2 Target Occupancy in the Brain Than Deutetrabenazine Extended-Release: A PET Study

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Background: Inhibition of vesicular monoamine transporter 2 (VMAT2) is a proven approach for successfully treating tardive dyskinesia. Target occupancy (TO) is the percentage of a target (e.g., VMAT2) that is bound by a drug and can be measured with positron emission tomography (PET) imaging. A relationship between VMAT2 TO and clinical efficacy was predicted in a previously published analysis linking PET data to efficacy. This crossover study in healthy male adults was conducted to measure brain VMAT2 TO after single doses of two VMAT2 inhibitors: INGREZZA® (valbenazine [VBZ]), a once-daily medication; and AUSTEDO XR® (deutetrabenazine extended-release [DTBZ XR]), a once-daily formulation of DTBZ with no published clinical safety or efficacy data.

Methods: Study participants (N=8) received VBZ (40 or 80 mg) followed by ≥7-day washout and then DTBZ XR (24 or 48 mg), or vice-versa (i.e., DTBZ XR, then washout, then VBZ). [^{18}F] AV-133 PET scans were conducted when plasma concentrations for the active dihydrotetrabenazine (HTBZ) metabolites were expected to be maximal: 6-8 hours post-dose for VBZ metabolite ([+]-α-HTBZ); 3-5 hours post-dose for DTBZ XR metabolites (total of [+/-]-α-deuHTBZ and [+/-]-β-deuHTBZ). Outcomes included VMAT2 TO and plasma concentrations of HTBZ metabolites for 24 hours after VBZ and DTBZ XR doses, which were modeled to calculate half-maximal effective concentration (EC_{50}). Pharmacokinetic exposure modeling and EC_{50} values enabled predictions of steady-state TO.

Results: VMAT2 TO levels were higher after single doses of VBZ (40 and 80 mg) than single doses of DTBZ XR (24 and 48 mg). A linear mixed-effects model yielded a least-squares (LS) mean VMAT2 TO of 76.5% for VBZ and 38.3% for DTBZ XR, with a LS mean difference of 38.2% (P=0.0002). EC_{50} values for VBZ and DTBZ XR were 3.9 and 30.3 ng/mL, respectively. Predicted steady-state VMAT2 TO levels were higher for VBZ (82% for 40 mg, 92% for 80 mg) than for DTBZ XR (52% for 24 mg, 68% for 48 mg). 24-hour plasma concentrations of HTBZ metabolites showed high inter-individual variability with DTBZ XR and a more consistent-dose dependent pattern with VBZ.

Conclusion: Substantially greater VMAT2 occupancy predicted at steady state, based on EC_{50} values and predicted steady-state plasma concentrations, suggests greater potency (i.e., quantitatively higher engagement of the VMAT2) with VBZ than with DTBZ XR. Furthermore, less variability in plasma metabolite concentrations suggests more predictable, dose-dependent interpatient exposure with a once-daily medication (VBZ) than with a once-daily formulation (DTBZ XR).

M245: Multi-locus Genetic Dosage Shapes Cognitive Disease Progression in Parkinson's: 15-year meta-analysis of 24 cohorts

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Background: Progression from Parkinson's disease (PD) to dementia is a major clinical concern. Although several progression-associated loci have been identified, their cumulative effects on cognitive decline have not been systematically evaluated. To assess the dose-dependent effect of five candidate progression loci linked to synaptic vulnerability (RIMS2, TMEM108, GBA1) and amyloid–tau pathology (APOE, WWOX) on dementia risk in PD with large-scale longitudinal data.

Methods: We analyzed 7,745 participants with PD from 24 longitudinal cohorts representing three types of longitudinal study designs (12 biomarker cohorts, 7 population-based cohorts, and 5 clinical trial cohorts) in the International Genetics of Parkinson's Disease Progression (IGPP) consortium, comprising 28,737 longitudinal clinical visits with cognitive assessments and 15 years of follow-up (median, 3.3 years). Patients were classified according to the number of progression-associated loci carried (0, 1, 2, or ≥3 loci). Dementia risk was evaluated using random-effects meta-analyses of cohort-specific Cox proportional hazards models and frailty Cox models applied to pooled individual-level data.

Results: Dementia risk increased monotonically with the number of progression loci (0, 1, 2, or ≥3). A single locus conferred a 1.56-fold increase in risk (hazard ratio (HR) = 1.56, 95% CI: 1.28–1.89), rising to 3.21-fold for two loci (HR = 3.21, 95% CI: 2.19–4.70) and 7.49-fold for three or more loci (HR = 7.49, 95% CI: 4.98–11.28). Individually, GBA1 (HR = 2.09), APOE ε4 (HR = 1.71), RIMS2 (HR = 1.90), TMEM108 (HR = 2.05), and WWOX (HR = 1.56) were associated with dementia risk, but there was heterogeneity between clinical trials, biomarkers, and population-based cohorts.

Conclusion: Multi-locus dosage increases dementia risk in a monotonic manner and may improve stratification and clinical trial design in PD.

M246: Patterns of Use and Clinical Utility of Alpha-Synuclein Skin Biopsy at a Rural Tertiary Neurology Center

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Background: Detection of alpha-synuclein via skin biopsy is a validated biomarker for synucleinopathies: Parkinson disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and pure autonomic failure [1]. The objective of this study was to characterize patterns of its utilization and impact on clinical management at a single academic neurology center.

Methods: We retrospectively reviewed patients in which alpha-synuclein skin biopsies were ordered between July 2024 and March 2026 within Geisinger Health System. Clinical documentation was reviewed to determine testing indications, specialty of ordering provider, diagnostic yield, changes in clinical management following results, and – when applicable – concordance with dopamine transporter (DAT) scan findings.

Results: Seventy-two out of 124 patients (58%) had completed biopsy results available by the end of the study period and were included in the analysis. Just over half of biopsy orders (51%) were placed by cognitive neurologists, with the remainder ordered by general or neuromuscular neurologists. The most common indication (41%) was differentiation of synucleinopathies from other causes of parkinsonism or tremor, including essential tremor, drug-induced parkinsonism, vascular parkinsonism, and normal pressure hydrocephalus. In this subgroup, biopsy results changed clinical management in 46% of cases. Testing was used to exclude synucleinopathies in five patients with suspected tauopathies: progressive supranuclear palsy and corticobasal degeneration. In 22% of cases, biopsies were obtained to distinguish Alzheimer disease (AD) from DLB or to assess for alpha-synuclein co-pathology in patients with AD. In the remaining cases, the working diagnosis was a synucleinopathy - most commonly idiopathic PD - and biopsy served as a diagnostic adjunct. Overall, 26% of biopsies were abnormal, with most abnormal results occurring in patients whose pre-test diagnosis was PD or DLB. Thirteen patients also underwent DAT imaging. Among these, seven demonstrated discordant findings, with one modality normal and the other abnormal.

Conclusion: Alpha-synuclein skin biopsy was most frequently used to distinguish synucleinopathies from mimics, mirroring patterns of DAT scan utilization [2]. An emerging application was the assessment of alpha-synuclein co-pathology in patients with AD to predict therapeutic response for anti-amyloid disease-modifying therapy. The predominance of normal biopsy results suggests that the test is commonly used to rule out synucleinopathies. Interestingly, none of the biopsies were ordered by movement disorder specialists, perhaps owing to higher confidence in their clinical judgment. Discordance between skin biopsy and DAT imaging could not be fully explained by tauopathy diagnoses alone and warrants further investigation.

M247: Non-Motor Medication Trajectories in Early Parkinson's Disease by Dopaminergic Therapy Status

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Background: Non-motor symptoms commonly emerge across the course of PD, including prodromal period, and often prompt pharmacological management. Whether

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longitudinal patterns of non-motor medication use diverge according to dopaminergic therapy status during the early phases of PD remains unclear. Our goal is to characterize early longitudinal trajectories of non-motor medication use in Parkinson's disease (PD) according to dopaminergic therapy status.

Methods: We analyzed longitudinal data from 1,376 individuals with PD enrolled in the Parkinson's Progression Markers Initiative (mean age 62.0 years; 549 male), with medication records anchored to PD diagnosis (Time 0) and extending through five years of follow-up (5,111 observations). Concomitant medications for common non-motor symptoms (sleep, depression/anxiety, constipation) were classified by clinical indication. Mixed-effect logistic regression models (separate for medication classification; outcome: use vs. non-use) tested years since diagnosis, dopaminergic therapy status (time-varying yes/no), and their interaction, adjusting for age, sex, education, and early-onset PD (< 50 years), with random intercepts for participant.

Results: Sleep-related medication use showed a significant interaction between years since diagnosis and dopaminergic therapy status (OR = 2.07, 95% CI = 1.33 – 3.22), indicating a steeper increase in the odds of sleep -medication use over time among participants receiving dopaminergic therapy compared with those not receiving therapy. For depression/anxiety medications, participants receiving dopaminergic therapy had lower odds of use at time 0 (OR = 0.33, 95% CI = 0.14 – 0.77). Odds declined over time among those not receiving therapy (OR = 0.65 per year, 95% CI = 0.44 – 0.96), but the significant interaction indicates that patients receiving therapy showed a significantly attenuated decline over time (interaction OR = 1.89, 95% CI = 1.25 – 2.86). For constipation-related medications, dopaminergic therapy was associated with lower odds of constipation-medication use at time 0 (OR = 0.20, 95% CI = 0.05 – 0.77), but odds increased more rapidly over time among those receiving dopaminergic therapy (interaction, OR = 2.85, 95% CI = 1.42 – 5.74). No additional main effects of interactions reached statistical significance.

Conclusion: Non-motor medication trajectories diverge early after PD diagnosis by dopaminergic therapy status and non-motor symptom domain, with the strongest separation observed for autonomic symptoms, followed by sleep and mood symptoms. These early, domain-specific divergences suggest parallel, non-synchronous neurodegenerative processes unfolding alongside nigrostriatal motor pathway degeneration and provide a mechanistic framework for the high predictive value of REM sleep behavior disorder in PD.

M248: Integrative Medicine Use in Parkinson's Disease: A Mixed-Methods Study of the UCLA Center for East-West Medicine

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Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by both motor and non-motor symptoms which impact quality of life. While pharmacologic therapies such as levodopa remain the cornerstone of treatment, many patients continue to experience persistent symptoms, medication-related side effects, and unmet supportive care needs. Integrative medicine combining conventional medical treatments with evidence-based non-pharmacologic therapies has emerged as a promising approach to address these gaps. The UCLA Center for East-West Medicine (CEWM) provides a clinical setting where integrative modalities including acupuncture, Tai Chi, and mind-body interventions-are incorporated into longitudinal PD care. However, real-world data on utilization patterns, patient-reported outcomes, and perceived benefits of integrative modalities in PD remain limited.

Methods: We conducted a mixed-methods study of PD patients receiving care at the UCLA CEWM. A retrospective electronic medical record review was performed to characterize patient demographics, clinical features, and utilization of integrative therapies. Quantitative outcomes included symptom domains documented in clinical encounters, such as pain, sleep disturbances, mood symptoms, and motor function. Additionally, qualitative interviews were conducted with a subset of patients to explore their experiences with IM therapies, perceived benefits, barriers to access, and motivations for seeking integrative care. Thematic analysis was performed on interview transcripts to identify recurring patterns in patient perspectives.

Results: We identified a cohort of patients with Parkinson's disease (N=236) receiving care at the UCLA CEWM and are characterizing patterns of integrative therapy utilization. Ongoing analyses are evaluating associations between specific integrative modalities and key symptom domains, including pain, sleep disturbances, and mood symptoms. In addition, the study examines healthcare utilization outcomes, including opioid use, emergency department visits, and referral indications to integrative medicine services. Concurrent qualitative interviews are being conducted to further explore patient perspectives on integrative care, including perceived benefits, motivations for use, and barriers to access.

Conclusion: Integrative medicine represents a valuable adjunct in the management of Parkinson's disease, particularly for addressing non-motor symptoms and enhancing quality of life. Findings from this mixed-methods study highlight the real-world applicability and patient-perceived benefits of integrative medicine within an academic health system. Expanding access to integrative therapies, improving referral infrastructure, and incorporating these approaches into multidisciplinary PD care models may help address existing gaps in care. Future studies can focus on standardized outcome measures and multi-site collaborations to further evaluate the efficacy of integrative neurology interventions.

M249-K: Robust and multi-mechanistic Enhancement of Neuronal Autophagy to Rescue Parkinson Disease

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Farah, BS, Johns Hopkins University, Yifei Yang, BS, Johns Hopkins University, Lan Wang, PhD, Johns Hopkins University

Background: Parkinson disease (PD) is an incurable and neurodegenerative movement disorder imparting disabilities on patients due to progressive motor and non-motor symptoms. Degeneration of susceptible neurons in PD is related to toxic misfolding and aggregation of the protein alpha-synuclein (asyn), exacerbated by a decline in the protein-clearance pathway of autophagy. Although pharmacologic stimulation of autophagy is a putatively attractive therapeutic intervention, this strategy fails to produce rescue effects due to neuronal resistance to these stimulatory agents, due to genetic and regulatory inhibitory effectors that are enriched in PD neurons. In particular, we found that an autophagy axis operating through the transactivator, TFEB, and the chaperone, BAG3, were hypofunctional in human neurons with PD pathology. However, the optimal strategy for leveraging this pathway to rescue neurodegeneration remains undefined.

Methods: To study the molecular pathobiology of PD and candidate therapy strategies with unprecedented detail, we stably integrated a new Tet-ON rapid differentiation cassette into the genomes of human induced pluripotent stem cells (iPSCs) to enable efficient (>99%) differentiation into mature dopaminergic neurons (iDNeurons) within 14 days. To model PD, we used iPSCs expressing a homozygous mutation in SNCA (c.209G>A, p.A53T), or a heterozygous GBA1 mutation (c.1226A>G, p.N370S). To potentiate the autophagy, we used lentiviral delivery of CRISRPa to modify genetic targets of interest, then assessed effects on asyn, autophagy substrates, mitochondrial health, and cell viability.

Results: In WT and PD iNeurons, overexpression of TFEB or BAG3 lead to significant clearance of both autophagy substrates LC3-II and p62, but also oligomeric and aggregated forms of asyn in PD neurons, and improved markers of mitochondrial homeostasis. Overexpression of these factors also increased cell survival in PD iNeurons. Genetic knockdown of these factors exacerbated PD pathology in WT neurons. A screen of pharmacologic inducers of neuronal autophagy that enhancing expression of these factors also produced similar phenotypic rescue in PD neurons. These effects were abrogated by bafilomycin, but not bortezomib.

Conclusions: Genetic and pharmacologic enhancement of the TFEB-BAG3 pathway not only promoted autophagic degradation of toxic forms asyn, but also rescued neurodegeneration in multiple heritable forms of PD. Together, our findings inform discrete and specific molecular targets of high translational potential for therapy development for PD and related synucleinopathies.

M250: Identifying Proteins of Mitochondria-Lysosome Contact Sites with a Proximity-Labling Approach

Presenting Author(s): *Robert Coukos, Northwestern University - Feinberg School of Medicine, Chicago, IL*

Background: Several causal and risk genes implicated in Parkinson's disease are mitochondrial and lysosomal genes. Mitochondria and lysosomes are essential subcellular organelles that participate in key energetic, metabolic, and protein quality control pathways. Therefore, functional crosstalk of these organelles may be a point of convergence which integrates the effects of diverse pathogenic mechanisms. Our lab has demonstrated that the interplay between mitochondria and lysosomes includes their physical association at mitochondria-lysosome contacts (MLC). A primary function of MLC is regulating organelle dynamics, including the fission of mitochondria and the motility of lysosomes. Our group and others have also demonstrated important roles of these contacts in cellular metabolism, including transfer of metabolites such as calcium and amino acids, axonal transport of mRNA, and mitochondrial quality control. Multiple proteins participating in functions at mitochondria-lysosome contacts have been reported. However, a broader survey of MLC proteins is still needed. Capturing the proteome of MLC in an unbiased manner will suggest novel functions which occur at these contact sites and will enable us to identify dedicated molecular tethers between these organelles.

Methods: To identify MLC proteins, we employed a biotin ligase proximity labeling approach. TurboID is an engineered enzyme that nonspecifically conjugates biotin (vitamin B7) to nearby proteins in living cells. Using streptavidin-based affinity purification techniques, biotin-labeled proteins are enriched and identified by mass spectrometry. To capture MLC proteins, we adapted a split version of TurboID, in which the enzyme is separated into two domains that are independently targeted to the outer mitochondrial membrane and to the lysosomal membrane. With split TurboID, protein labeling occurs only at MLC, where association of the two domains reactivates biotin ligase activity.

Results: Using split TurboID, we generated a dataset of proteins labeled in the vicinity of MLC. As expected, the data shows substantial enrichment of mitochondrial and lysosomal proteins. We further compared the data to baseline mitochondrial and lysosomal proteomes generated with full-length TurboID targeted to those compartments. The result is a list of proteins with specific, high-confidence enrichment at MLC. One notable category of hits included proteins that interact with Rab GTPases, which regulate endosomal/lysosomal activity. Another category was membrane trafficking proteins, including SNARE proteins.

Conclusion: We are now employing orthogonal biochemical analyses to validate the enrichment of top-scoring proteins at MLC. We are also examining how these proteins contribute to the frequency and stability of mitochondria-lysosome contacts in living cells.

M252*: Low Density Lipoprotein Receptor-related Protein 1 (LRP1) Regulates Microglial Uptake of Alpha-synuclein

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Background: Alpha-synuclein (aSyn) is the major protein constituent of Lewy bodies and Lewy neurites and its aggregation plays a pathogenic role in Parkinson disease and other synucleinopathies. Blocking the transmission of pathological aSyn within neural networks represents a promising therapeutic strategy to slow or halt disease progression. Although the exact mechanisms underlying the transmission of pathological aSyn aggregates remain to be elucidated, mounting evidence suggests that multiple cell surface receptors including lymphocyte activation gene 3 (LAG3) and amyloid precursor-like protein 1 (APLP1) facilitate binding and uptake of aggregated aSyn in neurons and glia. Low-density lipoprotein receptor-related protein 1 (LRP1) was shown to mediate uptake of aSyn in iPSC-derived neurons, and neuronal deletion of LRP1 mitigated spreading of aSyn pathology in mice. Because LRP1 is also highly expressed in microglia, which are involved in spreading of aSyn pathology, we hypothesized that LRP1 may be involved in microglial phagocytosis of aSyn.

Methods: We used complementary pharmacologic and genetic models to investigate the role of LRP1 in aSyn uptake by microglia, using fluorescently labeled recombinant aSyn monomer protein and pre-formed fibrils.

Results: The LRP1 antagonist receptor-associated protein (RAP) inhibited uptake of aSyn monomer in immortalized BV2 microglial cells in a dose-dependent manner. Using human induced pluripotent stem cell (iPSC)-derived microglia-like cells (iMGL) lacking LRP1, we found that LRP1 deletion markedly reduced uptake of aSyn monomer, and modestly but significantly reduced uptake of aSyn pre-formed fibrils.

Conclusion: These results are aligned with other studies demonstrating that LRP1 regulates tau uptake by neurons and microglia. Additional studies are needed to further explore the impact of these findings on spreading of aSyn pathology and neurodegeneration, but these results may contribute to the molecular understanding of how microglia regulate the pathogenesis of synucleinopathies.

M253: Neuroinflammation in REM Sleep Behavior Disorder

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Background: REM sleep behavior disorder (RBD) is a feature of prodromal synucleinopathy and can precede the onset of Parkinson's disease (PD) by years. Emerging evidence supports a role for inflammation in PD, but the immune response in the prodromal phase remains largely uncharacterized.

Methods: Single-cell RNA-sequencing analysis was performed on CSF and blood from 69 subjects (32 RBD, 13 PD with RBD, 12 PD without RBD, and 12 age-matched controls). Proteomics analysis was performed on CSF and plasma using the NULISA platform. Immune cell populations and protein levels were compared across disease conditions and within the RBD group based on clinical variables including the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), dopamine transporter (DaT) imaging, hyposmia testing, CSF α-synuclein seed amplification assay, and likelihood ratios generated from the MDS prodromal PD calculator, among other measures.

Results: We identified a low-grade CSF pleocytosis in RBD compared to healthy controls with a specific increase in CSF macrophage number and frequency. CSF macrophages expressed microglia-like markers and showed enrichment of inflammatory pathways in RBD, including JAK/STAT signaling and TNFα pathway genes. Proteomic analysis demonstrated a bimodal pattern of inflammatory marker elevation, with an initial peak in CSF TNFα levels in RBD subjects with low motor severity (MDS-UPDRS Part III total scores) and a second peak in established PD.

Conclusion: We identified immune activation in RBD characterized by increased CSF macrophage abundance and enrichment of inflammatory pathways, including TNFα and JAK/STAT signaling. Based on accumulating evidence, we designed "PRISMS", a prospective, randomized, placebo-controlled clinical trial to assess whether immune-targeted therapy with the anti-TNFα monoclonal antibody adalimumab can slow progression from RBD to overt synucleinopathy (PD, DLB, or MSA).

M254: Boosting Education and Awareness Together for people with Parkinson's Disease (BEATs-PD): Results to Inform a Community Centered Parkinson's Dance and Music Program

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Background: People with Parkinson's Disease (PD) can experience improvements in gait and quality of life through dance, music and rhythm-based therapy. Access to these programs remains limited in communities where specialized care is historically scarce. In response to these barriers, BEATs-PD was developed using a community-based participatory research approach. BEATs PD aims to create a community informed dance and music program for people with PD and their caregivers in Baltimore City.

Methods: A community advisory board and academic team co-developed a survey to assess community dance and music preferences and barriers to participation. The survey was administered to 78 community members with a relationship to PD at 16 tabling events across Baltimore City from May-August 2025. Descriptive frequencies and weighted rankings were used to summarize responses. Results are presented as percentages of respondents for survey items and percentages of total weighted ranking points for ranked preference items.

Results: Respondents were evenly distributed across North/NE/NW, West, East, South/SW, and Central Baltimore, with the largest share from North/NE/NW (31%). Respondents ranged in age from 18 to 91+ years, with nearly 49% of respondents between 61 and 80 years old. Most respondents were female (77%) and 95% identified as African American/Black. 87% of respondents were interested or somewhat interested in attending dance and music classes for PD. Singing accounted for 39% of total weighted class preference points, dancing for 36%, and instrument-based classes for 25%. For singing, the highest ranked music styles were R&B/Soul (17%), Gospel/Spiritual (17%), Blues (9%), and Jazz (9%). For dance, the highest ranked styles were line dancing (18%), gospel aerobics (15%), and chair dancing (14%). The leading music preferences for dance were R&B/Soul (65%), Jazz (64%), and Gospel/Spiritual (63%). Transportation (38%) and scheduling (33%) were the most frequently reported barriers to attendance. 100% of respondents ranked transportation vouchers as the top support needs. Weekly classes (46%) with morning and afternoon time slots (36%) were preferred. Respondents also requested opportunities for social time (68%), shared meals (62%), and learning more about PD (59%).

Conclusion: Taken together, these findings suggest that community members in Baltimore City want an accessible music and movement program built around their preferences, daily routines, and need for social connection. This work showcases the importance of engaging community members early in program design. BEATs-PD offers a model for developing more meaningful and equitable music/movement interventions for people with PD.

M255: Patient Experiences and Perspectives During a One-Week Dopaminergic Medication Washout in Early-Stage Parkinson's Disease: A Qualitative Study

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Background: Therapeutic washout protocols in Parkinson's disease (PD) are used in clinical trials to evaluate disease progression without the overt influence of effective symptomatic treatments. While prior washout studies focused on clinical outcomes, the evaluation of early-stage PD patient experience of undergoing a one-week dopaminergic washout has yet to be examined. This qualitative study addresses this knowledge gap by characterizing early-stage PD patients' expectations, symptom experiences, emotional responses, and post-washout reflections following a one-week dopaminergic medication washout.

Methods: Twenty early-stage PD patients enrolled in this one-week dopaminergic washout study (Vanderbilt IRB#191683; 15M/5F; aged 65.7±6.9 years; medication duration 1.6±0.9 years; levodopa equivalent daily dose 490±414mg). One-hour semi-structured interviews were audio-recorded, transcribed, and coded by two trained coders utilizing a hierarchical coding system. Transcripts were analyzed in an inductive-deductive fashion to identify common themes and develop a conceptual framework.

Results: All 20 patients were interviewed, including one patient who withdrew on day 5 due to intolerable parkinsonian symptoms. Motivations for study participation included a desire to contribute to research in hopes of benefiting other PD patients and learning more about their own disease. Some patients entered the washout with fears that stopping the medication would exacerbate their symptoms, while others predicted the washout would not be difficult. Patients were relieved that study personnel could be easily contacted if needed, which reduced pre-washout anxiety. Symptoms experienced during the washout included sleep disruptions, restless legs, stiffness, and a gradual decline in functional and motor ability that, for many, intensified only in the latter half of the washout. Some patients stated the washout was worse than expected while others indicated it was easier than anticipated. Many patients reflected on new knowledge gained from the washout experience. Some stated that the study confirmed that their medication was controlling symptoms they had not fully appreciated, and others reflected that the washout offered a glimpse of future disease progression. Nearly all participants expressed interest in future research.

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Conclusion: This study provides the first characterization of subjective patient experiences following a one-week dopaminergic washout in early-stage PD. Participants articulated diverse expectations, symptom experiences, and emotional responses, with most expressing willingness to engage in future research. Understanding these patient perspectives is critical for optimizing clinical trial designs, enhancing participant support, and improving retention, all of which influence trial feasibility.

M256: Neural Correlates of Limb-Kinetic Apraxia in Parkinson's Disease: A Scoping Review

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Background: Parkinson's disease (PD) is associated with disabling deficits in fine motor control that extend beyond bradykinesia and interfere with activities of daily living. Limb-kinetic apraxia (LKA) – characterized by loss of precise, independent, coordinated finger and hand movements beyond what is attributable to bradykinesia - has been proposed as a contributor to impaired skilled-movement execution in PD. However, LKA's clinical overlap with the cardinal motor features of PD complicates its diagnosis, and neuroimaging data remain limited, methodologically heterogeneous, and insufficiently integrated, leaving its neural correlates incompletely characterized. The objective of this review is to synthesize available neuroimaging evidence related to LKA in PD.

Methods: A scoping review was conducted in accordance with PRISMA-ScR guidelines. A systematic search of PubMed, Scopus, Web of Science, and Embase (from inception through December 2025) identified original neuroimaging studies in adults with PD that explicitly evaluated LKA or dexterity-related deficits. Screening was performed using Rayyan. Data extraction included imaging modality, task-based and resting-state findings, perfusion and structural alterations, and reported associations with limb-kinetic performance.

Results: Three case-control studies comprising 93 participants were included. Among individuals with PD, disease duration ranged from 2.9 to 7 years. Impaired performance on the coin rotation task was consistently observed, and approximately one-fifth of PD participants (n=10; 10.8%) met criteria for LKA. Neuroimaging findings converged on alterations within the left-lateralized praxis network, particularly the inferior and superior parietal lobules and ventral premotor cortex, along with supplementary motor, premotor, and lateral prefrontal regions.

Reported abnormalities included patterns of compensatory hyperactivation, regional hypoperfusion, altered functional connectivity, and subtle structural changes (cortical thinning).

Conclusion: Although based on a limited number of studies, available evidence suggests a converging neurofunctional pattern involving left-hemispheric praxis and motor-control networks. These findings support the conceptualization of LKA as a distinct motor-cognitive phenotype within PD and highlight the need for larger, methodologically harmonized neuroimaging investigations.

M257: Deep Learning Networks to Predict Phenoconversion in Individuals with Isolated REM Sleep Behavior Disorder

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Background: Isolated REM sleep behavior disorder (iRBD) is a prodromal synucleinopathy that often precedes Parkinson's disease (PD) and dementia with Lewy bodies (DLB). However, noninvasive biomarkers that predict the timing of phenoconversion remain limited. This study aims to estimate time to phenoconversion to PD or DLB using resting-state fMRI and deep learning (DL) to model early brain network changes associated with disease progression.

Methods: iRBD subjects from Shanghai (n=24), Seoul (n=8), and Manhasset (n=8) cohorts underwent longitudinal resting-state fMRI and clinical follow-up. The diagnosis of iRBD was confirmed by polysomnography in all subjects; clinical follow-up was obtained an average of 8.4±1.0 years after the last pre-conversion imaging time point.

Imaging data were preprocessed using FSL and ICA-AROMA, and group independent component analysis was performed using GIFT. A deep learning model (ResNet101) with biologically guided data augmentation and explainable AI was trained using phenoconverters to discriminate those who converted in the initial 5 post-imaging years (≤5 years) from those who converted in the second 5-year period (>5 years). The model was trained and validated on 40 rs-fMRI scans (baseline, 24 and 48 months) from 18 subjects with documented conversion to PD or DLB.

Results: The most discriminative components were distributed across the visual (IC22: occipital cortex), frontal (IC16, IC12: middle frontal cortex, insula, and cerebellum), default

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mode (IC17: precuneus, posterior cingulum), and attention (IC13: occipital cortex) networks. This highlights the importance of higher-order associative and learning subnetworks in differentiating early (≤ 5 years; n=21) from late (> 5 years; n=19) phenoconversion times. Using five-fold cross-validation, we found that the predictive model exhibited excellent, well-balanced performance with area under the curve (AUC) = 0.88. A significant inverse correlation (r=-0.71, $p < 0.0001$; Pearson correlation) was seen between DL phenoconversion network expression and the time to conversion. The overall classification accuracy reached 90%, indicating strong reliability across validation folds. Sensitivity, specificity, and F1 score were at or near 90%, reflecting excellent model performance. Collectively, these findings provide preliminary evidence for the stability, robustness, and translational potential of the proposed approach.

Conclusion: Deep learning analysis of rs-fMRI identified a distributed phenoconversion network that predicts time to conversion to PD or DLB in individuals with iRBD. Network expression was strongly associated with faster phenoconversion, and the model demonstrated high predictive accuracy. These findings support rs-fMRI-based deep learning biomarkers as a potential noninvasive tool for predicting phenoconversion in prodromal PD and DLB and enabling earlier clinical intervention strategies.

M258: Long-term Wildfire Smoke Exposure and Parkinson Disease Diagnoses

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Background: Prior research identifies environmental risk factors for Parkinson's Disease (PD), including ambient air pollution. Long-term exposure to wildfire smoke, an an increasingly important source of air pollution in the Western US, has been previously associated with other neurodegenerative outcomes including dementia diagnoses. Whether long-term exposure to wildfire smoke is associated with PD remains unknown.

Methods: We conducted an open cohort study using electronic health record data from 2008–2023 from Kaiser Permanente Southern California (KPSC), a provider of care to 4.7+ million people. Members aged 50 years and older were eligible for inclusion. We excluded members with an existing PD diagnosis or missing residential address information (<1%). Incident PD was identified using International Classification of Diseases (ICD) 9 and 10 codes. For primary analyses, we assigned census-tract-level 5-year rolling means of wildfire- and non-wildfire-related fine particulate matter (PM2.5), estimated using monitoring and remote-sensing data and machine learning, to members' time-varying residence locations. We estimated the association between 5-year mean wildfire and non-wildfire PM2.5 and PD diagnosis using a discrete-time approach with pooled logistic regression with census tract-clustered standard errors, controlling for biological (age, sex) and social (race, ethnicity, marital status, census tract–level poverty, and population density) variables, smoking status, need for an interpreter during healthcare visits, and calendar year.

Results: Among 2.1 million KPSC members aged ≥50 years, we identified 8,970 incident PD diagnoses. Among those with PD, median (IQR) age was 70 years (63, 77), and most members were male (56%) and non-Hispanic white (58%). We found a 24% (95% CI: 15%, 34%) increase in the adjusted odds of a PD diagnosis per 0.5 μg/m3 increase in 5-year mean wildfire PM2.5 exposure but no association with non-wildfire PM2.5 (OR = 1.00, 95% CI: 0.99, 1.01, per 0.5 μg/m3 increase).

Conclusion: Our analysis identifies a robust association between long-term wildfire PM2.5 exposure and PD, underscoring the potential importance of wildfire smoke exposure as an environmental risk factor for neurodegenerative diseases including PD.

M259: One day accelerated 10 Hz rTMS for Focal Hand Dystonia: A Phase II Clinical Trial

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Background: FHD is a neurological disorder with involuntary postures and pain, and limited benefit from current therapies. We previously showed that a single session of 10 Hz rTMS over the primary somatosensory cortex (PSC) improves motor behavior in FHD. The objective is to evaluate the efficacy of four sessions of 10 Hz repetitive transcranial magnetic stimulation delivered in one day (rTMS) to patients with focal hand dystonia (FHD).

Methods: Nineteen FHD participants enrolled in the clinical trial (NCT 06015672). To date, four subjects were removed and data was collected over fifteen subjects. The study was a double-blind, crossover design. TMS was targeted to PSC using fMRI and electric field modeling. Each participant received a single day of four sessions of active 10 Hz rTMS (16,000 pulses at 90% resting motor threshold) and a separate day of four sessions of sham-TMS. The two study arms were delivered in randomized order with a 20-week washout. TMS effect was evaluated using multiple behavioral assays for hand movement, hand sensation, and hand function. For hand movement, kinematic writing and clinician ratings were collected. Hand sensation was measured using an assay called somatosensory temporal discrimination threshold (STDT). For hand function, a 9-hole peg board assay was collected. The primary outcome measure was the peak acceleration during kinematics writing. Data was statistically analyzed using a paired T-test to compare before and after, mixed-effects model was done for a longitudinal study for repeated measures followed by multiple comparison adjustment.

Results: Preliminary findings from fifteen FHD subjects indicate that one-day accelerated active 10 Hz rTMS significantly improved hand movement compared to sham-TMS for kinematic writing peak acceleration (mean difference -16.17 counts, p= 0.0005, mixed effects model). Active rTMS also improved hand sensation compared to sham-TMS at 4 weeks (-11.2 seconds, p=0.0012), and 12 weeks (-8.20 seconds, p=0.02), with a trend towards significance at 20 weeks (-6.63 seconds, p =0.07). Active rTMS also reduced the duration of task completion in a 9-hole pegboard task compared to sham-TMS at 16 weeks (mean difference -9.12 seconds, p=0.0002, mixed effects model).

Conclusion: Our preliminary findings suggest that a single day of accelerated 10 Hz rTMS to PSC may provide clinically meaningful benefit lasting up to 12 weeks, supporting its promise as a viable therapeutic option for FHD.

M26-LB: Levodopa Response as a Defining Axis of Freezing of Gait in Parkinson's disease: Convergent Evidence from Clinical Testing, Fluid Biomarkers and NET-PET Imaging

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Background: Freezing of gait (FOG) in Parkinson's disease (PD) shows variable levodopa responsiveness, suggesting subtypes with distinct mechanisms. We identified multimodal biomarkers associated with levodopa responsiveness in PD-FOG. The objective is to identify biomarkers of levodopa-responsive and levodopa-unresponsive FOG.

Methods: Mean age was 68.3±8.7 years and mean disease duration was 9.2±6.2 years. Group differences were observed in variables in all domains. Compared with NO-FOG, ONOFF-FOG showed greater functional impairment (MDS-UPDRS-II: d=0.91, p=0.007), worse episodic memory discrimination (Hopkins Verbal Learning Test: d=−0.93, p=0.003), elevated CSF Aβ42 (d=1.85, p=0.028), increased plasma ptau181 and POSTN (d=1.14, p=0.001; d=1.41,p<0.001, respectively), and decreased plasma DDC (d=−0.93, p=0.011). CSF Fractalkine (d=−0.13, p=0.077) and MHPG (d=−1.41, p=0.267) were marginally decreased. In contrast, OFF-FOG showed reduced NET uptake in thalamus, temporal cortex, and locus coeruleus (d≈−0.7 to −1.1, all p<0.05), with decreased DDC (d=−1.11, p=0.006) and VEGFD (d=−1.02, p=0.018) compared to NO-FOG. Several inflammatory / neuronal-injury markers were increased in ONOFF-FOG vs NO-FOG but decreased in OFF-FOG vs NO-FOG, including TREM1 (d=0.78, p=0.024), IGFBP7 (d=0.70, p=0.036), and NEFH (d=0.73, p=0.036). Pairwise classification was strongest for ONOFF-FOG vs. OFF-FOG (balanced accuracy = 83.5%), followed by OFF-FOG vs. NO-FOG (79.5%) and ONOFF-FOG vs. NO-FOG (76.2%).

Results: Multimodal biomarker profiles differentiated FOG phenotypes, with some plasma biomarkers changing in different directions, supporting distinct biology rather than a severity continuum. ONOFF-FOG was associated with cognitive impairment, broad proteomic alterations, and elevated CSF Aβ42, suggesting multisystem involvement and possible early/noncanonical amyloid-related processes. OFF-FOG showed more focal noradrenergic/subcortical alterations. These findings support biomarker-based stratification and subtype-specific therapies in PD-FOG.

Conclusion: Multimodal data were analyzed from 69 individuals with PD. Participants underwent testing in OFF- and super-ON (40% higher dosing than usual)-medication states and were categorized as no FOG (NO-FOG; n=32), levodopa-unresponsive FOG (ONOFF-FOG; n=26), or levodopa-responsive FOG (OFF-FOG; n=11). Data included 23 clinical/neuropsychological measures, 19 CSF and 131 plasma proteins, and norepinephrine transporter

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(NET) PET imaging. Measures assessed in both medication states were treated as separate variables in the analysis, yielding 309 variables. Variables were adjusted for disease duration, standardized to 5 years, and scaled to unit variance. Group differences were evaluated using linear models, η^2, and pairwise t-tests; Coηhen's d was calculated for OFF-FOG and ONOFF-FOG relative to NO-FOG. A cross-validated multinomial logistic regression model evaluated whether biomarkers differentiated groups. Pairwise binary classifiers additionally evaluated separation between each subgroup pair using leave-one-out cross-validation.

M262: Safety Profile of Deep Brain Stimulation for Essential Tremor: A Large-Scale Retrospective Database Study

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Background: Deep brain stimulation (DBS) is an established treatment for medication-refractory essential tremor (ET), providing substantial symptom control while entailing procedural, hardware-related, and stimulation-induced risks. Current safety evidence is largely based on small clinical cohorts, which may underestimate real-world complications. The FDA Manufacturer and User Facility Device Experience (MAUDE) database offers a structured, real-time surveillance platform to characterize postmarketing safety signals in ET DBS beyond the confines of controlled trial settings.

Methods: MAUDE database reports (2015-2025) for DBS systems (FDA code PJS) used in ET were retrieved via openFDA API, filtered for complete ET-specific cases, and classified into procedural, hardware, software, stimulation, and unspecified complications. Descriptive frequencies were calculated, and no inferential testing was performed due to a lack of denominator data.

Results: From the MAUDE database, we identified 1,635 reports, of which 1,459 met the inclusion criteria after screening. Median patient age was 70 years (range, 21 - 94), with 43.7% male; most involved the Activa™ system (76.8%), followed by Percept™ (20.3%). These yielded 3,529 adverse events, led by hardware issues (65.2%), especially extension wire failures (18.7%) and IPG battery failures (15.4%), followed by stimulation-related problems (17.0%), including loss of benefit/tremor return (7.3%) and paresthesia (5.5%), and procedural complications (8.4%) such as lead misplacement (3.9%) and infections (2.6%). Reports comprised 73.2% malfunctions, 26.6% injuries, and 3 deaths (0.2%). All deaths were attributed to complex medical or perioperative factors and were not related to confirmed device malfunction.

Conclusion: Postmarket ET DBS adverse events in MAUDE are predominantly hardware-related, whereas stimulation and procedural complications are less frequent but clinically significant. These findings represent surveillance signals, not incidence estimates or proof of device-attributable harm, and should be interpreted alongside cohort and registry data.

M264: Long-Term Safety and Efficacy of Once-Daily INGREZZA® (Valbenazine) in Huntington's Disease Chorea: Results From the 5-Year KINECT®-HD2 Study

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Background: In KINECT®-HD, a 12-week phase 3 clinical trial, chorea associated with Huntington's disease (HD) significantly improved with INGREZZA® (valbenazine) versus placebo. Participants from this placebo-controlled trial, along with other eligible individuals, were included in KINECT®-HD2 (NCT04400331), a 5-year, open-label study designed to evaluate long-term safety/tolerability of valbenazine and its maintenance of effect in adults with HD chorea.

Methods: KINECT-HD2 participants received valbenazine for up to 5 years, at doses up to 80 mg once-daily (per investigator assessment of response and tolerability). Off-treatment follow-up was conducted 2 weeks after end of treatment or early discontinuation. Treatment-emergent adverse events (TEAEs), including serious TEAEs, were monitored throughout the study. Valbenazine effects on chorea severity were assessed using the UHDRS® Total Maximal Chorea (TMC) score. Mean values are presented with standard deviation.

Results: Of 154 enrolled participants, 78 (50.6%) were female and 144 (93.5%) were white; mean age was 54.1±11.5 years. The median duration of valbenazine exposure was 980 days (~2.7 years), with a range of 1 to 1803 days (~4.9 years). TEAEs were reported in 151 (98.1%) participants and were consistent with previous clinical trials of HD chorea. Three TEAEs were reported in ≥20% of participants: fall (45.5%), somnolence (26.0%), and fatigue (21.4%). Serious TEAEs were reported in 38 (24.7%) participants, with fall (3.2%) being the only serious TEAE reported in ≥2% of participants. The majority of serious TEAEs were judged as unrelated to treatment, and most were managed with symptomatic treatment and/or dose

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reduction. The mean TMC score at baseline was 12.0±3.5, with mean TMC changes from baseline as follows: Wk50 (~1 year, n=115), -5.7±4.1; Wk104 (2 years, n=89), -5.1±4.6; Wk156 (3 years, n=51), -3.5±5.3; Wk208 (4 years, n=42), -3.4±6.2; Wk260 (5 years, n=3), -7.3±3.5; off-treatment follow-up (n=52), -0.8±4.6.

Conclusion: To date, the open-label KINECT-HD2 study is the longest clinical trial of any vesicular monoamine transporter 2 (VMAT2) inhibitor for any indication. The TEAEs in this study were consistent with HD-related symptoms (e.g., fall) and/or adverse events reported in previous clinical trials of VMAT2 inhibitors for HD chorea (e.g., somnolence, fatigue). Improvements in chorea were maintained in participants who received up to 5 years of once-daily valbenazine and returned to baseline after treatment discontinuation. The results of this open-label study complement the findings of the placebo-controlled KINECT-HD study, support the long-term safety/tolerability of valbenazine, and demonstrate its maintenance of effect on chorea in individuals with HD.

M265*: Continued Evaluation of Participants With Parkinson's Disease Through 4 Years After Bemdaneprocel Administration

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Background: Bemdaneprocel is an investigational cell therapy composed of embryonic stem cell-derived midbrain dopaminergic neuron progenitors, under development for the treatment of Parkinson's disease (PD).

Methods: In exPDite (NCT04802733), a Phase 1 open-label trial, 12 participants with PD received low-dose (n=5; 0.9 million cells/putamen) or high-dose (n=7; 2.7 million cells/putamen) bemdaneprocel injected bilaterally into the postcommissural putamen in a single surgical session. A 1-year immunosuppression regimen began immediately preoperatively. Following trial completion, all participants enrolled in a continued-evaluation study through 5 years post transplantation (NCT05897957) for further assessment of safety and clinical outcomes.

Results: Participants (N=12) were a median of 67.0 years of age, 75% male, and 67% White. Median time since PD diagnosis was 9.0 years. Predefined safety, tolerability, and feasibility criteria were met at 1 year; trends toward improvement or stability in clinical assessments were observed through 2 years. Through 3 years post transplantation, adverse events (AEs) were mostly mild or moderate in severity; none were related to bemdaneprocel. Eight treatment-emergent serious AEs occurred, all unrelated to bemdaneprocel. There were no deaths or graft-induced dyskinesias. No intracerebral hemorrhages or mass lesions were observed by MRI. At 3 years post transplantation in the high-dose group, mean (SD) change from baseline in MDS-UPDRS Part III ON scores were −5.7 points (7.5) and OFF scores were −17.9 points (8.5); mean (SD) change from baseline in patient-reported ON times without troublesome dyskinesia was +2.1 hrs (3.2) and in OFF times was −2.0 hrs (3.2). Overall, efficacy measures in the low-dose cohort were stable at 3 years compared to baseline. Results through 4 years will be presented at ANA 2026.

Conclusion: Overall, bemdaneprocel demonstrated a favorable safety profile and maintained improvements or stability across clinical assessments through 3 years. Bemdaneprocel is currently being evaluated in exPDite-2, a Phase 3, multicenter, randomized, double-blind, sham surgery-controlled trial (NCT06944522).

M266: Differential Functions of FIG4 and PIKfyve in PAS Complex Regulation of Peripheral Myelination

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Background: Charcot–Marie–Tooth neuropathy type 4J (CMT4J) is caused by loss-of-function mutations in FIG4, a phosphatase within the PIKfyve–ArPIKfyve–Sac3 (PAS) complex that regulates the endolysosomal phosphoinositide PI(3,5)P2. However, the respective contributions of FIG4 and the PI(3,5)P2-generating kinase PIKfyve to Schwann cell myelination in the peripheral nervous system (PNS) remain poorly defined.

Methods: We used conditional mouse genetics to dissect the functions of Fig4 and Pikfyve in Schwann cells. Fig4flox/flox and Pikfyveflox/flox mice were separately crossed with Mpz-Cre to generate Schwann cell–specific knockouts (scFig4−/− and scPikfyve−/−). Peripheral nerve function was evaluated by nerve conduction studies, morphometric analysis, and behavioral assays.

Results: At 3 months of age, after completion of developmental myelination, scFig4−/− mice exhibited significantly reduced conduction velocity, loss of large myelinated axons, and dysmyelination characterized by small-caliber fibers, irregular myelin, and thin myelin sheath ($P<0.05$). In contrast, 24-month-old scPikfyve−/− mice showed normal nerve conduction and intact myelin architecture with unchanged axonal diameter and myelin thickness compared to littermates Pikfyveflox/flox mice. Following sciatic nerve crush, however, scPikfyve−/− mice developed a significant decline in compound muscle action potential amplitude between 9 and 19 weeks post-injury ($P<0.05$). Gait analysis

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revealed decreased Stand Index (P<0.05) and Max Contact At % (P<0.01), with increased Maximum Contact Area and Print Area of the injured front paw (P<0.05), and increased hindlimb clasping (P<0.01), indicating impaired functional recovery.

Conclusion: FIG4 is essential for Schwann cell-mediated myelination in the PNS, whereas PIKfyve ablation does not cause myelination abnormality, but results in functional impairments. These findings highlight distinct roles of FIG4 and PIKfyve within the PAS complex and suggest that FIG4-specific mechanisms may represent promising therapeutic targets in FIG4-related neuropathies such as CMT4J, while modulation of PI(3,5)P2-dependent pathways may influence regenerative outcomes after nerve injury.

M268-K: Somatosensory Gating Impairment in Adults with Chronic Tic Disorder

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Background: Nearly two-thirds of children and adults with chronic tic disorder (CTD) experience tactile over-responsivity, defined as heightened awareness of and/or behavioral reactivity to commonplace tactile stimuli. In CTD populations, tactile over-responsivity is associated with more severe tics and psychiatric symptoms, as well as worse quality of life. The neurobiological mechanisms underpinning tactile over-responsivity in CTD are unclear, but somatosensory gating impairment is implicated. Somatosensory gating is the physiological process of filtering out repetitive tactile stimuli at early perceptual stages. In the current study, we sought to determine if adults with CTD exhibit impaired somatosensory gating and if somatosensory gating indices are associated with tactile over-responsivity in this population.

Methods: Neurotypical controls and adults with CTD completed rating scales assessing tactile responsivity (tactile items of Sensory Perception Quotient, SPQ-Tactile), tics, and psychiatric symptoms. Participants were then monitored with dense-array EEG during a somatosensory gating paradigm, during which pairs of non-noxious, pneumatic stimuli (25 kPa, 20 ms-duration, 500 ms inter-stimulus interval) were repeatedly administered to the fingerpad of the non-dominant hand second digit (100 trials, 7-7.5 s inter-trial interval). Analyses focused on EEG data from a 10-electrode cluster overlying sensorimotor cortex contralateral to the pneumatic stimulus. Using event-related spectral perturbation analysis, frequency band (i.e., delta 1-4 Hz, theta 4-8 Hz, alpha 8-12 Hz, beta 12-30 Hz, and gamma 30-55 Hz) power was calculated for 100-ms epochs following first and second pneumatic stimuli (S1 and S2, respectively). To contrast band power between groups, we used multiple linear regression analyses, comparing nested models with and without CTD status; models included age, sex, and psychiatric comorbidity status as covariates.

Results: To date, data have been collected for 37 neurotypical (14 M: 23 F, 33.8±12.9 years) and 33 CTD (14 M: 19 F, 31.9±9.5 years) adults. Both groups show reduced deviation from baseline in delta, theta, beta, and gamma power after S2, relative to S1, consistent with gating within each of these frequency bands. Multiple between-group differences are evident in beta and gamma bands. After adjusting for covariates, adults with CTD exhibit: smaller decrease in beta power (i.e., reduced beta desynchronization) in the 100 ms prior to S2 (Wald $\chi\chi2(5)=11.9$, $p<0.05$, $R2=0.13$; $\Delta R2=0.07$), consistent with aberrant processing in anticipation of a predictable stimulus; increased gamma power in the 400 ms after S2 (range of results from gamma band models across these epochs: Wald $\chi\chi2(7)=16.7\text{-}26.0$, all $p<0.05$, $R2=0.31\text{-}0.44$; $\Delta R2=0.09\text{-}0.20$), consistent with impaired gamma band gating; and larger decrease in beta power (i.e., increased beta desynchronization) 300-500 ms after S2 (Wald $\chi\chi2(7)=23.5\text{-}39.9$, all $p<0.01$, $R2=0.29\text{-}0.43$; $\Delta R2=0.07\text{-}0.11$), consistent with impaired beta band gating. Additional between-group differences are evident in other bands, after S1 (theta 0-200 ms) and S2 (delta 400-500 ms). Among CTD adults, increased alpha power in the 100-200 ms epoch post-S1, the time window most strongly linked with tactile awareness, is associated with greater self-reported tactile responsivity ($|rs|=0.37$, $p<0.05$). **CONCLUSION:** Preliminary findings reveal impaired gating of beta and gamma band activity in response to non-noxious tactile stimuli in adults with CTD. Enrollment is ongoing to ensure the study sample size permits sufficiently powered analyses to address the study'shypotheses.

M269: Atypical Parkinsonian Disorders Differential Diagnosis: A Survey of Movement Disorders Specialists

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Background: The atypical Parkinsonian disorders (APDs), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), share many presenting clinical features. Accordingly, the separate diagnostic criteria for these conditions have a large degree of overlap, leading to misdiagnosis, and delays in care and clinical trial enrollment. We aimed to characterize how movement disorders neurologists approach the differential diagnosis of APDs in clinical practice, with the goals of better understanding diagnostic gaps, and informing future development of a clinical decision support (CDS) tool for APDs.

Methods: We developed a Qualtrics survey hosted by the University of Vermont comprised of three sections: 1) Demographics: capturing training status and experience, 2)

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Clinical Questionnaire: where participants categorized whether 14 history-based and 18 examination-based clues from "A General Neurologist's Practical Diagnostic Algorithm for APDs" (Bruno, Neurology Clinical Practice, 2024) were supportive of diagnosis of one or more of the four APDs, and 3) Clinical Use: evaluating familiarity with and utilization of the formal APD diagnostic criteria, and interest in a CDS tool.

Results: 31 movement disorders neurologists (28 in practice, 3 in training) completed the survey, with a mean of 12.06 years' of clinical experience. For MSA, PSP, and CBD, the five most frequently selected clinical clues were highly consistent (each with >93%), whereas DLB showed less consistent clue attribution beyond the two most frequently selected features. When compared to the benchmark of the General Neurologist's Algorithm, respondents more often identified the full set of concordant clues for MSA, PSP, and CBD than for DLB. At the individual clue-level, however, all four APDs were represented among the highest-concordance clues. Awareness of individual APD criteria was high (≥87% for each). Clinical usage patterns were similar: most respondents (>58.1%) reported using each individual APD criteria in >50% of suspected cases. Most respondents indicated receptivity to CDS: >80% reported they would be "Likely" or "Very likely" to use an EHR-based application to assist with criteria application.

Conclusion: Movement disorders specialists showed high concordance in identifying clinical clues specific to MSA, PSP, and CBD. In contrast, responses for DLB were more discordant, possibly reflecting its cross-disciplinary nature.

Respondents reported familiarity with and usage of the published individual criteria, and to a lesser degree, the General Neurologist's Algorithm. Despite the overall high degree of familiarity with the existing diagnostic criteria, respondents overwhelmingly expressed a need for a CDS tool for APDs.

M270: Case Series of Creutzfeldt Jakob Disease presenting as Progressive Supranuclear Palsy

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Co-Author(s): *Maria Noelle Florendo, MD, University of California Davis, Sacramento, CA, Alexandra Duffy, DO, University of California Davis, Sacramento, CA*

Background: Creutzfeldt Jakob Disease (CJD) is a fatal rapidly progressive neurodegenerative disorder with symptoms of dementia, myoclonus, and ataxia. Parkinsonism is a rare presentation of CJD, with even fewer cases presenting with akinetic rigidity and vertical ophthalmoplegia mimicking Progressive Supranuclear Palsy (PSP).

Methods: Case Series

Results: We present three cases of sporadic CJD presenting as PSP. HF was a 67 year-old male with 1 month history of progressive falls, tremor, and ataxia. He was wheelchair bound after 6 months. Exam on presentation was notable for upgaze palsy, profound bradykinesia, and axial rigidity. Initial MRI report was normal, but subsequent MRI at 7 months revealed DWI and FLAIR changes in bilateral cortices. CSF showed positive RT-QuIc, elevated tau, and elevated 14-3-3. HF died 12 months after symptom onset. RG was a 58 year-old male with progressive decline in motor function leading to loss of independence and wheelchair bound by 5 months. Exam was notable for upgaze palsy, bradykinesia, rigidity, ataxia and startle myoclonus. Initial MRI showed mild atrophy. MRI 6 months later revealed DWI and FLAIR changes in bilateral basal ganglia, thalami, and cortex. CSF showed markedly elevated tau and 14-3-3 with negative RT-QuIc. Patient transitioned to hospice and died two weeks after his CJD diagnosis. BK was a 74 year-old male with 8 month history of falls, ataxia, and cognitive decline. Exam was notable for slowed vertical saccades, bradykinesia, and rigidity. Initial MRI showed cortical atrophy. CSF 4 months later showed positive RT-QuIc, elevated tau, and elevated 14-3-3. Patient died 9 months after symptom onset.

Conclusion: Our cases highlight that CJD can present with exam findings consistent with PSP but with distinguishing features of a rapidly progressive course and supportive imaging and CSF analysis. Exam findings included a predominance of upgaze palsy with marked bradykinesia and axial rigidity. One case had supportive features of startle myoclonus. MRI features evolved overtime and CSF findings supported CJD diagnosis. This work adds to the limited, but growing reports of CJD presenting as atypical parkinsonism, specifically PSP. Our case series highlights specific exam findings consistent with PSP including predominance of upgaze palsy along with parkinsonism and features supportive of CJD including startle myoclonus. We hope that the presentation, diagnosis, and natural history of these cases can help contribute to the literature in this field.

M271: Mortality Trends and Demographic Disparities in Progressive Supranuclear Palsy in the United States: A CDC WONDER-Based Analysis (2014-2020)

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Background: Progressive supranuclear palsy (PSP) is a rare and aggressive neurodegenerative disorder characterized by early falls, vertical supranuclear gaze palsy, axial rigidity, and cognitive decline. It is a primary 4-repeat tauopathy, and

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recent studies have identified distinct clinical phenotypes along with emerging fluid and imaging biomarkers that may allow earlier and more accurate diagnosis. Despite advances in understanding disease mechanisms and ongoing tau-targeted clinical trials, PSP remains without an effective disease-modifying treatment.

Methods: We extracted all death records coded with ICD-10 G23.1 from the CDC WONDER Multiple Cause of Death database for 2014 to 2020, restricting analysis to adults aged 45 years and older. Age-adjusted mortality rates (AAMR) were calculated per 100,000 population using the 2000 United States Standard Population. Joinpoint regression (NCI Joinpoint Program v5.0.2) was used to calculate annual percent change (APC) and average annual percent change (AAPC). Stratified analyses were performed by sex, race/ethnicity, age group, census region, urbanization level, and state.

Results: A total of 8,619 PSP-related deaths were recorded. Overall AAMR rose from 0.05 per 100,000 in 2014 to 1.34 per 100,000 in 2020 (AAPC = 97.83%; 95% CI: 73.93–125.01; $p < 0.001$), with a single join point in 2016 (APC = 603.11%; $p = 0.010$) followed by a more gradual increase through 2020. Males accounted for 53.6% of deaths and carried a 53% higher age-adjusted mortality burden than females (AAMR 0.43 vs. 0.28; rate ratio = 1.53). White Americans comprised 90.1% of all deaths; however, Asian or Pacific Islanders demonstrated the steepest sustained increase (AAPC = 15.50%; $p = 0.002$). The 75–84 year age group bore the greatest burden (42.6% of total deaths). The Midwest recorded the highest regional AAMR (0.36); Vermont (0.74) and Minnesota (0.72) had the highest state-level rates, and Mississippi (0.20) the lowest.

Conclusion: This is the first national population-level mortality analysis of PSP using the CDC WONDER database. The dramatic increase in recorded deaths around 2016 most likely reflects improved ICD-10 G23.1 coding practices rather than a true rise in disease incidence. Significant sex-based and geographic disparities underscore the need for targeted clinical awareness campaigns, standardised death certificate coding education, and more equitable access to neurological subspecialty care.

M272: Anxiety as a Primary Predictor of Pain Severity in Parkinson's Disease: A Cross-Sectional Study Using the King's Parkinson's Disease Pain Scale in a Georgian Population

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Background: Pain is a highly prevalent and disabling non-motor symptom of Parkinson's disease (PD), affecting over 80% of patients, yet its clinical determinants remain incompletely defined. This study evaluates the association between pain severity and clinical and neuropsychiatric factors, with a particular focus on anxiety and depression, using the King's Parkinson's Disease Pain Scale (KPPS).

Methods: In this cross-sectional study, 100 patients with PD (aged 45–86 years) were assessed in a specialized movement disorders center in Georgia. Pain severity and subtypes were evaluated using KPPS. Anxiety, depression, cognitive function, disability, and disease severity were assessed using standardized scales (GAD-7, BDI, MoCA, ADL, MDS-UPDRS). Correlation and multiple regression analyses were performed.

Results: Anxiety severity demonstrated a moderate positive correlation with KPPS total score and multiple pain domains and emerged as a significant predictor of KPPS Domains 1, 3, 4, 5, and 6, as well as total pain score. Disease severity independently predicted KPPS Domain 4 (fluctuation-related pain). Depression showed weak correlations and limited predictive value. No significant associations were found between pain severity and sex, cognitive function, or disease duration.

Conclusion: Anxiety is the strongest independent predictor of pain severity in PD, supporting a potential causal relationship. These findings highlight anxiety as a key therapeutic target for reducing pain burden and improving quality of life in patients with PD.

M273: Cognitive and Neuropsychiatric Effects of Home-based, Remotely Supervised Strength Exercise Combined with Guideline-based Aerobic Physical Activity Modification in Parkinson's Disease

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Background: Although physical exercise has been proposed as a non-pharmacological intervention that may improve cognitive and neuropsychiatric outcomes in Parkinson's disease (PD), the effects of different exercise modalities and delivery formats remain unclear. This trial aimed to evaluate the effects of a 24-week home-based, remotely supervised strength exercise program combined with guideline-based aerobic physical activity modification on cognitive function and neuropsychiatric symptoms in PD, and to explore potential biological mechanisms using exercise-related plasma biomarkers.

Methods: In this single-blinded randomized controlled trial, 64 patients with PD (Hoehn and Yahr stage ≤3, age 50–80 years) were randomly assigned to an exercise group (n=32) or a control group (n=32). The intervention consisted of four weeks of face-to-face training followed by 20 weeks of remotely supervised strength training via video-conferencing twice weekly, combined with individualized aerobic physical activity modification. Controls maintained usual activities. The primary outcome was change in Dementia Rating Scale-2 (DRS-2). Secondary outcomes included Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Apathy Scale (AS), and Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) Part 3. Exploratory outcomes included DRS-2 subdomains and exercise-related plasma biomarkers (BDNF, myostatin, VEGF, and IGF-1).

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Results: Of the 64 participants, 62 completed the study, with two dropout in the control group. After 24 weeks, there were no significant between-group differences in changes in the DRS-2 total (p=0.401) or subdomain scores.
However, the exercise group showed greater improvements than the control group in BDI (−1.5 [−2.0 to 1.0] vs. 1.0 [−2.8 to 2.0]; p=0.008), AS (−2.0 [−5.8 to 1.8] vs. 0.0 [−2.0 to 3.8]; p=0.026), and MDS-UPDRS Part 3 (−3.0 [−5.0 to 0.0] vs. 2.0 [−1.0 to 4.0]; p<0.001) scores. BAI score changes did not differ between the groups (p=0.481). In exploratory analyses, plasma BDNF and IGF-1 levels increased significantly in the exercise group compared with the control group.
Conclusion: A 24-week exercise program did not improve cognitive performance in patients with PD but improved depressive symptoms, apathy, and motor function, and increased circulating neurotrophic factors.

M274: *Staged, Bilateral Magnetic Resonance-guided Focused Ultrasound Pallidothalamic Tractotomy in Advanced Parkinson's Disease

Presenting Author(s): *Lindsay Knight, PhD, Insightec, Miami, FL*
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Background: Motor fluctuations and dyskinesia are common in advanced PD and often persist despite optimized medical therapy. MRgFUS is an incisionless technique that enables precise targeting of the pallidothalamic tract at the H1/Field of Forel. This multicenter, phase III study investigates outcomes following staged, bilateral MRgFUS PTT, recently approved by the FDA for advanced PD.
Methods: This prospective, open-label, single-arm trial (NCT04728295) enrolled 84 participants (≥30 years old) across nine international centers. Those eligible underwent unilateral MRgFUS PTT, with eligibility for contralateral treatment assessed after at least 6 months. Primary efficacy was measured by change in MDS-UPDRS Part III OFF (bilateral upper/lower extremity score) at 3 months post-bilateral treatment. Secondary endpoints included MDS-UPDRS Part IV and total Part III OFF scores. Safety was assessed throughout by related adverse events.
Results: Of 84 enrolled, 54 received unilateral treatment; 40 proceeded to bilateral. At 3 months post-unilateral treatment, Part III OFF (treated side) improved by 50% (20.9 ± 5.3 to 10.0 ± 5.4), and Part IV by 56.3% (10.5 ± 3.5 to 4.6 ± 3.7). Following bilateral treatment, bilateral extremity scores improved by 34%, total Part III OFF by 32% (51.3 ± 12.4 to 33.4 ± 11.4), and Part IV by 68% (10.7 ± 3.2 to 3.6 ± 2.9), all statistically significant (p < 0.0001). Improvements were sustained through at least 12 months. Adverse events were mostly mild, with imbalance, dysarthria, and fatigue being most common.
Conclusion: Staged, bilateral MRgFUS PTT offers a safe and effective incisionless option for patients with advanced PD.

M275: Understanding Individual Challenges in Treating and Living with Essential Tremor: Results from a Lived-Experience Focus Group

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Background: ET is a common movement disorder that significantly impacts daily life. In ∼50% of people, medications do not provide ample benefit or cause side effects. For medication-refractory ET, advanced treatments like botulinum toxin, deep brain stimulation, and magnetic resonance-guided focused ultrasound are endorsed by the International Parkinson and Movement Disorder Society but underutilized.
Methods: Eleven people with ET (9M/2F, av. age 74.4yrs, av. tremor 28.6yrs) participated in a two-week asynchronous virtual platform, comprised of private questions and open forum dialogue that promoted participant interaction (aided by RM, LK and KG). Focus group data were compared to database (n=63,611) of ET survey responses to see if there is concordance between large cohort data and individual perspectives.
Results: Participants had a formal diagnosis of ET and reported moderate-severe tremor impact, even with mild tremor severity. All participants tried medication, with 9% reporting satisfaction. Tremor mainly managed by general neurologists (36%) and primary care (36%), less by movement disorder specialists (18%); 9% see no physician. Tremor treatment information obtained only 9% from a physician, while 73% utilized the internet and 18% word-of-mouth. Notably, the database (ET=63,611) similarly reported trying medication (99%) with low satisfaction (12%), and tremor managed by general neurologists (46%) and primary care (43%), not movement disorder specialists (<4%). Key focus group insights discuss a lack of treatment information/awareness, impact on quality of life, variability in treatment experience/effectiveness, desire for non-invasive treatments, community/support, and need for better physician engagement/education.
Conclusion: Individual ET perspectives show notable similarities to large cohorts in daily life, medication satisfaction and tremor management. Negative impacts on quality of life, and lack of satisfaction in current medication and clinical care suggest advanced treatments are warranted, with clinician communication vital.

M276: Long-Term Safety of MR-Guided Focused Ultrasound Thalamotomy in Essential Tremor and Parkinson's Disease: Updated Evidence from Clinical Trials and Real-World Data

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Background: MRgFUS is FDA-approved for the unilateral and staged, bilateral treatment of ET and PD. Over 25,000 procedures have been performed globally. Both clinical trial

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and real-world data demonstrate immediate and sustained symptom improvement, with most adverse events (AEs) being mild and transient.

Methods: Reviewed and compared long-term safety outcomes from pivotal clinical trials (ET thalamotomy [ET-T], recently published ET continued access study [ET-CA], ET staged, bilateral [ET-SB], Parkinson's disease thalamotomy [PD-T], Parkinson's disease pallidotomy [PD-P]) and real-world sources including published literature and post-market surveillance (PMS) data.

Results: Across pivotal trials, most AEs were generally mild (74% ET-T; 85% ET-CA; 85% ET-SB; 72% PD-T; 75% PD-P). Related severe events were rare. The most common treatment-related AEs in thalamotomy procedures were paresthesias (38% ET-T; 34% ET-CA; 33% ET-SB; 25% PD-T) and gait disturbance (36% ET-T; 38% ET-CA; 24% ET-SB; 45% PD-T), with dysarthria more frequent after staged, bilateral MRgFUS (2% ET-T; 12% ET-CA; 24% ET-SB). In pallidotomy treatments, the most common AEs were dysarthria, gait disturbance, and loss of taste (2.9% each). Many AEs resolved within 6 months, and no new or worsening AEs were seen at longer-term follow-up. No declines in cognition have been reported in ET or PD. Literature indicates similar safety, with mostly mild and transient events; two recent case reports describe isolated and rare hemorrhages. The most recent PMS data indicate AEs were reported in 0.41% of 6997 clinical procedures.

Conclusion: Unilateral and staged, bilateral MRgFUS continues to demonstrate a favorable safety profile in ET and PD. Ongoing surveillance is essential to identify rare events, but overall, MRgFUS remains a safe and well-tolerated treatment option in clinical practice.

M277: Tubulin modulation as a potential mechanism for toxicity of the Parkinson's Disease-associated pesticide trifluralin in iPSC-derived models

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Background: Gene environment interactions have been defined in epidemiological cohorts and experimental models of PD, but statistical power and co-exposures have limited the ability to use epidemiology alone to uncover suspected interactions (Sanders 2017, Ritz 2016). Our previous work combining a pesticides wide association study with in vitro treatment of dopamine neurons identified ten pesticides that are directly toxic to neurons (Paul 2023). One of these, trifluralin, acts synergistically with other co-applied pesticides and has effects on non-mammalian microtubule function. Deeper mechanistic understanding of such pesticides can inform neuroprotection strategies and regulatory decisions.

Methods: A recently developed iPSC rapid transgenic synuclein model (Wang et al. Ann of Neurol 2023 Poster S279) was used to examine changes in gene expression following pesticide treatment via bulkRNAseq. Recombinant mammalian tubulin (Cytoskeleton, Inc) was mixed with pesticides and polymerization was measured by plate reader fluorescence. Cytoplasmic and membrane extraction of alpha synuclein was performed as described (Ramalingam 2021) and quantified via multiplex Western Blot (LiCOR). Dopaminergic organoids were treated with pesticides and analyzed via immunocytochemistry and snRNAseq (as in Nolbrant 2025).

Results: Transcriptional changes were measured in high alpha synuclein expressing cortical neurons 72 hours after treatment with trifluralin. Changes in tubulin-related (tbce) and aggregation-related (serf1a) genes are among the transcripts regulated. In a recombinant assay, trifluralin modulated polymerization of mammalian tubulin at sub-lethal doses. Trifluralin treatment of cortical neurons also increased the cytosolic fraction of alpha synuclein.

Dopaminergic neuron organoid models from pooled human iPSC cohorts also demonstrated responses to PD-associated pesticides.

Conclusion: In vitro exposure to the PD-associated dinitroaniline pesticide trifluralin results in a variety of alterations relevant to PD pathology. Unbiased transcriptional analysis suggests functions related to microtubules and protein aggregation. Disruption of mammalian tubulin polymerization and shifting more alpha synuclein to the cytoplasm have implications for neuronal function and alpha synuclein aggregation. More complex pooled organoid models have potential to inform gene x environment interactions of PD-relevant pesticides.

M278: Living with Parkinson's: Development and Planned Evaluation of an Immersive Virtual Reality Simulation for Empathy and Education

Presenting Author(s): *Henry Lewis, Undergraduate Student, University of California, Los Angeles, Daniel Island, SC*

Background: Parkinson's disease (PD) is often recognized for its visible motor symptoms, yet public understanding of its non-motor features and daily burden remains limited. This gap in understanding may contribute to stigma and reduce appreciation of the lived experience of individuals with PD. Immersive virtual reality (VR) offers a promising educational approach by allowing users to experience symptoms rather than observe them passively. This study describes the development of an immersive VR simulation of PD and outlines a planned evaluation of its effects on empathy, symptom knowledge, and attitudes toward the disease.

Methods: This project builds on an existing, functional VR pilot developed in Unity with C# that models both motor

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and non-motor aspects of PD through interactive daily living tasks across progressive disease states. The simulation incorporates controller-based haptic feedback, slowed task performance, timing logic, and adaptive task disruption to represent symptoms such as tremor and bradykinesia. Non-motor symptoms are conveyed through environmental modulation and narrative design, and a medication mechanic dynamically alters symptom burden and task difficulty to reflect treatment timing and symptom fluctuation. To evaluate the simulation's effects on empathy, symptom knowledge, and attitudes toward PD, participants will include students, trainees, and community members, allowing assessment across audiences with varying baseline familiarity with Parkinson's disease. Participants will complete pre-experience assessments of baseline empathy and symptom knowledge, engage with the VR simulation for approximately 15 minutes, and then complete post-experience assessments evaluating changes in understanding and perception. A comparison educational condition using a 45-minute lecture on Parkinson's symptoms and patient experiences will use the same pre- and post-survey instruments.

Outcome measures will include a Likert-scale empathy assessment, a knowledge-based multiple-choice quiz, self-reported attitudinal change, and open-ended reflections. In parallel, structured interviews with individuals living with PD and caregivers will inform development of patient-centered storylines to strengthen narrative authenticity and better represent diverse lived experiences.

Results: A functional VR pilot has been successfully developed and introduced at the University of California, Los Angeles, where it has undergone early refinement based on feedback from students and faculty. Formal evaluation of the simulation's effects on empathy, symptom knowledge, and attitudes toward PD is planned using pre- and post-experience assessments and a comparison lecture condition.

Conclusion: By translating the clinical features of Parkinson's disease into embodied experience, this project seeks to bridge clinical knowledge and lived experience while expanding how immersive technologies can be used for patient-centered education, stigma reduction, and public engagement in neurologic disease.

M279: Alteration of Myelin Polarity as an Early Detection of Myelin Abnormalities in a HNPP model

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Background: Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) is caused by a heterozygous deletion of PMP22, a tetraspan membrane protein of the claudin superfamily with cholesterol-interacting motifs. PMP22 deficiency in HNPP disrupts myelin junctions and increases myelin permeability, which predicts an increase in myelin capacitance. We hypothesized that PMP22 haploinsufficiency increases myelin dielectric polarity (a proxy for increased capacitance), thereby contributing to impaired nerve conduction in the disease.

Methods: Myelin polarity was assessed using Nile Red spectral confocal imaging in peripheral nerves of Pmp22+/− mice (a mouse model of HNPP) and dermal nerves from patients with HNPP.

Results: Pmp22+/− nerves showed significantly elevated myelin polarity in spinal roots and sciatic nerves at 1 and 3 months versus Pmp22+/+ littermates. Elevations were greatest within tomacula, yet were also present in morphologically normal myelinated segments. Polarity elevations were detectable by postnatal day 8 in spinal roots, preceding tomacula; thus, the polarity change is not secondary to tomacula but appears to be a very proximal event. Total cholesterol did not differ between the wild-type and mutant groups, whereas dehydration abolished polarity differences, implicating excess intramyelin water as the primary driver of the increased myelin polarity in HNPP nerves. Dermal myelinated fibers from patients with HNPP showed myelin polarity changes similar to those in Pmp22+/− nerves.

Conclusion: Greater myelin polarity is an early feature in HNPP driven by increased intramyelin water content. The increase in the effective dielectric constant, as reflected by myelin polarity, would increase myelin capacitance and explain impaired nerve conduction in the disease. Nile Red-based lipid-polarity imaging detects polarity abnormality in human nerves and holds translational promise as a minimally invasive biomarker for HNPP and potentially other myelin disorders.

M280: Peripheral Administration of a Novel Stabilized Fc-GDNF Protein Protected Against the Loss of Dopaminergic Neurons in an MPTP Model of Parkinson's Disease

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Background: OBJECTIVE: To assess whether peripherally administered Fc-GDNF can reduce the loss of dopaminergic neurons in an MPTP murine model of Parkinson's disease (PD). BACKGROUND: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Glial cell line-derived neurotrophic factor (GDNF) is a protein that supports neuronal survival. While GDNF has been proposed as a potential therapeutic agent for PD, systemic administration is challenging due to its

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short plasma half-life and limited ability to cross the blood-brain barrier. Therefore, we evaluated the effect of a stabilized Fc-linked GDNF variant in the MPTP mouse model of PD.
Methods: DESIGN/METHODS: Beginning on day minus 7, 10-week-old C57Bl/6 mice were dosed intraperitoneally with vehicle or Fc-GDNF (10 mg/kg) twice weekly. Starting on day 0, mice received MPTP twice daily for 2 days. A sham control group receiving vehicle was included. On day 6, mice were assessed by kinematic gait analysis, and the study was terminated on day 7. Ex vivo analysis quantified tyrosine hydroxylase (TH) neurons in the SNpc and striatal dopamine metabolite levels.
Results: MPTP administration significantly worsened the kinematic gait score, reduced the number of TH-positive neurons in the SNpc, and decreased striatal dopamine levels. Administration of Fc-GDNF was associated with improved kinematic gait score compared to MPTP vehicle-treated mice ($p<0.05$) and was similar to sham controls. MPTP Fc-GDNF-treated mice had a significantly greater number of TH neurons in the SNpc than MPTP vehicle-treated mice ($p<0.0001$), which was comparable to that of sham controls. Finally, striatal dopamine ($p<0.0001$), 3,4-dihydroxyphenylacetic ($p<0.0001$) acid, and homovanillic acid ($p<0.001$) levels were significantly higher in the Fc-GDNF-treated mice when compared to the MPTP vehicle.
Conclusion: Collectively, these data indicate that a peripherally delivered stabilized form of GDNF protected dopaminergic neurons, thereby preserving motor function, and provides rationale for clinical development as a potential treatment option for PD.

M281: Parkinson's Dyskinesia-Hyperpyrexia Syndrome in a Patient with Newly Prescribed Foscarbidopa/Foslevodopa Infusion Pump

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Background: Dyskinesia-hyperpyrexia syndrome (DHS) is a rare but increasingly recognized hyperkinetic emergency in advanced Parkinson's disease (PD), classically characterized by severe continuous dyskinesia, altered mental status, autonomic instability, rhabdomyolysis, and hyperthermia, most often triggered by excessive dopaminergic stimulation. Early stages or milder presentations may occur without high fever. We report a severe case of DHS in a PD patient recently started on continuous subcutaneous foscarbidopa/foslevodopa infusion (CSCI) pump.
Methods: Case Report
Results: An 85-year-old man with a 14-year history of Parkinson disease who presented to the emergency room with confusion and involuntary movements within 24 hours of titration of CSCI pump. He started on a CSCI pump 1 month ago for severe "off" episodes, and the dose was titrated in the clinic the day prior to the presentation from levodopa 1142mg/day to 1468mg/day. On exam he was somnolent and intermittently oriented, with marked trunk and limb rigidity (worse in the legs) and sudden dystonic posture of arms with arm extension every few minutes; there were no choreiform movement or focal deficits. He remained afebrile but persistently hypotensive, and labs showed leukocytosis and elevated creatine kinase (peak 922 U/L). Infectious workup was negative. CSF analysis only showed elevated protein and normal WBC. Supportive care was initiated and dopamine dose was decrease to previous dose of 1142mg/day on hospital day 3. However, clinical features did not improve. While other results were pending on day 5, intravenous immunoglobulin (IVIG) was given for possible autoimmune encephalitis, with minimal improvement. On day 10, IV dantrolene was given for presumed neuroleptic malignant syndrome, without effect. The levodopa infusion rate was later increased to improve mobility without success. His hospital course was complicated by severe deconditioning, sacral ulcer, and deep venous thrombosis with pulmonary embolism. He was subsequently discharged to a skilled nursing facility (SNF). He remained nonverbal and never returned to baseline. Unfortunately, he died 2 weeks at the SNF.
Conclusion: DHS is typically triggered by formulary changes or dose increase of dopaminergic medications. The CSCI pump is a newly approved wearable device for advanced PD which provides 24-hour continuous, subcutaneous infusion. Dyskinesia is a possible side effect from CSCI especially during titration period. Although rare, dystonia can be a presentation of dyskinesia. Clinicians need to counsel PD patients and their family about this potential risk of DHS while on the CSCI pump and avoid sudden changes in its setting.

M282-LB: *DT-216P2, a Gene-Targeted Small Molecule, Produces Rapid Dose-Dependent Clinical Improvements and Comprehensive Frataxin Biomarker Activity in Friedreich Ataxia: RESTORE-FA 4-week IV Cohorts Results

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Background: Friedreich ataxia (FA) is a life-shortening autosomal recessive neurodegenerative disease caused by a GAA

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trinucleotide repeat expansion in intron 1 of the FXN gene, resulting in transcriptional silencing and reduced frataxin (FXN) protein. DT-216P2 is a first-in-class bifunctional small molecule that recognizes the expanded GAA repeat region of the FXN gene and engages the transcriptional apparatus to restore endogenous FXN expression, addressing the root cause of FA. Nonclinical studies demonstrated wide tissue distribution including CNS.

Methods: DTX-216P2-101 (RESTORE-FA) is a multi-part open-label, multiple-ascending-dose Phase 1/2 study in participants with FA. A total of 16 participants received 4-weekly IV doses at 0.1, 0.3, 0.6 and 1.0 mg/kg (n=4/cohort). Clinical endpoints included Modified Friedreich Ataxia Rating Scale (mFARS) score, Upright Stability Score (USS), and PROMIS Fatigue T-score. Pharmacodynamic activity was assessed by FXN mRNA and protein in whole blood and skeletal muscle.

Results: Dose-dependent improvements in clinical endpoints and FXN biomarkers were observed across all IV cohorts. At 1.0 mg/kg, participants demonstrated a mean improvement from baseline of -6.4 points in mFARS at 4 weeks, substantially exceeding omaveloxolone (−1.6) and placebo (−1.0) at 4 weeks in MOXIe (cross-study comparison). A dose-dependent improvement in USS was observed, reaching −2.7 points at 1.0 mg/kg after 4 weeks, compared to 0.0 for omaveloxolone and +0.3 for placebo at 12 weeks in MOXIe; a 1-point USS improvement exceeds placebo responses previously reported in FA (Rummey 2026). On PROMIS Fatigue, a greater than 6-point improvement was observed at 1.0 mg/kg, exceeding the 3-point minimal important change threshold, with 75% achieving a ≥5-point response. Improvements were observed in participants also receiving omaveloxolone. At 1.0 mg/kg, whole blood FXN mRNA increased by 65% from baseline ($p<0.001$) and skeletal muscle FXN mRNA increased by 42% ($p=0.015$), confirming target tissue engagement. Whole blood FXN protein levels increased 22–27% at 2 weeks post-final dose ($p<0.001$), consistent with the known half-life of endogenous FXN protein and therefore confirmed translation of mRNA increases into protein. DT-216P2 was generally well tolerated with no serious adverse events and no AE-related discontinuations; all adverse events were mild or moderate.

Conclusion: DT-216P2 demonstrated rapid, dose-dependent, and clinically meaningful improvements in mFARS, USS and patient-reported fatigue in FA, accompanied by dose-dependent statistically significant increases in FXN mRNA and protein providing mechanistic support for the clinical observations. These data support accelerated development of DT-216P2 as a potentially disease-modifying therapy for FA.

M283: Long-Read Genome Sequencing for Cerebellar Ataxia

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Background: Hereditary cerebellar ataxias are genetically heterogeneous disorders characterized by progressive cerebellar degeneration. Despite advances in conventional genetic testing, including exome sequencing, repeat-expansion testing, and targeted gene panels, many cases remain without a molecular diagnosis. Multiple tests are often required, and diagnostic yield remains limited. Long-read genome sequencing (LR-GS) can improve detection of structural variants, repeat expansions, and phasing, and may consolidate multiple tests into a single assay.

Methods: We performed LR-GS on 148 DNA samples (100 archived DNA and 48 fresh samples) from patients with cerebellar ataxia and prior negative clinical genetic testing. Inclusion was not limited by prior test type. From these, 58 archived and 45 fresh samples were successfully analyzed. Variant calling and annotation were performed using a standard PacBio pipeline.

Results: Prior genetic testing was variable, most commonly including exome sequencing and repeat-expansion testing. Seventeen of 103 cases (16.5%) yielded a diagnostic or likely diagnostic finding. Seventeen candidate variants were also identified and require further validation. In one case, LR-GS assisted in the interpretation of two previously identified *SYNE1* variants by establishing that they were in trans. In another case, LR-GS identified an *MT-TK* mitochondrial DNA variant not detected on prior testing.

on. In one case, LR-GS assisted in the interpretation of two previously identified SYNE1 variants by establishing that they were in trans. In another case, LR-GS identified an MT-TK mitochondrial DNA variant not detected on prior testing.

Conclusion: LR-GS can identify disease-causing variants in hereditary ataxia and may streamline genetic diagnosis. Although high–molecular-weight DNA is generally recommended for LR-GS, 58% of previously extracted DNA samples were successfully analyzed, supporting the feasibility of reanalyzing archived specimens. Diagnostic or likely diagnostic findings were identified in 17 of 103 cases (16.5%). While many of these variants could theoretically be detected by short-read genome sequencing, LR-GS enables comprehensive detection of multiple variant classes in a single assay and simplifies the diagnostic workflow.

M284-K: Dissecting Neural Circuits Regulating Sleep State Transitions in a Mouse Model of Parkinson's Disease

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Background: Parkinson's disease (PD) is a common neurodegenerative disease and significant source of disability. While PD is classically defined by motor symptoms, up to 90% of PD patients experience sleep disturbances, which profoundly impact quality of life. Sleep fragmentation – increased switching between sleep and wake states – is a core feature of sleep dysfunction in PD and progressively worsens over the course of disease. The basal ganglia are an interconnected set of subcortical nuclei known to be central to the motor phenotype seen in Parkinson's disease, but circuits underlying sleep fragmentation in PD are less clear. It has therefore been challenging to target treatments for sleep symptoms in PD. The goal of this study is to examine circuit mechanisms of sleep fragmentation in a dopamine depletion model of PD.

Methods: Mice underwent unilateral stereotaxic injection of the neurotoxin 6-hydroxydopamine (6-OHDA) or saline in the medial forebrain bundle to generate parkinsonian mice and controls. Parkinsonian mice and controls were then implanted with EEG and EMG recording devices for continuous recording of sleep. Sleep states were classified as either Wake, REM, or NREM based upon spectral analysis. The number of sleep state transitions per minute were calculated as a measure of sleep fragmentation.

Results: Mice injected with 6-OHDA show near complete loss of dopamine neurons. Parkinsonian mice demonstrated decreased movement velocity and rotate ipsilateral to the injected side compared to saline treated controls. We found that parkinsonian mice exhibited more frequent sleep-wake transitions, indicative of increased sleep fragmentation, compared to saline treated controls.

Conclusions: Many of the sleep changes observed in people with PD are attributed to progressive neuropathology in brainstem regions regulating sleep. In this study, dopamine depleted mice demonstrated robust sleep fragmentation. This result suggests that sleep fragmentation may be related to circuit dysfunction downstream of dopamine loss, rather than directly due to underlying pathology in other brain areas. Future work will examine how changes in basal ganglia activity may contribute to sleep fragmentation.

M285: Metabolic Approach to Understanding Microglial Dysfunction in Parkinson's Disease

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Background: *Emerging evidence suggests that neuroinflammation plays an important role in Parkinson's disease (PD) as well as other neurodegenerative diseases. In this study, we hypothesized that lysosomal dysfunction in patient-derived microglia results in hyperinflammatory microglial states that contribute to disease pathogenesis. To test this hypothesis, we examined the metabolic and functional impact of PD genetic variants associated with lysosomal dysfunction in induced pluripotent stem cell (iPSC)-derived microglia.*

Methods: Using CRISPR-cas9 gene editing of a healthy background iPSC line, we generated four cell lines with knock-in mutations in the glucocerebrosidase beta 1 (GBA1), galactosylceramidase (GALC), progranulin (GRN), and leucine-rich repeat kinase 2 (LRRK2) genes. These PD risk genes, have important roles in regulating lysosomal function and may have larger implications in phagocytic cell types, like microglia. We first generated a functional profile for microglia derived from these cell lines using flow-cytometry based phagocytosis and lysosomal proteolysis assays. Next, we characterized the metabolic profile of microglia derived from these lines with the use of targeted metabolomics on a panel of over 300 hydrophilic metabolites and validated mechanisms of metabolite dysregulation by western blot.

Results: Functional profiling of iPSC-derived microglia with knock-in variants in GALC, GBA1, GRN, and LRRK2 demonstrates defects in phagocytic capability and lysosomal proteolysis in the GALC, GBA1, and LRRK2 mutants. Metabolomic profiling of the variant microglia identifies several groups of differentially dysregulated metabolites, and notably showed a strong, significant, and convergent depletion in NAD+. Western blot analysis also shows an increase in the NADase CD38, a known NAD+ regulator in inflammatory cell types. To probe the interplay between function and metabolism, we are next performing rescue experiments using media supplementation with the NAD+ precursor NR and reprofiling the functional and metabolic status of the derived microglia.

Conclusion: We have demonstrated that microglia with genetic variants associated with PD and lysosomal dysfunction have an impairment in phagocytosis as well as lysosomal proteolysis and a significantly decreased NAD+ level. Next, we will investigate the potential role of NAD+ in microglial function and characterize how lysosomal dysfunction leads to changes in cellular metabolism. Defining mechanistic pathways mediating neuroinflammation in PD could be pivotal in identifying novel targets for therapeutic interventions in PD and related disorders.

M286*: VPS39 Variants Cause a Spectrum of Neurological Disorders Through Impaired Lysosomal Function and Autophagy

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Background: VPS39 encodes a core subunit of the HOPS complex, which mediates fusion of autophagosomes and late endosomes with lysosomes. Pathogenic variants in other HOPS subunits, including VPS11, VPS16, and VPS41, are associated with neurological disorders. However, the contribution of VPS39 to human disease and its impact on lysosomal function has not previously been characterized. Here, we characterize a novel neurological disorder caused by biallelic VPS39 variants, define its clinical spectrum, and investigate the impact of VPS39 variants on autophagy and lysosomal function.

Methods: Affected individuals were identified through exome or genome sequencing studies. Clinical data, including neurological features and brain MRI findings, were collected retrospectively. The effects of identified VPS39 variants on protein expression were assessed by expressing plasmids encoding wild-type and mutant VPS39 in mammalian cell lines. The impact of missense variants on protein structure and interactions was evaluated using biophysical analyses of the HOPS complex in yeast and human VPS39. Autophagy and lysosomal function were evaluated in patient-derived fibroblasts from four patients using electron microscopy, biochemical analysis and functional assays.

Results: Fourteen individuals from 10 families were identified with VPS39 variants. Twelve distinct variants were detected, including missense, splice-site, frameshift, and nonsense variants, occurring either in the homozygous or compound heterozygous state. Two clinical phenotypes emerged: (i) a severe neonatal-onset disorder characterized by hypotonia, encephalopathy, profound developmental delay, early lethality, and features consistent with a systemic lysosomal storage disorder; and (ii) a milder phenotype with survival beyond early infancy, manifesting as developmental delay and progressive cerebellar ataxia. Neuroimaging predominantly showed cerebellar atrophy and corpus callosum abnormalities. Protein expression studies showed that most VPS39 variants resulted in reduced protein levels. Biophysical analyses indicated that missense variants affect distinct structural regions and interactions: three are buried within the N-terminal β-propeller, two disrupt the RAB2A–VPS39 interaction, and two localize to the C-terminus, likely altering interactions with VPS11 and VPS18. Predicted free-energy changes supported loss-of-function effects for all missense variants. Fibroblasts from affected individuals showed impaired lysosomal function, including reduced proteolysis, impaired acidification, and decreased glucocerebrosidase activity. Autophagy impairment, with reduced autophagic flux and accumulation of multilamellar bodies, was observed in cells from the more severely affected individuals.

Conclusion: Biallelic VPS39 variants cause a spectrum of neurological disorders, ranging from a severe neonatal lysosomal storage–like disease to a milder neurodevelopmental phenotype with prominent cerebellar ataxia. These findings establish a role for VPS39 in lysosomal homeostasis and autophagy and expand the spectrum of HOPS complex–related disorders.

M287-K: Dissecting the Mechanisms of BORCS5-related Lysosomal Dysfunction

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Background: BORCS5 encodes a subunit of the BORC complex, a lysosome-associated multi-protein assembly that mediates ARL8/kinesin-dependent anterograde lysosome transport. We previously demonstrated that pathogenic BORCS5 variants cause a spectrum of neurodevelopmental and neurodegenerative disorders. While truncating variants abolish BORCS5 protein expression and impair anterograde lysosome movement, the missense variants R95Q and H99P preserve peripheral lysosome distribution in patient fibroblasts and iPSC-derived neurons. Nevertheless, both complete BORCS5 loss and missense variants disrupt lysosome activity.

However, the mechanisms by which BORCS5 and its pathogenic missense variants contribute to lysosomal dysfunction and neuronal pathology remain unknown. Here, we aim to characterize the pathological mechanisms underlying BORCS5 missense variants and elucidate the role of BORCS5 in lysosome homeostasis beyond its canonical function in anterograde lysosomal transport.

Methods: To dissociate the role of BORCS5 in lysosome homeostasis from its role in anterograde transport, we generated the following cellular models: (1) HeLa knock-in (KI) cell lines homozygous for R95Q or H99P; (2) BORCS5 knockout (KO) HeLa cells stably re-expressing wild-type (WT) BORCS5; and (3) BORCS5 KO HeLa cells stably expressing KBS-LAMP1, a synthetic construct comprising three SKIP-binding kinesin motifs (KBS) fused to LAMP1, which restores anterograde lysosome movement independently of BORC. Additionally, BORCS5 KO and R95Q/

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H99P KI iPSCs stably expressing NGN2 were differentiated into induced neurons (iNeurons).
Lysosomal proteolytic activity was assessed by DQ-BSA assay via flow cytometry (HeLa cells) or live-cell imaging (iNeurons). Lysosome distribution, axonal lysosome trafficking, and morphology in mature iNeurons were examined by confocal microscopy, live-cell microscopy, and transmission electron microscopy (TEM). Lysosomal proteomes will be profiled using lysosomal immunoprecipitation (LysoIP) coupled with TMT-based quantitative proteomics of both lysosomal and whole-cell fractions.
Results: As anticipated, BORCS5 KO caused perinuclear collapse of the lysosome network and elevated LC3-II levels in HeLa cells, indicating impaired lysosomal trafficking and autophagosome clearance. In contrast, R95Q and H99P KI cells maintained normal lysosome distribution and LC3-II levels. However, all three genotypes — KO, R95Q, and H99P — exhibited reduced lysosomal proteolytic efficiency by DQ-BSA assay, demonstrating that the missense variants impair lysosome function despite preserving anterograde movement. To further dissociate transport from function, we expressed BORCS5-WT or KBS-LAMP1 in KO cells. Both constructs restored anterograde movement; however, only BORCS5-WT rescued LC3-II levels and recovered cathepsin B (CTSB) and glucocerebrosidase (GCase) protein levels, indicating that restoring lysosome positioning alone is insufficient to correct lysosomal dysfunction and autophagy impairment caused by BORCS5 loss. In iNeurons, BORCS5 KO produced predominantly immobile, enlarged lysosomes confined to the soma, while R95Q/H99P KI iNeurons showed near-complete recovery of axonal lysosome trafficking. BORCS5 KO iNeurons exhibited several features of lysosomal dysfunction, including reduced GCase activity, decreased CTSB and GCase protein levels, elevated LC3-II and LAMP1/2, and autophagosome accumulation by TEM — consistent with impaired autophagosome clearance. LysoIP confirmed depletion of CTSB and GCase within endolysosomal fractions of KO iNeurons.
Conclusions: BORCS5 depletion and bi-allelic variants lead to lysosomal dysfunction. BORCS5-depleted cells exhibit reduced lysosomal proteolysis and decreased CTSB and GCase levels and activity, which cannot be rescued by restoring anterograde lysosome movement, indicating that BORCS5 plays a role in lysosome homeostasis beyond its canonical function in anterograde transport. Quantitative proteomics of whole-cell and lysosomal fractions is ongoing to comprehensively define how BORCS5 loss and missense variants remodel the lysosomal proteome.

M289: The Silence of the Aqueduct: Web and Stenosis Masquerading as Neurodegeneration

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Background: Aqueductal obstruction from congenital webs or acquired stenosis can go unnoticed for decades before producing late-onset neurological symptoms that resemble neurodegenerative conditions. Conventional MRI may fail to detect the obstruction, and advanced sequences, such as phase-contrast cine imaging and three-dimensional high-resolution T2-weighted sequences, are often required for diagnosis. Here, we describe two elderly patients with late-onset obstructive hydrocephalus secondary to aqueductal web and multifocal aqueductal stenosis, highlighting the diagnostic workup and surgical outcomes.
Results: Case 1: A 75-year-old man presented with a history of progressive shuffling gait, start hesitation, and recurrent near falls for 4 months. Neurological examination showed a wide-based gait with impaired tandem walking. The conventional MRI brain revealed triventricular ventriculomegaly. High-resolution T2-weighted and CSF cine flow sequences demonstrated severe narrowing of the cerebral aqueduct at the level of the inferior colliculus with a single web-like projection and absent aqueductal CSF flow, confirming an aqueductal web and obstructive hydrocephalus. He underwent endoscopic third ventriculostomy, with marked improvement in gait and balance within two days postoperatively. Case 2: A 70-year-old man presented with a history of progressive cognitive decline and bilateral action tremor for 3 years. Neuropsychological assessment showed prominent memory deficits with preservation of executive function, a pattern previously associated with fornix compression in aqueductal stenosis rather than the frontal-subcortical dysfunction typical of idiopathic normal pressure hydrocephalus. MRI brain showed ventriculomegaly, multiple sites of severe aqueductal stenosis, and web-like components, with markedly reduced aqueductal CSF flow on cine imaging. Due to a high-riding basilar artery precluding safe endoscopic third ventriculostomy, a ventriculoperitoneal shunt was implanted. At the follow-up visit, the patient showed cognitive improvement, and his symptoms stabilized.
Conclusion: These cases illustrate that the aqueductal web and multiple areas of aqueductal narrowing are often missed but can be treated with surgery in patients who develop late-onset obstructive hydrocephalus. Different surgical approaches underscore the importance of preoperative vascular imaging to assess basilar artery position when planning endoscopic third ventriculostomy. CSF cine flow imaging and three-dimensional high-resolution sequences should be incorporated into the diagnostic workup of elderly patients with unexplained ventriculomegaly and gait or cognitive symptoms, as early identification enables effective surgical treatment with meaningful clinical recovery.

M290: Are Lower-Limb Tasks Underrepresented? Dopaminergic Responsiveness Across Digital and Clinical Bradykinesia Measures in Early PD

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Background: Digital assessments of motor function may improve monitoring of Parkinson's Disease (PD). However, most studies assess only one digital method against clinician ratings and evaluate dopaminergic responsiveness using short OFF-medication periods. Upper-extremity bradykinesia tasks predominate amongst these tests, which leaves lower-limb dopaminergic responsiveness comparatively underexplored. To address these gaps, this study evaluated dopaminergic responsiveness across two types of digital methods (video kinematics, wearable accelerometer) and clinician ratings for both upper- and lower-limb bradykinesia after a one-week washout in early-stage PD.

Methods: Nineteen participants with early-stage PD (aged 65.2±7.1 years, 14/19 male, medication duration 1.6±0.8 years, levodopa equivalent daily dose 490±425mg) completed a one-week washout study (IRB#191683). Motor tasks (finger tapping, hand movements, toe tapping, and leg agility) were evaluated for both ON and one-week OFF dopaminergic medications. Videotaped MDS-UPDRS-III examinations were blindly rated by a movement disorders specialist and used to calculate VisionMD (VMD) scores (mean speed, mean amplitude) for all four bradykinesia tasks. Motor tasks were also completed using the Kinesia One (K1) wearable accelerometer.

Dopaminergic medication responsiveness was evaluated with paired t-tests and Cohen's d effect sizes. Cross-device concurrent validity was assessed using the OFF-state Spearman correlation between VisionMD and Kinesia One.

Results: Leg agility had the strongest and most consistent responsiveness across all three measures (MDS-UPDRS d=-0.81, p=0.002; VMD amplitude d=0.74, p=0.006; VMD speed d=0.99, p=0.001; K1 amplitude d=-0.66, p=0.01). Hand movement revealed significant results across all three methods for MDS-UPDRS (d=−0.85, p=0.002) and speed (VMD d=0.58, p=0.021; K1 d=−0.66, p=0.010), while amplitude effect size was large and significant for Kinesia One (d=−0.68, p=0.008) but not VMD (d=0.34, p=0.16). VMD uniquely detected significant ON-OFF changes for toe tapping (speed: d=0.61, p=0.019; amplitude: d=0.52, p=0.04), but not for K1 or MDS-UPDRS-III. Finger tapping only showed significant results for K1 amplitude (d=−0.49, p=0.047) and speed (d=−0.48, p=0.049). OFF-state device agreement was significant only for leg agility (speed: ρ=-0.65, p=0.003; amplitude ρ=−0.68, p<0.002), not for other motor tasks.

Conclusion: In this early-stage PD cohort, leg agility showed the largest and most consistent dopaminergic responsiveness across clinician ratings, wearable sensors, and video-based assessment. These convergent findings reinforce the dopaminergic sensitivity of kinematics and suggest that lower-limb bradykinesia measures may be underrepresented in current digital endpoint development relative to upper-limb tasks.

M291: Clinical Characteristics and Insurance-Based Disparities in Huntington's Disease Care at an HDSA Center of Excellence: A 12-Year Retrospective Analysis

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Background: The Huntington's Disease Society of America (HDSA) designates centers of excellence (COE) based on access to multidisciplinary care for Huntington's Disease (HD). However, the sociodemographic composition, impact of social determinants of health, and clinical utility of these centers remain poorly characterized. We sought to describe the clinical and sociodemographic profile of patients at an HDSA COE in Southern California and evaluate associations between insurance status, diagnostic delay, and HD-specific clinical outcomes.

Methods: We conducted an electronic health record review of 458 persons with HD seen at UCLA between 2012 and 2024. We evaluated sociodemographics, diagnostic timelines, and pharmacologic management. To investigate the impact of social determinants of health, we first defined time-to-diagnosis as age of diagnosis minus age at symptom onset. Delays to specialty care was defined as the interval from age diagnosed to age at first COE visit. Linear regressions evaluated associations between insurance payer and time-to-diagnosis, and delays to first COE visit. Sequential models adjusted for biological factors (sex, race, CAG length) and socioeconomic (SES) variables (neighborhood ADI). Logistic regressions evaluated associations between insurance and chorea medications, reported falls, suicidal ideation, and access to psychiatry and physical therapy.

Results: Of 458 patients, 262 (57%) were female. For race and ethnicity, 61% identified as White Non-Hispanic, 26% Hispanic/Latino, 6% Black, and 3.5% Asian. At first COE visit, 29% had private insurance, 25% had Medicare, 16% had Medicaid, and 30% were self-paying. Mean time from symptom onset to diagnosis was 3.35 years (SD 7.19), with most patients (52%) reporting motor symptoms at time of disease onset. Nearly half of all patients received an HD diagnosis before presenting to UCLA (194, 51%). For disease management, 227 (55%) received antipsychotics, while 92 (20%) received VMAT2 inhibitors. Publicly insured patients had significantly longer diagnostic delays across all models (SES-adjusted β 3.98, CI 1.39–6.57). Insurance was not associated with delays in COE access. Publicly insured patients did show a higher likelihood of VMAT2 inhibitor and antipsychotic use (biologically adjusted RR 3.50, CI

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1.11–11.04). This association lost significance once adjusted for SES.

Conclusion: This 12-year COE characterization reveals a racially and socioeconomically diverse HD population, with public insurance independently associated with prolonged diagnostic delay and differential treatment patterns. These findings underscore the need for multicenter COE benchmarking and highlight the impact of patient socioeconomics on HD care delivery.

M292: Bezisterim (NE3107) in Early Parkinson's Disease (SUNRISE-PD): Initial Results and Observations from a Phase 2 Hybrid Design Trial

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Background: Functional disability in Parkinson's disease (PD) is due to neurodegeneration that is mediated in part by chronic inflammation, insulin resistance, and oxidative stress. Currently approved treatments do not fully address PD-associated disability, which can worsen over time as the disease progresses. Bezisterim (NE3107) is an oral, blood-brain barrier–permeable, insulin-sensitizing, anti-inflammatory agent that binds extracellular signal-regulated kinase and inhibits inflammatory nuclear factor-kappa B and tumor necrosis factor alpha signaling and thus has the potential to mitigate some of the aberrant inflammatory processes that drive PD progression.

SUNRISE-PD (NCT06757010), a phase 2, double-blind, randomized trial was conducted to explore the safety and efficacy of bezisterim in early PD using a hybrid design. We will summarize topline results from this exploratory, novel trial of bezisterim in the treatment of motor and non-motor symptoms of early PD will be presented.

Methods: SUNRISE-PD (NCT06757010) was a phase 2, double-blind, randomized, placebo-controlled study comprising a 12-week treatment period and a 4-week follow-up period. Symptomatic adults 41 to 80 years of age were included if they were diagnosed with idiopathic PD within 4 years of screening, had a baseline modified Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score greater than 11, and were naïve to levodopa or similar medications. Eligible participants were randomized to twice daily 20-mg bezisterim or placebo and completed the study fully at home or through clinic visits. Motor symptoms were assessed via a central rating system using a modified MDS-UPDRS part III. Non-motor symptoms were evaluated with MDS-UPDRS parts I and II. Other assessments included a fit for purpose composite, the Early Parkinson's Neuroinflammatory Composite-15 (EPNIC-15), and laboratory assessments for DNA methylation and plasma biomarkers.

Results: Bezisterim demonstrated statistically significant improvements versus placebo across motor and non-motor manifestations of PD as assessed by MDS-UPDRS Parts I, II, and III, as well as EPNIC-15, in participants with higher baseline platelet concentration as a surrogate marker of inflammation. Bezisterim also met prespecified pharmacodynamic objectives, improving blood-based inflammatory markers and favorably affecting biomarkers associated with neurodegeneration, neuroinflammation, and systemic inflammation. Safety evaluations and adverse events reported for bezisterim were similar to placebo.

Conclusion: This study provided evidence of bezisterim's activity against both motor and non-motor symptoms. The results support the continued development of bezisterim as a treatment for PD with the potential for both symptomatic and disease modifying benefits. The results also convey the robust generative capabilities of the adopted hybrid trial design for a difficult-to-capture population.

M294: Caregiver Networks, Social Programs, and Care Delivery for Aging Individuals with Huntington's Disease

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Co-Author(s): *Angie Ramirez, Undergraduate, UCLA, Los Angeles, CA, Adys Mendizabal, Los Angeles, CA*

Background: Huntington's disease (HD) is associated with early disability and prolonged caregiving demands years, or at times decades, before Medicare eligibility There is limited understanding about structural and cultural factors that influence access to supportive services and continuity of neurologic care for aging individuals with HD (50 and older). In this pilot study, we seek to understand the relationship among caregiving networks, social support programs, and HD-specific care, in supporting the needs of aging patients with HD and their households.

Methods: We are conducting semi structured interviews with 10 HD patient-caregiver dyads in Southern California to explore caregiving, access to HD specialty care, and utilization of social support programs. Interviews are conducted virtually in two separate 90-minute sessions. Before each interview, caregivers also complete the Zarit Caregiver Burden Interview (ZBI-22) to assess emotional, physical, and social strain. For participant recruitment, the study is using a purposeful sampling approach focused on variation in healthcare settings, and racial and ethnic diversity. Healthcare settings of interest include Huntington's Disease Society of America (HDSA) Centers of Excellence (COEs) and non-COEs. COE dyads have been recruited from UCLA's HDSA COE. Non-COE dyads are recruited through community events hosted by the HDSA Los Angeles chapter. An ethnically diverse community advisory panel (CAP) composed of HD patients, caregivers, healthcare professionals, and disease advocates was established to support interpretation and dissemination of findings.

Results: To date we have recruited seven diverse dyads (4 COE; 3 non-COE; 3 Spanish Speaking-Latino; 1 Middle Eastern). All non-COE dyads receive care within the Kaiser Permanente Health system. Caregivers are mostly female

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(5/7) and spouses (6/7). One caregiver is a sibling. Four dyads have completed interviews so far (2 COE; 2 non-COE; 2 Spanish-speaking Latina spouses). Preliminary thematic analysis identified three themes: (1) Families report significant administrative barriers to obtaining disability and social services which are facilitated by social workers, including those outside of COEs (2) Immigrant Latino caregivers reported greater caregiving burden and reliance on social support programs due to limited caregiving networks and presence of children under 18 in the household (3) Families receiving non-COE care report a lack of empathy by employers, healthcare systems, and social services due to a limited knowledge of HD.

Conclusion: Preliminary findings highlight distinct caregiving and support challenges among individuals with HD, shaped in part by early disease onset and the presence of young adults in the household, suggestive of unique social support needs for HD family households.

M295: Deferiprone in Parkinson's Disease: Motor, Imaging, and Safety Outcomes Across Randomized Trials

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Background: Iron accumulation in the substantia nigra (SN) contributes to oxidative injury and neurodegeneration in Parkinson's disease (PD). Deferiprone (DFP), a brain-penetrant iron chelator, has been evaluated as a potential disease-modifying therapy, with inconsistent trial-level results. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to quantify the effects of DFP on motor outcomes, neuroimaging biomarkers, and safety in PD.

Methods: Pubmed and ClinicalTrials.gov were searched for RCTs comparing DFP versus placebo in PD. Random-effects meta-analyses (REML estimator) were performed. Outcomes assessed were motor (MDS-UPDRS Part III), MRI iron measures (SN, caudate, and putamen), serum ferritin, cognition, (MoCA/MMSE), quality-of-life (PDQ-39), and adverse events. Effect sizes were expressed as standardized mean differences (SMD) or mean differences (MD). Heterogeneity was quantified using I2.

Results: Four RCTs (n = 474 participants) were included. Pooled analysis demonstrated no significant improvement in motor symptoms with DFP versus placebo (SMD −0.11, 95% CI −0.43 to 0.21; p = 0.51; I2 = 0%).

Dose-stratified 9-month analyses showed no significant effect across 300–1200 mg/day (MD 0.30, 95% CI −1.93 to 2.52; I2 = 64%). MRI iron outcomes showed no significant pooled effect in the SN (SMD 0.20, 95% CI −0.78 to 1.19; I2 = 79%), caudate (SMD −0.05, 95% CI −1.20 to 1.11), or putamen (SMD 0.01, 95% CI −0.95 to 0.96). DFP significantly reduced serum ferritin (MD −45.4 ng/mL, 95% CI −78.0 to −12.9; p = 0.006; I2 = 0%). No significant between-group difference were observed for quality-of-life (MD 1.04, 95% CI −3.26 to 5.33) and cognition (SMD −0.10, 95% CI −0.48 to 0.28; p = 0.62). Risk of any adverse event was higher with DFP (RR 1.49, 95% CI 1.23–1.81; p < 0.001), with a non-significant increase in serious adverse events and hematologic toxicity.

Conclusion: Across randomized evidence, deferiprone does not improve motor, cognitive, or quality-of-life outcomes in PD despite demonstrable iron chelation. Increased adverse events and lack of clinical efficacy do not support routine use of DFP as symptomatic or disease-modifying therapy in PD.

M297: Staged Bilateral MR-Guided Focused Ultrasound in Essential Tremor: Safety, Efficacy, and Rising Adoption of Second-Side Treatment

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Background: Staged, bilateral MRgFUS was FDA-approved in 2022 for ET, broadening its clinical utility. MRgFUS is an incisionless technique that enables precise targeting and is the leading advanced therapy for ET, prompting renewed interest in its bilateral application. By addressing the complete clinical presentation of bilateral disorders, like ET, MRgFUS may help bridge existing therapeutic gaps.

Methods: In a prospective, open-label, single-arm, seven-center study, 51 subjects underwent staged, bilateral MRgFUS thalamotomy at least 9 months after unilateral treatment. The primary endpoint was change in tremor/motor score (CRST parts A+B) at 3 months; secondary outcomes included tremor severity, functional disability, and safety through 1 year. Utilization data review of unilateral and second-side MRgFUS treatments.

Results: Mean tremor/motor scores improved by 66% reduction (P<0.001, 17.4 at baseline to 6.4 at 3 months), with sustained improvement to at least 12 months. Tremor severity and functional disability improved from 2.5 to 0.6 (81% reduction; P<0.001) and from 10.3 to 2.2 (73% reduction; P<0.001), respectively. Of 188 total related adverse events (AEs), 85% were mild, 13% moderate, and 1 was a severe urinary tract infection. The most common AEs included numbness/tingling, dysarthria, and ataxia. As clinical experience grows and outcomes remain favorable, utilization of both unilateral and staged bilateral MRgFUS treatments increased 30% and 69%, respectively, from 2023 to 2024, reflecting a need and patient preference.

Conclusion: Staged, bilateral MRgFUS thalamotomy provides significant and durable tremor improvement with an acceptable safety profile. Growing clinical adoption of both unilateral and bilateral treatments underscores the potential of MRgFUS as a viable, incisionless, and effective treatment option capable of addressing the inherently bilateral nature of essential tremor.

M298: Alien Limb Syndrome as a Manifestation of Intracranial Hemorrhage: A Case Report

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Background: Alien limb syndrome is a rare neurological phenomenon that has been noted to arise in the setting of stroke, vascular malformations, tumors, and trauma. Here, we report this phenomenon in a patient with intracerebral hemorrhage secondary to head trauma.
Methods: Case Report
Results: 74-year-old female presented to the hospital after a fall. Upon presentation, the patient was noted to have right-sided weakness and headache. CT Head revealed hemorrhage in the region of genu and splenium of the corpus callosum, along with blood products in the left occipital region. Surgical intervention was not advised by Neurosurgery. On the second day of admission, the patient developed rhythmic involuntary movements of the right arm. The patient felt as if she had no control over her right arm. There was no associated loss of consciousness, staring spells, agraphia, acalculia, or visual field deficits. Examination revealed rhythmic sinusoidal movements of the right upper extremity, with movements noted to the midline over the chest. Repeat CT Head revealed stable appearance of the ICH. EEG monitoring did not reveal epileptiform activity. The patient was monitored over the next few days and the abnormal involuntary movements reduced in frequency and were minimal on discharge.
Conclusion: This case exhibits alien limb syndrome caused by intracerebral hemorrhage. Given its rarity, clinicians should be cognizant of this phenomenon in order to adequately manage the manifestations of this unique disorder.

M299: Determinants of Psychiatric Care Utilization in Huntington's Disease: A Cross-Sectional Analysis

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Background: Huntington's Disease (HD) is a fatal, genetic neurodegenerative disorder that is characterized by a triad of symptoms: motor dysfunction, cognitive decline, and psychiatric disturbance. While psychiatric symptom manifestation often precedes motor impairments and is widely prevalent in persons with HD, access to psychiatric care remains challenging among persons with HD. Furthermore, disparities within the healthcare system, particularly those related to socioeconomic factors, impact an individual's ability to receive appropriate psychiatric care. To that end, our primary objective was to evaluate factors shaping access to psychiatric care among HD patients seen at our Huntington's Disease Society of America (HDSA) Center of Excellence (COE).
Methods: Between June 2024 and September 2025, HD patients seen at UCLA's HDSA COE were asked to complete a three-item survey evaluating HD symptomatology and health services prior to patients establishing care at our COE. Descriptive analyses, one-way ANOVA, and logistic regression analyses were used to evaluate associations between participant characteristics and receipt of psychiatric care.
Results: A total of 89 patients completed the survey during the study period (66% completion rate). Twelve patients received HD care prior to their first visit at our COE, provided by general neurologists, psychiatrists, primary care physicians, etc. In the sample, most respondents had commercial insurance (45%), most commonly reported a bachelor's degree as their highest level of education (28%), and 34% identified as Hispanic. 29% had long-term disability insurance (LTDI), and private insurance was the most prevalent coverage type. One-way ANOVA identified several factors significantly associated with receipt of mental health services. Level of education ($p=0.05$), LTDI status ($p=0.04$), and receiving HD-related care prior to evaluation at an HDSA COE ($p=0.004$) were statistically significant predictors. Using logistic regression, receiving HD-related care prior to being seen at an HDSA COE was significantly associated with increased odds of receiving psychiatric care (OR=10.14, 95% CI [1.76, 58.38], $p=0.009$). LTDI demonstrated a positive but non-significant association (OR=2.07, 95% CI [0.72, 5.94], $p=0.176$).
Conclusion: Psychiatric care utilization in individuals with HD may be more closely associated with prior engagement in care than with sociodemographic factors alone. Individuals who received HD-related care before evaluation at a COE were favored to access psychiatric services, suggesting that earlier interaction with the healthcare system may facilitate referral and care continuity. Given our small sample size, larger multicenter and administrative claims studies are needed to better understand the role of healthcare services outside of HDSA COEs in access to psychiatric services for HD patients.

M300*: Heterogeneity of alpha-Synuclein Seed Amplification Assay Time-to-threshold Across Diseases: A Cross-sectional Study

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Background: CSF alpha-synuclein seed amplification assays (aSyn-SAA) accurately detect the presence of misfolded aSyn seeds in the setting of Lewy body pathology. The time-to-threshold (TTT) of aSyn-SAA reactions has been associated with cognitive decline in Parkinson's disease (PD) and the likelihood of disease progression in prodromal cohorts. However, such studies are typically focused on single disease cohorts, which limits the understanding of how aSyn-SAA TTT may vary across diseases. Here we investigate TTT

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values across different cohorts of participants with PD, dementia with Lewy bodies (DLB), Alzheimer's disease (AD), mild cognitive impairment (MCI) and participants with normal cognition (NC).

Methods: CSF aSyn-SAA testing was performed by Amprion, where staff are blinded to clinical diagnoses, between 2022-2025. The runtime of the aSyn-SAA in those years was either 20h or 24h. Only participants with Type-1 seeding were analyzed. Mean and standard deviation TTT (sdTTT) values were derived from samples run in triplicate. Participants clinically diagnosed with PD (n=875), DLB (n=141), AD (n=147), MCI (n=132), and NC (n=66) who had participated in the Parkinson's Progression Markers Initiative (PPMI, n=704), the PD Biomarkers Program (PDBP, n=96), the DLB Consortium (DLBC, n=46), the AD Neuroimaging Initiative (ADNI, n=268) and two clinical cohorts from academic centers (Kassel Germany n=87 and Perugia Italy n=160) were analyzed.

Results: Participants with DLB had the fastest meanTTT (8.5h[SD1.8]), followed by PD participants (10.2h[SD2.2]) ($p<0.001$). NC participants and those with MCI or AD had slower meanTTT times (11.3h[SD1.8], 11.0h[SD1.8], 10.8h [SD1.8] respectively), than participants with DLB or PD ($p<0.01$ for all). sdTTT values were also larger for NC, MCI, and AD participants, indicating greater variance between replicates ($p<0.004$ for all). There was a step-wise decrease in meanTTT when comparing PD-NC (n=832), PD-MCI (n=35), PDD (n=8), and DLB participants (n=141)($p<0.001$). The coefficient of variance for TTT measurements averaged 7.5% [IQR 3.9-9.5%].

Conclusion: In this large, multicohort study, there are statistically significant differences in meanTTT and sdTTT values across different diseases. Participants with PD or DLB with positive Type-1 seeds have faster and more consistent amplification than groups comprising NC, MCI or AD participants. Differences in reaction speed could be due to CSF milieu, aSyn seed amount, or different aSyn seed species, and are of interest for further investigation. Faster meanTTT values were noted with increasing degrees of cognitive impairment in Lewy body diseases. A low coefficient of variance across the triplicate replicates was observed (<10%), indicating that TTT is a reproducible value.

M301: Delayed Recognition of Oromandibular Dystonia: A Systematic Review of Misdiagnosis as Temporomandibular Disorder

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Background: Background: Oromandibular dystonia (OMD) is a focal cranial dystonia involving the lingual, perioral and platysma muscles. Studies show that more than half of the patients are often misdiagnosed or undiagnosed. Patients with OMD are commonly present with jaw pain, abnormal mandibular movements, dysarthria, dysphagia, and impaired chewing. These manifestations substantially overlap with temporomandibular disorder (TMD). Patients are often evaluated at the dental care facilities initially misclassified as having TMD. This diagnostic overlap may delay recognition of a treatable movement disorder which exposes patients to unnecessary dental and maxillofacial interventions. The aim of this study is to systematically review the literature addressing diagnostic overlaps between OMD and TMD, with emphasis on delayed referral and neurologic recognition, recurrent misclassification as Temporomandibular Disorder.

Methods: Methods: A systematic review was conducted using databases, e.g. PubMed, Embase, Web of Science, and Cochrane to identify relevant studies. Articles published between 2011 and 2026 were reviewed using MeSH terms "oromandibular dystonia", "temporomandibular disorder", "diagnostic overlap", "diagnostic delay", "association between OMD and TMD", and "differential diagnosis of OMD and TMJ." In the literature set available for review, n=19 records were identified, duplicate articles (n=4) were removed, and unique reports (n=15) underwent full-text review. Directly relevant studies or studies met the inclusion criteria (n=8) were included for qualitative synthesis. Studies without direct relevance to diagnostic overlap and primary patient data were excluded.

Results: Results: Across the included literature, OMD was consistently described as a movement disorder that commonly presents symptoms typically attributed to TMD. Patients were frequently diagnosed and treated for dental or temporomandibular conditions before diagnosis of underlying dystonia. The literature also consistently highlighted phenomenological clues that favor OMD over primary TMD, particularly task specificity, stereotyped patterned contractions, sensory tricks, fluctuation with voluntary activity, and improvement during sleep. These findings suggest a recurrent pattern of late diagnosis of OMD because of its overlapping symptoms of TMD.

Conclusion: Conclusions: OMD should be recognized as focal cranial dystonia rather than refractory temporomandibular pain syndrome. The existing literature suggests that diagnostic error contributes to delayed neurologic identification, postpones effective treatment, and exposes patients to unnecessary dental and maxillofacial interventions. By synthesizing the recurring phenomenological features of OMD from TMD, this systematic review may help clinicians identify OMD earlier in future practice and reduce misdiagnosis as TMD and promote earlier referral for appropriate movement-disorder management.

M302: Temporal and Demographic Trends in Mortality from Parkinson's Disease and Sepsis in U.S. Older Adults From 1999 to 2025

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Background: Parkinson's disease is one of the most common neurodegenerative movement disorders. It is characterized by bradykinesia, rigidity, tremor, and postural instability. There is increasing evidence showing an association of sepsis in the etiology of Parkinson's disease, which may negatively affect treatment adherence, disease management, and survival outcomes. In this study, we aim to discuss the temporal and demographic trends in mortality from this comorbidity amongst the adult population in the United States.

Methods: Mortality data were obtained from the CDC WONDER database, and the ICD-10 codes used for older adults (aged ≥65 years) with Parkinson's disease and sepsis were G20 and A41 and A42, respectively. Joinpoint regression was used to calculate APC (annual percent change) and AAPC (average annual percent change) values per 100,000, with $p < 0.05$ considered statistically significant and denoted by an asterisk (*)

Results: Between 1999 and 2025, Parkinson's disease and sepsis in older adults led to 48,616 deaths, with the most deaths recorded at medical facilities-inpatient (58.60%). AAMR decreased from 4.81 in 1999 to 4.27 in 2025 with an associated AAPC of -0.50*. In 1999, men had an AAMR of 7.86, while women had an AAMR of 3.05. This trend decreased in 2025, where men had an AAMR of 6.76 (AAPC: -0.41*), while women had an AAMR of 2.43 (AAPC: -0.73*). Asian or Pacific Islander individuals had an AAMR of 5.5 in 2025 (AAPC: 1.40*), while Black or African American individuals had an AAMR of 3.66 in 2025 (AAPC: 0.67; $p = 0.059$). White individuals experienced an AAMR of 4.26 in 2025 (AAPC: -0.38*). Geographically, the West had the highest AAMR of 4.58 in 2025 (AAPC: 0.86*), followed by the Northeast with an AAMR of 4.38 in 2025 (AAPC: -0.71*), then the South with an AAMR of 4.26 (AAPC: -0.33*) and the Midwest with an AAMR of 3.73 (AAPC: -0.95*).

Conclusion: conclusion, mortality associated with the coexistence of Parkinson's disease and sepsis showed a modest decline from 1999 to 2025. Despite this overall improvement, notable disparities persist across sex, race, and geographic regions, with increasing trends seen in certain populations such as Asian and Pacific Islanders and residents of the Western region. These findings highlight the need for targeted public health strategies to address high-risk groups and further reduce mortality

M303: Dorsal and Ventral STN Exhibits Opposing Dynamics Between Spiking Synchrony, Beta Power, and LFP Coherence in Parkinson's Disease

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Background: Beta oscillations (12–30 Hz) in the subthalamic nucleus (STN) are a hallmark of Parkinson's disease (PD). The STN is organized along a functional gradient, with dorsolateral regions subserving motor function and ventromedial regions associated with associative and limbic processing. We examined relationships between spiking synchrony, local beta power, and inter-electrode LFP coherence across the dorsoventral axis of a 5-contact directional DBS lead implanted in the Parkinsonian STN.

Methods: Electrophysiological recordings using microelectrodes (Alpha Probe, NeuroOmega) were obtained from 5 PD patients undergoing STN DBS implantation. The microelectrode consisted of one central omnidirectional tip contact and four cardinal directional contacts, 2.3 mm from the tip of the electrode. Multiunit activity was isolated by rethresholding the high-pass-filtered signal at 2.5 SD above mean noise. Across 20 recording depths and 5 patients, 196 pairs were analyzed (4 excluded due to absent signal at one contact). PP was derived from the central peak of cross-correlograms between multiunit threshold crossings. Beta power was extracted from the same pairs using peri-event spectrograms (±25ms window). PP, beta power, and LFP coherence were z-scored within patient to remove between-patient baseline differences. Pearson correlations with 95% confidence intervals were computed across all pairs (n=196) and separately within ventral-to-dorsal pairs (tip to directional contacts, n=80) and within-plane dorsal pairs (between directional contacts, n=116). Based on the known functional topography of the STN, the ventral tip likely sampled associative/limbic territory; dorsal contacts sampled motor territory.

Results: At the pair level, no significant correlations were observed between any of the three measures (all $p>0.05$). Spatial subgroup analysis revealed that within-plane dorsal pairs exhibited significantly higher PP than ventral-to-dorsal pairs ($p<0.001$), indicating stronger co-firing between adjacent motor contacts. Within ventral-to-dorsal pairs, PP positively correlated with spike-locked beta power ($r=0.260$, $p=0.020$) and negatively correlated with coherence ($r=-0.234$, $p=0.036$), revealing a dissociation between spiking synchrony and putatively network-level phase-locking across the limbic-to-motor pathway. Between within-plane dorsal pairs, beta power was negatively associated with coherence ($r=-0.183$, $p=0.050$), indicating that local oscillatory power and inter-electrode phase-locking dissociate within the motor territory of the STN.

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Conclusion: These findings indicate that the functional organization of the STN shapes the relationships between spiking synchrony, beta power, and coherence in Parkinson's disease. The opposing directions of the beta power–coherence and PP–coherence relationships may reflect phase differences between STN neural populations across functional territories. These spatially specific coupling patterns have implications for directional DBS optimization. Future work will examine phase relationships and include more patients.

M304: Multi-Nodal Measures of Network Oscillatory Activity Associated with Longitudinal Deep Brain Stimulation Therapy for Dystonia

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Background: Unlike other indications of deep brain stimulation (DBS), therapeutic benefits of pallidal DBS for dystonia are delayed, taking weeks to months to manifest. The underlying network changes mediating clinical benefit have not been identified.

Methods: Simultaneous cortical EEG, local field potentials (LFPs), and surface EMG recordings were collected at rest and during finger-tapping movements at baseline, 1, 2 and 3 months after DBS initiation. Following filtering and artifact rejection, continuous data were divided into 1s epochs, from which power spectral densities (PSDs), cortico-pallidal coherence spectra, and frequency-domain directional Granger causality (GC) spectra were derived. Significance was predefined as exceeding the 95th percentile of a permutation distribution of each measure. The Unified Dystonia Rating Scale (UDRS) was assessed at each visit.

Results: Neurophysiological recordings were collected from 4 participants (2F, 2M, mean age 54 $\pm$ 12 yrs) with dystonia with DBS therapy targeting the globus pallidus internus (GPi). In participant 1, beta band (13-30 Hz) coherence increased significantly ($\alpha = 0.05$) from month 1 to 3 between GPi/Cortex both ipsilateral (+248%, left hand; +144%, right hand) and contralateral (+99.6%, left hand; +144%, right hand) to the hand performing finger taps. GC measures revealed asymmetric information flow, with significant changes occurring in beta activity from GPi to cortex (mean beta GPi $\rightarrow$ Cortex = .008), but not cortex to GPi (mean beta Cortex $\rightarrow$ GPi = 4.16 $\times$ 10^-4). These findings were associated with a 16-point improvement in dystonia clinical ratings. In participants 2, 3, and 4, significant beta coherence and GC arose at 3 months follow-up, one month follow-up, and at initiation of DBS therapy, respectively. Data collection is still ongoing in participants 3 and 4.

Conclusion: The present work, to our knowledge, is the first to assess multiple motor network nodes during longitudinal DBS therapy for dystonia. Oscillatory shifts were found across theta, alpha, and beta band frequencies, with beta changes most prominent. This is consistent with prior implications of beta activity in Parkinson Disease and dystonia. Our results suggest that multi-nodal measures of network activity, such as coherence and GC, may provide additional information beyond PSD, which is a single-node measure. Further work should aim to uncover whether these changes are merely a downstream effect of DBS, or if they may serve as a biomarker that could help optimize therapeutic settings.

M305-LB: PDCP Expression Correlates with Domain-Specific Cognitive Performance Following One-Week Dopaminergic Washout in Early-Stage Parkinson's Disease

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Background: The Parkinson's Disease Cognitive Pattern (PDCP) is a validated metabolic network whose expression correlates with executive, memory, visuospatial, and processing speed deficits in Parkinson's Disease (PD). These correlations have been demonstrated in mixed-stage cohorts, typically imaged on dopaminergic medications or after overnight withdrawal. PDCP expression has been shown to increase over time in early PD, but whether PDCP-cognition correlations are detectable in this very early stage remains unknown. This study examines these associations in an exclusively early-stage PD cohort following a one-week dopaminergic medication washout.

Methods: Nineteen early-stage PD patients (mean age 65.2 $\pm$ 7.1 years; 14/19 male; medication duration 1.6 $\pm$ 0.8 years; levodopa equivalent daily dose 490 $\pm$ 425 mg; Montreal Cognitive Assessment score 26.4 $\pm$ 2.7) completed a one-week dopaminergic medication washout study. Participants underwent FDG-PET imaging and neuropsychological testing in both ON- and OFF-medication states; this analysis focuses on the one-week OFF condition. PDCP expression was computed using established spatial covariance methods. Cognitive domains assessed included executive function (CANTAB One Touch Stockings [OTS], Tower Achievement Score), memory (Hopkins Verbal Learning Test-Revised [HVLT-R] total recall and delayed recall, Pattern Recognition Memory [PRM]), visuospatial function (Judgment of Line Orientation [JLO]), and processing speed (Symbol Digit Modalities Test

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[SDMT]). Associations were evaluated using Spearman correlations with 95% confidence intervals.

Results: PDCP showed significant negative correlations with measures of executive function and memory, including CANTAB One Touch Stockings (OTS) ($\rho = -0.56$, 95% CI [−0.81, −0.14]) and CANTAB Pattern Recognition Memory (PRM) ($\rho = -0.52$, 95% CI [−0.79, −0.08]). Across other domains, PDCP expression showed consistent but non-significant negative correlations, including executive function (D-KEFS Tower Achievement: $\rho = -0.44$), memory (HVLT-R total recall: $\rho = -0.41$; delayed recall: $\rho = -0.26$), visuospatial function (JLO: $\rho = -0.40$), and processing speed (SDMT oral: $\rho = -0.25$; SDMT written: $\rho = -0.28$), with confidence intervals overlapping zero. Overall, higher PDCP expression was associated with poorer cognitive performance across these prespecified domains.

Conclusion: This is the first study to test PDCP-cognition correlations in an early-stage PD cohort following a one-week dopaminergic washout. Higher PDCP expression was associated with worse cognitive performance in executive function and memory, which extends findings previously established only in mixed-stage cohorts to early-stage PD. The extended washout design further suggests these associations reflect disease-intrinsic network pathology rather than medication-related metabolic effects.

M307: HISHS-3001 Treatment Preserves the Nigrostriatal Dopaminergic Pathway by Restoring Striatal and SNpc Dopamine and Maintaining Tyrosine Hydroxylase Immunoreactivity In 6-OHDA-Induced PD Model in Rats

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Background: HISHS-3001 is a novel, long-acting GLP-1/GIP/GCG tri-receptor agonist with preclinical efficacy at lower doses than tirzepatide (TZP). Here, effects of HISHS-3001 were investigated in 6-hydroxydopamine (6-OHDA)-induced Parkinson's disease model.

Methods: In male Sprague–Dawley rats, lesions were produced under anesthesia by stereotaxic injection of 6-OHDA (20 μg in median forebrain bundle of right brain). Sham control (SC) received vehicle. After lesioning, rats were treated with HISHS-3001 every alternate day (q2d) (10, or 20, or 30 nmol/kg, s.c.), or TZP (30 nmol/kg, s.c., q2d), or daily liraglutide (LIR) (200 μg, s.c.) for 30 days. On day 31, apomorphine-induced (0.05 mg/kg, s.c.) rotation test was conducted (30 min; 1-min counts every 10 min); rats were euthanized, striatum and substantia nigra pars compacta (SNpc) were dissected for measuring dopamine, TNF-α, IL-1β levels (ng/g) by ELISA and tyrosine-hydroxylase (TH) expression by western blot and IHC. Data were analyzed with unpaired t-test for control vs SC/disease control (DC) groups (p values given by #). All other groups were compared with DC group by using ANOVA followed by Bonferroni's test [p values given by * (DC), $ (LIR), @ (TZP)].

Results: The DC rats displayed a significant increase in contralateral rotations ($103.3\pm61.27^{\#\#\#}$ vs 2.5 ± 4.42 control and 3.3 ± 4.82 SC). HISHS-3001 reduced rotations to 15.0 ± 10.22*** at 30 nmol/kg along with TZP (20.0 ± 11.80***) and LIR (26.3 ± 13.13***). In striatum, lesioning reduced dopamine levels; $72.9\pm 9.2^{\#\#\#}$ against 368.4 ± 31.31 control and 343.3 ± 28.12 SC, which was restored with HISHS-3001 treatment in a dose-dependent manner [at $10\text{-}100.2\pm14.32$; at $20\text{-}206.5\pm15.08$***; at $30\text{-}311.0\pm45.76$***$^{\$\$\$}$], and improvement with TZP(267.9 ± 35.8***) and LIR (216.5 ± 37.76***) respectively. TNF-α level changes were: {Control 0.26 ± 0.02; SC $0.29\pm0.01^{\#}$; DC $1.13\pm0.08^{\#\#\#}$; HISHS-3001 $10\text{-}1.15\pm 0.13$; $20\text{-}0.76\pm0.18$*; $30\text{-}0.53\pm0.20$***; TZP-0.64 ± 0.26***; LIR-0.51 ± 0.10***}. IL-1β levels were: {Control 0.96 ± 0.19; SC 1.15 ± 0.11; DC $2.31\pm0.35^{\#\#\#}$; HISHS-3001 $10\text{-}2.16\pm0 .24$; $20\text{-}1.58\pm0.40$*; $30\text{-}1.16\pm0.11$***; TZP-1.67 ± 0.63; LIR-1.73 ± 0.22}. In SNpc, the relative TH content was markedly reduced after lesioning, which was improved by treatments {Control 0.78 ± 0.23; SC 0.85 ± 0.13; DC $0.11\pm0.05^{\#\#\#}$; HISHS-3001 $10\text{-}0.19\pm0.06$; $20\text{-}0.36\pm0.07$***; $30\text{-}0.81\pm0.13$***$^{\$\$\$}$; TZP-$0.71\pm0.05$***$^{\$\$\$}$; LIR-$0.49\pm0.07$***}. TNF-α level changes were: {Control 0.27 ± 0.02; SC 0.26 ± 0.02; DC $1.12\pm0.08^{\#\#\#}$; HISHS-3001 $10\text{-}0.95\pm0.14$*; $20\text{-}0.53\pm 0.04$***; $30\text{-}0.29\pm0.04$***$^{\$}$; TZP-$0.42\pm0.06$***; LIR-$0.45\pm0.10$***}. HISHS-3001 treatment produced marked reduction in IL-1β levels, which was superior to LIR and TZP {Control 1.03 ± 0.08; SC 1.11 ± 0.12; DC $2.37\pm0.28^{\#\#\#}$; HISHS-3001 $10\text{-}2.08\pm0.11$; $20\text{-}1.92\pm0.15$*; $30\text{-}1.33\pm0.09$***$^{\$\$\$@@}$; TZP-$1.93\pm0.32$*; LIR-$2.24\pm0.32$}.

Conclusion: HISHS-3001 produced robust nigrostriatal dopaminergic restoration at 30 nmol/kg. The reduction in inflammatory markers in striatum and SNpc are likely to improve insulin sensitization. Profound reduction of IL-1β, a potent mediator of neuroinflammation, may suggest inhibitory effect on NLRP3 inflammasome activation pathway, indicating a potential of HISHS-3001 for treatment of neurodegenerative diseases.

M308: Cerebrospinal Fluid Biomarkers in Autoimmune Atypical Parkinsonism: A Prospective Case-Control Study

Presenting Author(s): *Meena Thevarkalam, MBBS, MD, Kochi, Kerala*

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Background: Autoimmune atypical parkinsonism represents a distinct subset of parkinsonian disorders with probable immunological mechanisms. CSF biomarkers including α-synuclein, amyloid-beta (Aβ), and tau proteins have been studied in classical neurodegenerative parkinsonism, but their profile in autoimmune variant remains unexplored.
This is the first study worldwide to examine these biomarkers in autoimmune atypical parkinsonism.

Methods: We conducted a prospective case-control study from September 2023 to September 2025 at Amrita Institute of Medical Sciences, Kochi, India. Twenty-three patients with autoimmune atypical parkinsonism (15 progressive supranuclear palsy, 2 corticobasal syndrome, 2 multiple system atrophy, 1 PSP-MSA overlap, 3 uncharacterized) and 20 age- and sex-matched controls were included. We measured α-synuclein, Aβ40, Aβ42, phosphorylated tau (p-tau), and total tau (t-tau) using enzyme-linked immunosorbent assays (ELISA). Statistical analyses included Mann-Whitney U tests and independent t-tests.

Results: Controls (n=20, age 69.5±5.5 years, 55% female) and cases (n=23, age 65.4±9.6 years, 52% female) were well-matched for age (p=0.098) and sex (p=1.000). Compared to controls, cases showed significantly reduced CSF α-synuclein (77.7% reduction, p=0.0029), Aβ40 (23.7% reduction, p=0.0095), Aβ42 (17.2% reduction, p=0.048), and p-tau (11.3% reduction, p=0.018). Ratios of α-synuclein to Aβ42 (p=0.0078), t-tau (p=0.0032), and p-tau (p=0.0050) were also significantly reduced. Total tau levels did not differ between the two groups (p=0.971).

Conclusion: Autoimmune atypical parkinsonism exhibits a distinct CSF biomarker profile characterized by marked reduction in α-synuclein and concurrent decreases in amyloid and phosphorylated tau. This profile differs from classical neurodegenerative parkinsonism and may reflect unique pathophysiological mechanisms.

M309: PDCP Expression Correlates with Domain-Specific Cognitive Performance Following One Week Dopaminergic Washout in Early-Stage Parkinson's Disease

Presenting Author(s): *Ella Tobias, High School Diploma, Scottsdale, AZ*

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Background: The Parkinson's Disease Cognitive Pattern (PDCP) is a validated metabolic network whose expression correlates with executive, memory, visuospatial, and processing speed deficits in Parkinson's Disease (PD). These correlations have been demonstrated in mixed-stage cohorts, typically imaged on dopaminergic medications or after overnight withdrawal. PDCP expression has been shown to increase over time in early PD, but whether PDCP-cognition correlations are detectable in this very early stage remains unknown. This study examines these associations in an exclusively early-stage PD cohort following a one-week dopaminergic medication washout.

Methods: Nineteen early-stage PD patients (mean age 65.2 ± 7.1 years; 14/19 male; medication duration 1.6 ± 0.8 years; levodopa equivalent daily dose 490 ± 425 mg; Montreal Cognitive Assessment score 26.4 ± 2.7) completed a one-week dopaminergic medication washout study. Participants underwent FDG-PET imaging and neuropsychological testing in both ON- and OFF-medication states; this analysis focuses on the one-week OFF condition. PDCP expression was computed using established spatial covariance methods. Cognitive domains assessed included executive function (CANTAB One Touch Stockings [OTS], Tower Achievement Score), memory (Hopkins Verbal Learning Test-Revised [HVLT-R] total recall and delayed recall, Pattern Recognition Memory [PRM]), visuospatial function (Judgment of Line Orientation [JLO]), and processing speed (Symbol Digit Modalities Test [SDMT]). Associations were evaluated using Spearman correlations with 95% confidence intervals.

Results: PDCP showed significant negative correlations with measures of executive function and memory, including CANTAB One Touch Stockings (OTS) ($\rho = -0.56$, 95% CI [−0.81, −0.14]) and CANTAB Pattern Recognition Memory (PRM) ($\rho = -0.52$, 95% CI [−0.79, −0.08]). Across other domains, PDCP expression showed consistent but non-significant negative correlations, including executive function

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(D-KEFS Tower Achievement: $\rho = -0.44$), memory (HVLT-R total recall: $\rho = -0.41$; delayed recall: $\rho = -0.26$), visuospatial function (JLO: $\rho = -0.40$), and processing speed (SDMT oral: $\rho = -0.25$; SDMT written: $\rho = -0.28$), with confidence intervals overlapping zero. Overall, higher PDCP expression was associated with poorer cognitive performance across these prespecified domains.

Conclusion: This is the first study to test PDCP-cognition correlations in an early-stage PD cohort following a one-week dopaminergic washout. Higher PDCP expression was associated with worse cognitive performance in executive function and memory, which extends findings previously established only in mixed-stage cohorts to early-stage PD. The extended washout design further suggests these associations reflect disease-intrinsic network pathology rather than medication-related metabolic effects.

M310: Fmnl2 Splice Mutation Prevents Motor System Development By Overpromoting Actin Polymerization in Cellular Migration Structures

Presenting Author(s): *Joyce Tran, La Jolla, CA*

Background: Actin is a ubiquitous protein that regulates cellular morphology for processes like migration. These processes are particularly critical during development, where cellular changes are necessary for tissue development. Formins regulate actin and microtubule dynamics through the binding of their specialized domains to the actin polymerizing end. Many formin mutations have been shown to lead to constitutively active proteins, which contribute to a myriad of human diseases. A deeper investigation of these mutations can help elucidate the mechanisms behind diseases without a known cause and provide the foundation for future therapeutics.

Methods: Through a chemical mutagenesis screening, we discovered a hindlimb hypotonic mouse homozygous for the recessive nmf418 mutation.

Results: The few surviving mice display improper bone fusion in the posterior skull and vertebral skeleton. These mice also exhibit anterior-posterior cerebellar elongation and abnormal vermis foliation. Forebrain analysis revealed corpus callosum thinning and a reduction in. By positional cloning and RNA-sequencing, we identified a single nucleotide on formin like 2 (Fmnl2), generating an alternatively spliced transcript lacking exon 10. Total Fmnl2 transcript levels in Fmnl2418/418 mutant mice are unchanged compared to wild type (WT) mice, but protein levels are reduced in the brain and other organs. Interestingly, a complete Fmnl2 knockout mouse shows no cerebellar or spinal defects and mild loss of myelination in the corpus callosum and supraoccipital bone formation, suggesting that a complete loss of function mechanism fails to fully explain the phenotypes seen in the chemically induced mutant.

Conclusion: FMNL2, a diaphanous-related formin, is a cytoskeletal regulator that has previously been shown to drive actin polymerization at lamellipodia and filopodia tips during cancer cell metastasis. Cells expressing mutant FMNL2Δ25, derived from the fmnl2418 allele lacking the 25bp transcribed by exon 10, have an increased rate of migration. Additionally, these cells exhibit increased accumulation of FMNL2Δ25 at filopodia tips and an increase in parallel stress fiber formation, possibly contributing to the increase in migration. This suggests the mutation may over-promote F-actin polymerization at filopodia tips as well as within the cell the cell body.

These results imply the cerebellar and skeletal defects seen in Fmnl2 mutant mice may be due to rapidly invading cells with improper actin cytoskeleton structure during development, possibly due to a gain of function mechanism. This study reveals a new role for FMNL2 in mouse development and sheds light on possible mechanistic etiologies for humans with a similar constellation of symptoms

M311: Generalized Chorea in an Older Adult: A Neuronal Intermediate Filament Antibody–Associated Paraneoplastic Syndrome

Presenting Author(s): *Ricardo Vivanco Menoscal, Lexington, KY*

Co-Author(s): *Mario Yepez, MD, University of Kentucky, Lexington, KY, Andrew Welleford, MD, PhD, University of Kentucky, Lexington, KY, Zain Guduru, MD, Lexington, KY*

Background: Chorea is a rare paraneoplastic manifestation representing fewer than 2% of paraneoplastic neurological syndromes. It is most associated with CRMP-5 and ANNA-1 antibodies in the setting of small cell lung carcinoma (1). Neuronal intermediate filament (NIF) antibodies are an emerging cause of paraneoplastic CNS autoimmunity, typically presenting with cerebellar ataxia or encephalopathy in the context of neuroendocrine neoplasia, with chorea reported rarely (2). We report a case of NIF antibody-associated paraneoplastic disease presenting as generalized chorea.

Methods: Describe a rare presentation of disease as case report.

Results: Case Presentation An 82-year-old man developed progressive involuntary movements beginning in February 2025 with intermittent right-hand pronation while typing. Over months, the movements evolved into continuous generalized chorea with marked right-sided predominance involving the face, head, right arm and leg, with subtle left-hand choreoathetosis. He developed dysphagia, gait instability, and marked weight loss despite a preserved appetite. Brain MRI showed chronic microvascular changes without basal ganglia lesions. There was no exposure to dopamine receptor-blocking agents, and family history was negative for movement disorder.

Initial metabolic, endocrine, infectious and systemic autoimmune evaluation was unrevealing. A longstanding right paravertebral soft tissue mass, previously evaluated with fine needle aspiration, bone marrow biopsy, and peripheral blood flow cytometry had been considered likely to be benign on serial imaging. Serum paraneoplastic testing demonstrated NIF antibody positivity by tissue immunofluorescence (1:480) with confirmatory neurofilament heavy-chain antibody positivity; neurofilament light-chain and alpha-internexin antibodies were negative. Clinical Interpretation Given progressive generalized chorea, weight loss, and the

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known previously presumed benign right paravertebral soft tissue abnormality, a paraneoplastic autoimmune syndrome was favored. He was treated with tetrabenazine, intravenous methylprednisolone, and intravenous immunoglobulin, with noticeable improvement in chorea and oral intake. Subsequent PET-CT demonstrated FDG-avid unilateral perivertebral soft tissue thickening and intense uptake in the T3 vertebral body, highly suspicious for an underlying lymphoproliferative neoplastic process. Notably, the NIF antibody profile in this case was neurofilament light-chain negative, a pattern characterized as having uncertain clinical significance compared to the NfL-positive paraneoplastic subgroup (2). Additionally, CRMP-5 antibody testing was not performed; therefore, alternative paraneoplastic antibodies cannot be fully excluded.

Conclusion: This case expands the phenotypic spectrum of NIF antibody-associated paraneoplastic syndromes to include generalized chorea as a presenting manifestation. It reinforces the need for PET-CT when conventional imaging and tissue sampling are non-diagnostic. Finally, it supports early immunotherapy initiation to provide meaningful symptomatic benefit in this rare and underrecognized syndrome.

M312: Reversible Carbamazepine Induced Episodic Ataxia Without Cerebellar Atrophy

Presenting Author(s): *Ricardo Vivanco Menoscal, Lexington, KY*

Co-Author(s): *Andrew Welleford, MD, PhD, University of Kentucky, Lexington, KY, Tarek Ali, Lexington, KY*

Background: Episodic ataxia is a heterogeneous disorder with genetic and secondary causes. In patients with epilepsy, cerebellar dysfunction may arise from shared genetic mechanisms, seizure-related effects, or antiseizure medication toxicity (1). Carbamazepine is known to cause dose-related dizziness, nystagmus, and ataxia (2); however, delayed-onset episodic cerebellar syndrome occurring after years of stable dosing at therapeutic levels is uncommon and may mimic inherited or acquired cerebellar disease.

Methods: We conducted a retrospective, longitudinal case review of clinical features, diagnostic evaluation, and treatment response in a patient with focal epilepsy and recurrent episodic cerebellar symptoms.

Results: A 47-year-old man with drug-resistant nocturnal hypermotor focal epilepsy since adolescence developed recurrent episodes of gait instability, diplopia, nausea, vomiting, dysarthria, nystagmus, and dysmetria beginning in his late 30s. Episodes lasted hours to days and became increasingly frequent, with mild interictal gait impairment. During epilepsy monitoring, episodic cerebellar signs occurred while carbamazepine and other antiseizure medication levels were therapeutic. Evaluation for a unifying genetic or acquired cause was extensive. Targeted and genome-wide testing for inherited episodic ataxias and spinocerebellar ataxias was negative. Autoimmune, metabolic, infectious, vascular, cerebrospinal fluid, and neuroimaging studies were unrevealing, and brain MRI showed no cerebellar atrophy or structural abnormalities. Acetazolamide provided partial symptomatic benefit. In late 2025, the patient independently reduced carbamazepine by 400 mg/day.

Following dose reduction, episodic ataxia resolved completely, nystagmus normalized, and baseline cerebellar function improved, while seizure frequency was initially unchanged. He has remained free of episodic cerebellar symptoms for more than one year.

Conclusion: This case demonstrates carbamazepine induced episodic cerebellar dysfunction masquerading as a genetic or acquired ataxia. Notable features include delayed onset after years of apparent tolerability, occurrence at therapeutic drug levels, complete reversibility after dose reduction, and absence of cerebellar atrophy. This case expands the recognized spectrum of carbamazepine-induced cerebellar dysfunction and highlights how delayed, reversible toxicity can phenocopy genetic or acquired episodic ataxia without cerebellar atrophy.

M313-K: Projections from Hippocampal CA1 to Striatum are Biased Toward Either the Striosome or Matrix Compartments

Presenting Author: *Jeff Waugh, MD, PhD, University of Texas Southwestern*

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Background: Hippocampo-striate projections are essential for linking spatial and contextual memory with action selection, reward prediction, and goal-directed behavior. The hippocampus routes information to the striatum through polysynaptic circuits, innervating medium spiny neurons in one of two distinct tissue compartments, the striosome or matrix. Though the compartments are interdigitated throughout the striatum, they differ in their embryologic origins, relative abundance, intra-striate location, and afferent and efferent connectivity. We recently demonstrated in humans that striosome and matrix have markedly different functional connectivity networks and are engaged in different phases of tasks. Therefore, hippocampo-striate projections that synapse in striosome may underpin different functions and engage with different functional networks than inputs that synapse in matrix. However, it was unknown whether hippocampo-striate projections are organized differently for striosome and matrix, or if compartment-specific organization differed between polysynaptic paths.

Methods: We used connectivity-based parcellation in healthy adults (probabilistic diffusion tractography, N=930, Human Connectome Project) and anterograde viral injections with subsequent immunohistochemistry in mice to assess structural and functional connectivity between CA1 and the striatal compartments. We identified subject-specific CA1, striosome-like, and matrix-like masks in each human subject based on structural and diffusion MRI-based parcellations. We defined three hippocampo-striate pathways, each constrained to pass through one of three intermediary nuclei (subiculum, medial prefrontal cortex, or lateral septum) with stringent selection for anatomically-validated streamlines. In mice, we injected the viral tracer YFV-17D in dorsal or

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ventral CA1. After eight days (optimized to identify hippocampo-striate projections) we quantified immunofluorescent soma within striosome or matrix using calbindin immunohistochemistry.

Results: In mice, each CA1 viral injection labeled projections that were either striosome-favoring or matrix-favoring – none were unbiased. Therefore, our viral vector's diffusion diameter (∼1mm) appeared to be enclosed within segregated somatotopic zones that preferentially projected to only one striatal compartment. Consistent with this finding, in humans we identified discrete somatotopic zones, interspersed throughout CA1, that were biased either toward striosome- or matrix-like voxels. Striosome-biased CA1 volume was 3.5-fold larger than matrix-biased volume. Each hippocampo-striate path was striosome-biased (medial prefrontal > subiculum > lateral septum), but the somatotopic zones for each hippocampo-striate path were largely segregated from the zones of other paths (overlap, two-paths: 5.7%; overlap, three-paths: 0.12%). Projections to randomly-selected striatal voxels (negative control) lost this bias. Resting state functional activation in CA1 was correlated with striosome-like voxels but anti-correlated with matrix-like voxels.

Conclusions: Hippocampo-striate projections may be segregated into distinct networks that serve striosome-or matrix-specific functions.

M315*: Mechanisms of α-Synuclein mediated circuit dysfunction in prefrontal and posterior cortical circuits

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Background: Cognitive impairment is a common non-motor symptom of Parkinson's disease (PD) and a defining feature of Dementia with Lewy Bodies (DLB). Neuropsychological studies have defined a dual syndrome of cognitive impairments in PD and DLB. These include frontostriatal impairments in attention and executive function and posterior cortical impairments in visuospatial/perceptual function. Across populations, cognitive impairments correlate with the presence of α-synuclein (α-syn) pathology in limbic and neocortical brain regions. However, the specific role that α-syn pathology plays in driving cortical circuit dysfunction and cognitive impairment remains controversial. We hypothesized that inducing α-syn pathology directly in the prefrontal cortex (PFC) or the primary visual cortex (V1) would impair neuronal activity, leading to impairments in attention or visuoperceptual function, respectively.

Methods: To test this hypothesis, we injected α-syn preformed fibrils (PFF) into the PFC or V1 of mice to seed endogenous α-syn pathology. We then used translationally inspired behavioral assays, including an attentional set-shifting task (ASST) and a coherent motion discrimination task, to measure attention and visuoperceptual cognitive abilities. Using longitudinal in vivo two-photon (2P) calcium imaging, we also recorded the activity of pyramidal cells in layer 2/3 (L2/3) and quantified α-syn pathology using C05-05, a fluorescent ligand that binds aggregated α-syn.

Results: In mice with V1 injections, we found a greater percentage of neurons in PFF-injected mice were responsive to visual stimuli with lower direction selectivity compared to controls at 4-5 months post-injection (MPI). Within PFF-injected mice, neurons with large somatic Lewy-like inclusions had significantly lower visually evoked activity compared to neighboring neurons without inclusions. Conversely, neurons without somatic inclusions showed increased activity, positively correlated with the nearby burden of α-syn pathology. Surprisingly, we found no impairments in visuoperceptual ability in PFF-injected mice up to 6 MPI. In contrast, in mice with PFC injections, extradimensional set-shifting performance was impaired at 3 and 6 MPI compared with controls.

Neuronal activity recordings from the PFC are in progress.

Conclusion: Our results demonstrate, for the first time in vivo, that α-syn pathology leads to cell autonomous reductions in neuronal activity and reciprocal changes in local population activity. In V1, these may be compensatory, helping to preserve visuoperceptual function. Conversely, impairments in set-shifting in mice with PFC injections suggests there may be differential susceptibility to α-syn pathology across distinct cortical circuits. Future studies incorporating risk factors for dementia in PD will increase our understanding of the heterogeneity of cognitive symptoms and α-syn pathology across patients.

M317: Visualizing the Developing Brain: Accelerated Golgi Staining Optimization for Early Postnatal Mice

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Background: Increasing evidence suggests that early neurodevelopment perturbations contribute to the pathogenesis of numerous neurological disorders. However, efficient methods for visualizing cellular morphology in immature brain tissue remain limited. Golgi staining is widely utilized for comprehensive visualization of neuronal architecture, but conventional protocols were developed primarily for adult brain tissue and typically require prolonged impregnation periods of approximately two weeks. Accelerated methods using elevated temperatures have been reported in adult brains, yet their suitability for early postnatal tissue has not been systematically evaluated. Here, we establish a rapid Golgi staining workflow for postnatal day 10 (P10) mouse brains, a critical developmental stage marked by dynamic neuronal maturation and substantial differences in tissue size and cellular composition relative to adulthood.

Methods: To optimize the protocol for P10 mouse brains, fixation status (fixed for 5 or 40 minutes vs. unfixed) and

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incubation duration (24 hours vs. 48 hours at 37°C) were systematically varied. Staining outcomes in the cortex and striatum were qualitatively and quantitatively evaluated based on individual neuronal morphology, regional staining quality, and cell-type specificity. The optimal condition was subsequently applied to P10 wildtype and Huntington's disease brains for quantitative morphometric analysis of neuronal structure.

Results: Accelerated Golgi staining of P10 mouse brains using 24 or 48 hour impregnation at 37°C revealed region-specific differences in labeling quality. The 24 hour condition showed superior striatum staining, with clearer visualization of medium spiny neuron somata and dendritic arbors. In contrast, 48 hour impregnation produced stronger labeling in the cortex, with improved visualization of cortical neuronal cell bodies. Fixation status further influenced cell-type specificity in P10 mouse brains at both 24 and 48 hour conditions. Fixed tissue showed an increase in labeling of glial cells, whereas unfixed tissue favored neuronal labeling. This pattern was observed across fixation durations ranging from 5-40 minutes, suggesting fixation state rather than fixation length was the primary factor. To assess downstream applicability, the 48 hour condition was applied to P10 wildtype and Huntington's disease brains. Quantitative analyses identified measurable differences in neuronal morphology, supporting compatibility with morphometric analysis.

Conclusion: A rapid Golgi staining workflow for early postnatal mouse brain was established, reducing processing time from weeks to 24–48 hours while preserving high-quality structural detail. Importantly, optimal staining conditions were determined to be dependent on both brain region and fixation status. Collectively, these findings provide a practical framework for efficient morphological analysis during critical periods of postnatal brain development.

M318: Patient-reported Botulinum Toxin Response Scale (BTRS) for Cervical Dystonia: A Patient Experience and Perspective Study

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Background: Current clinical practice for determining the inter-injection interval of botulinum toxin (BTX) treatment for cervical dystonia (CD) does not account for the temporal course of individual patient response but rather adheres to relatively fixed intervals based on BTX formulation and insurance approvals. Furthermore, clinical determination of treatment response is assessed during follow-up injection visits with no inter-injection assessment and is highly subject to recall bias. We hypothesized that a patient-reported Botulinum Toxin Response Scale (BTRS) is needed to assess the treatment responses from BTX injections and inform patient- specific inter-injection intervals of BTX for CD.

Methods: Building upon our prior feasibility study (Gupta, Movement Disorders, 2019) and following IRB approval, we recruited 30 CD patients who had received at least one prior cycle of BTX injection at University of Vermont Medical Center. We collected demographic and clinical information and then conducted semi-structured interviews to characterize experiences with BTX injections and perspectives on the existing BTRS. Data were captured using REDcap and Ambient AI (Abridge) platforms, followed by appropriate statistical and thematic analysis using Google Colab.

Results: Mean age was 63.47 years with 22 female respondents. The parameters (mean ± SD) of the temporal aspects of BTX treatment were as follows: treatment duration (10.11 ± 8.75 years), inter-injection interval (13.60 ± 4.34 weeks), onset of benefit (6.77 ± 9.34 days), onset of peak benefit (18.03 ± 13.82 days), waning of benefit (9.53 ± 1.72 weeks), and termination of benefit (11.24 ± 1.83 weeks). Spearman Rank analysis showed that overall disability scores assessed by the existing BTRS were negatively correlated with the waning of benefit ($\rho = -0.591$, $p = 0.008$), termination of benefit ($\rho = -0.749$, $p < 0.001$), and longitudinal treatment duration ($\rho = -0.524$, $p = 0.021$). Thematic analysis of interview transcripts yielded four core themes with accompanying subthemes: Therapeutic Efficacy (functional restoration, symptom relief, and psychological impact); Temporal Instability (latency of onset and "wear off" effect); Procedural/Pharmacological Burden (procedure anxiety, pain, and side effects); and Systemic Friction (logistical and insurance barriers).

Conclusion: Quantitative results of our study suggest that patient-reported disability scores are correlated with suboptimal BTX treatment response, particularly the temporal dynamics, however, also show cumulative benefits from long-term therapy. Qualitative results provide patient feedback and perspectives regarding the existing BTRS and aspects of treatment experience, which will inform the development of a revised scale to enable a patient-centric, precision medicine approach to treating CD with BTX.

NEURODEGENERATION AND CELL DEATH

M320-K: Diffusion Tensor Imaging as a Data-Driven Classifier of Early Cerebral Adrenoleukodystrophy

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Objective: Childhood cerebral adrenoleukodystrophy (CALD) is a rapidly progressing neurological disorder that must be treated early to prevent neurocognitive decline. In current clinical practice, life-saving cellular therapies are initiated only after white matter changes from CALD appear on structural MRI. Our objective was to evaluate the sensitivity and specificity of region-based metrics from brain diffusion tensor imaging (DTI) for classifying and predicting early-stage CALD.

Methods: We analyzed a diffusion MRI dataset derived from scans of 119 boys with adrenoleukodystrophy (ALD) acquired between 2007–2025. Images were processed from 74 (62%) boys with CALD scanned prior to treatment and 45 (38%) boys with ALD and no lesion (NL-ALD). Of the CALD patients, 5 had sequential scans acquired 3-27 months before lesion development ("pre-lesion ALD"; PL-ALD).

Across all subjects, 266 total scans were categorized: CALD (n=87), PL-ALD (n=13) and NL-ALD (n=166). Single-shell DTI (b=1000 s/mm2) was acquired using two protocols (12-directional with voxel size 2×2×5mm3 and 66-directional with voxel size 2×2×2mm3). Fractional anisotropy (FA), radial, axial, and mean diffusivity (RD, AD, MD) were estimated for 57 atlas- defined white matter regions. Stepwise linear regression, stratified by age and DTI protocol, identified a minimal DTI feature set that predicted disease status (C-ALD, PL-ALD, or NL-ALD). To determine whether a logistic regression classifier could differentiate CALD from NL-ALD scans using the identified DTI feature set, cross-validation was performed with a 75%-25% train-test split with no patient overlap between datasets (5,000 permutations).

CALD lesion severity was quantified using a disease-specific radiological scoring system (Loes score).

Results: The NL-ALD cohort's baseline age (7±3 years) was slightly lower than that of the CALD cohort (8±2 years), p=0.08. The median pre-treatment Loes score among CALD patients was 3.0 (IQR 2.0-7.5; range: 1.0-21.5). Stepwise regression identified 85 DTI features, independent of age and DTI protocol, with a Pearson correlation of r=0.98 between predicted and actual disease status. In cross-validation, the logistic regression classifier identified CALD scans with 100% sensitivity (95% CI: 86–100%) and 100% specificity (95% CI: 95–100%). Notably, DTI features were present at the pre-lesion stage before a visible T2-weighted MRI lesion developed.

Conclusion: Using an automated algorithm, multi-region DTI analysis achieved high classification accuracy in differentiating scans with and without CALD lesions. Crucially, DTI features could detect white matter microstructural changes not yet evident on conventional MRI. This suggests that DTI could serve as a primary "early warning" biomarker to optimize treatment timing.

NEUROMUSCULAR DISEASE

M322-LB: Association of Use of Prescription Medications with Neuromuscular Adverse Effects with Frailty and Mobility Limitations Among Older Adults in the U.S

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Background: Prescription medications are commonly used among older adults, and many have potential neuromuscular adverse effects, including weakness, myopathy, neuropathy, tremor, gait disturbance, and impaired coordination. Concurrent use of multiple medications with these adverse effects may contribute to impaired mobility, reduced strength, and frailty. In this study, we analyze the association between use and concurrent use of medications with neuromuscular adverse effects and functional health, specifically mobility limitations and muscle strength among older adults.

Methods: This cross-sectional study used the National Health and Nutrition Examination Survey data for 4,241 adults 50 years and older to analyze frailty and mobility limitations. Data on prescription medication use were further classified using Multum Cerner based on their potential for neuromuscular adverse effects and categorized as 0, 1, 2, or 3 or more medications. Medications without neuromuscular adverse effects were also examined among adults not using medications with neuromuscular adverse effects. Outcomes included lower extremity mobility limitation and mean maximum grip strength. Lower extremity mobility limitation was defined as difficulty walking one-quarter mile or walking up 10 stairs. Grip strength was assessed using maximum handgrip strength.

Results: Among 4,241 adults aged 50 years or older, 26.7% (95% CI, 24.2%-29.2%) had at least one mobility limitation. Prevalence was 16.6% (95% CI, 13.5%-19.6%) among adults using no medications with neuromuscular adverse effects, 27.8% (95% CI, 23.8%-31.7%) among those using 1 or 2 medications, and 41.0% (95% CI, 34.5%-47.5%) among those using 3 or more medications with neuromuscular adverse effects. Among adults not using medications with neuromuscular adverse effects, mobility limitation was consistently lower at 16.82%, 12.12%, 7.81%, and 27.77% among those using 0, 1, 2, and 3 or more other medications, respectively. Overall, mean maximum grip strength was 31.98 kg (SD, 10.29) which declined with greater concurrent use of medications with neuromuscular adverse effects, from 33.7, to 32.8, 30.4%, and 28.9 kg among adults using 0, 1, 2, and 3 or more medications with neuromuscular risks, respectively.

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Conclusion: In this cross-sectional study, use of multiple medications with neuromuscular adverse effects was associated with higher prevalence of lower extremity mobility limitation and lower mean grip strength. These findings suggest that cumulative exposure to these medications may be a potentially modifiable factor associated with impaired mobility, reduced strength, and frailty.

M323: Beyond the Triad: An Atypical GQ1b-Positive Miller Fisher Syndrome

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Background: Miller Fisher Syndrome (MFS) is a rare variant of Guillain–Barré Syndrome (GBS) classically characterized by the triad of ophthalmoplegia, areflexia, and ataxia. However, incomplete or atypical forms can mimic other neuromuscular disorders, creating diagnostic challenges.
Methods: Case Report
Results: Case report : A 44-year-old male who presents with one day of difficulty walking due to binocular blurry vision. Two weeks prior, the patient experienced diarrhea while visiting Japan. On initial examination, he was noted to have bilateral ptosis and diminished extraocular movements in all directions. Strength was 5/5 throughout, reflexes were brisk throughout, and gait was normal. He was started on 500 mg of methylprednisolone as symptoms were initially thought to represent ocular myasthenia gravis. The following day, the patient developed nonreactive, 6–7 mm pupils bilaterally, along with nasal and slurred speech. IVIG was initiated due to concern for MFS, although myasthenia gravis, Lambert-Eaton myasthenic syndrome, and botulism were also considered in the differential diagnosis. MRI of the brain and orbits was unremarkable. AChR, MuSK, and VGCC antibodies were negative. During hospitalization, the patient's speech returned to baseline, and extraocular movements improved, though they remained limited. He was later found to have strongly positive GQ1b antibody titers.
Conclusion: The classical presentation of MFS is characterized by the triad of ophthalmoplegia, ataxia, and areflexia. However, the spectrum of neuropathies associated with GQ1b antibodies presents a diagnostic challenge for neurologists. This case highlights the diagnostic complexity of MFS. Few case reports have described the presence of acute bilateral areflexic mydriasis associated with positive GQ1b antibodies. In these reports, the treatment and recovery were variable. Our patient was treated with both corticosteroids and IVIG with a positive outcome. Further research is needed to determine the optimal treatment strategies for atypical presentations of MFS.

M324-K: NEIMY-Associated KIF5A Mutation Impairs Trak-Mediated Mitochondrial Transport

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Abstract: KIF5A is a neuron-specific heterotetramer belonging to the Kinesin-1 family, a group of microtubule motor proteins that plays a large role in anterograde axonal transport and cytoskeletal regulation. KIF5A is one of three kinesin-1 isoforms, alongside the more ubiquitously expressed KIF5B and the motor neuron-enriched KIF5C. All three paralogs share a common structure: 2 kinesin heavy-chain domains that dimerize to form a stalk and 2 kinesin light-chains. Both of these structures allow kinesin-1 to bind to cellular cargo through the association of adaptor proteins, such as Trak2 for mitochondrial trafficking. Mutations in KIF5A have been linked to two distinct disorders: Amyotrophic Lateral Sclerosis (ALS), a progressive motor neuron disease, and Neonatal Intractable Myoclonus (NEIMY), a fatal form of infant epilepsy. Despite sharing similar frameshift mutations within a common region of KIF5A's C-terminal domain, these disorders exhibit distinct clinical phenotypes. ALS-associated KIF5A is well-studied, however, the distribution and intracellular impact of NEIMY-associated KIF5A remain unexplored. To investigate these distinct phenotypes, cells expressing WT, ALS, and NEIMY KIF5A mutations were used to assess the effect of these mutations on cargo-complex assembly. Our studies revealed that ALS and NEIMY KIF5A variants exhibit protein accumulation in the neurite tip as compared to WT, depleting KIF5A in the soma. In cells expressing KIF5A NEIMY, large aggregates form and disrupt axonal integrity by increasing axonal swelling and cytoskeletal damage. In cells with no kinesin heavy chain, there was a reduction in overlap between Trak2 and NEIMY KIF5A suggesting reduced efficiency of formation of cargo-complex. Finally, mitochondrial transport was shown to be dysregulated in a mutation-specific manner for both ALS and NEIMY KIF5A. These results taken together suggest different pathological mechanisms for ALS and NEIMY KIF5A that result in the disruption of autoinhibition, reduced formation of the cargo-complex, and differences in mitochondrial trafficking. These findings enhance our understanding of the pathophysiology of both diseases and shed light on the underlying biology of KIF5A itself.

M325*: Towards a Digital Twin for Myasthenia Gravis

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Background: Accurate prediction of patient outcomes in clinical trials is a central challenge for rare and heterogeneous diseases as myasthenia gravis. We present a trajectory-based framework for forecasting individual patient responses by leveraging longitudinal clinical data across multiple studies. Our approach constructs temporal trajectories from repeated clinical measurements and extrapolates these to predict future outcomes, enabling early identification of patients whose disease course aligns with established response patterns.

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Methods: We integrate data from four clinical studies representing approximately 600 patients, a substantial cohort for a rare disease. These studies share common clinical outcome measures, including the Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis (QMG), and MG Composite (MGC) scores, facilitating development of a unified analytical framework. A central therapeutic objective across all studies is improvement in clinical outcomes. Key methodological challenges include heterogeneity in study design, variable follow-up durations, and missing longitudinal data. To address these, we developed tools to harmonize disparate clinical scales and construct continuous patient trajectories. We define a stochastic "score portrait" and establish a baseline "natural/standard trajectory," anchored by the placebo arms of the studies (Garbey et al., 2025). We then apply these constructs to interventional datasets to evaluate an "Index of Predictability," quantifying the extent to which early trajectory alignment predicts eventual treatment response (Garbey et al., 2026). Our framework also enables unsupervised clustering of patients based on trajectory similarity, revealing biologically and clinically meaningful subgroups.

Results: Preliminary findings suggest associations between trajectory-defined response patterns and covariates such as age and smoking status, highlighting potential modifiers of treatment efficacy. This study demonstrates the feasibility of integrating heterogeneous longitudinal datasets into a unified predictive framework.

Conclusion: Beyond improving trial efficiency and early decision-making, this approach represents a foundational step toward development of a digital twin for myasthenia gravis, with broader implications for precision medicine in rare autoimmune diseases.

M326-K: Long-Read Amplicon Sequencing Method to Measure CTG Repeat Length and Mosaicism for Correlation to Disease Severity in Myotonic Dystrophy Type 1

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Abstract: Myotonic dystrophy type 1 (DM1) is a multisystemic disease caused by expansion of a CTG repeat in the DMPK gene. In DM1 the pathogenic repeats range in length from 100s to 1000s of triplets in blood cells of affected individuals. Using current methods, the length of the inherited repeat in the blood is broadly correlated with disease severity (Pearson's R-0.44; Age-of-onset x modal CTG length), but accurate measurement of individual repeat lengths has technical limitations, particularly with larger alleles.

Identifying an accurate, cost-effective method for repeat length measurement is a critical step in ongoing efforts to identify novel genetic modifiers of DM1 or evaluate efficacy of repeat stabilizing therapeutics.

We set out to develop a method to measure CTG repeat length and mosaicism that is amenable to low sample input, economically feasible for large-scale analyses, and allows for sequence-level data. Using non-amplification methods as the standard, we compare

(1) Southern blot, (2) small-pool PCR, (3) Cas9-mediated genomic DNA enrichment followed by PacBio long-read sequencing, (4) long-range PCR, and (4) PacBio sequencing of long-range PCR products. Fidelity of all methods are examined using a test-set of patient-derived blood gDNA samples with variable length and mosaicism, and gDNA mixes of known repeat lengths from patient-derived cell lines. We analyze concordance between the methods, examine the limitations of detection of longer or shorter alleles dependent on method, and quantification of mosaicism. We show that our long-range PCR can amplify highly expanded CTG repeat alleles and represent mosaicism. Incorporation of unique molecular identifiers to perform bioinformatic amplification correction is explored. Next, to assess the correlation of CTG repeat length and mosaicism with disease severity, we used PacBio sequencing of long-range PCR products correlated to age-of-onset and grip strength in participants of the END-DM1 natural history study.

M327: Dual Neuromuscular Decline: A Case Report on Comorbid Myasthenia Gravis and AMSAN variant of Guillain-Barré Syndrome

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Background: Guillain-Barre syndrome (GBS) is an acute, immune-mediated polyneuropathy characterized by rapidly progressive, symmetric weakness and areflexia due to peripheral nerve demyelination or axonal injury. The acute motor and sensory axonal neuropathy (AMSAN) variant represents a severe form of GBS marked by widespread axonal degeneration affecting both motor and sensory fibers, often leading to poor functional recovery.

Pathogenesis is thought to involve molecular mimicry, resulting in immune-mediated destruction of peripheral nerves. Myasthenia gravis (MG), in contrast, is an autoimmune disorder of the neuromuscular junction caused by antibodies targeting postsynaptic acetylcholine receptors, leading to fluctuating, fatigable weakness-predominantly involving ocular, bulbar, and respiratory muscles. Overlap between MG and GBS is rare, with very few cases involving the AMSAN subtype, posing significant diagnostic and therapeutic challenges.

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Methods: Clinical data, including neurologic examination, imaging, CSF analysis, and electrophysiologic studies, were reviewed to characterize disease progression and response to therapy in this case report.

Results: A 47-year-old woman presented with a waddling gait, intermittent diplopia, dysphagia, and fatigue. Outpatient evaluation revealed positive acetylcholine receptor antibodies, establishing a diagnosis of MG, and pyridostigmine therapy was initiated. Within 10 days, she experienced rapid clinical deterioration and was admitted for suspected myasthenic crisis. Neurologic exam demonstrated bilateral ptosis (L>R), right-sided facial droop, preserved sensation, no ataxia, and a single breath count of 29. Strength testing revealed severe proximal weakness (bilateral deltoids 1/5; right biceps/triceps 3/5; left biceps/triceps 2/5; left wrist 3/5; right wrist 4/5; bilateral hip flexors 3/5; knee flexion/extension 4/5). MRI brain demonstrated right facial neuritis without evidence of central pathology. Initial cerebrospinal fluid (CSF) analysis was unremarkable; however, repeat CSF demonstrated albuminocytologic dissociation with elevated protein (163 mg/dl.) Despite treatment with plasmapheresis, IVIG, and subsequent Rituximab, the patient's condition worsened, progressing to ventilator-dependent quadriplegia over a one-month hospitalization. At three-month follow-up, she remained quadriplegic.

EMG and NCS revealed diffuse absence of motor and sensory responses without evidence of reinnervation, consistent with severe axonal neuropathy.

Conclusion: This case highlights a rare and severe overlap of MG and AMSAN, underscoring the importance of considering concurrent peripheral nerve pathology. Serial CSF analysis and EMG/NCS were critical in identifying evolution to an axonal GBS variant. Early recognition of this overlap is essential, as it carries a markedly worse prognosis and may warrant more tailored immunomodulatory strategies.

M328: Every Neuron Counts: Presymptomatic Disease Manifests as Degraded Computational Flexibility in a Mouse Model of SOD1-ALS

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Background: In amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases, affected networks have already experienced devastating cell loss prior to symptom onset, reflecting months to years of undetected disease activity. This has led to a two-stage model of these conditions, wherein the nervous system maintains performance despite accumulated injury ("compensation") until progressive symptoms explode into view. The compensatory phase provides the optimal window for intervention, yet remains the most poorly understood stage of disease. Understanding resilience at the network level is crucial: it will enable new methods for detecting presymptomatic disease and new pathways for slowing progression. If one were to detect a "first sign" of network injury, it has been argued that this would be observed at the emergent scale. As the brain's computations directly instruct behavior, network dysfunction should be reflected in the dynamics of behavior. Through this lens, it is loss of computational flexibility - the capacity to deploy diverse neural strategies - that should define the first stage of disease, not the degradation of crystallized functions like walking or memory. We challenge the truism that early network injury is "asymptomatic" and propose instead that the first stage of disease is defined by a network's attempt to maintain performance by sacrificing computational and behavioral flexibility.

Methods: Our work addresses this concept in ALS, focusing on behavioral and neural network dynamics in a mouse model of SOD1-ALS.

Results: We have developed a custom homecage for automated motor phenotyping, and find that hSOD1-G93A mice display simplification of their motor repertoire long before apparent motor impairment, but coincident with rising serum neurofilament light chain (sNFL) levels. Chronic M1 multielectrode array recordings reveal that cortical dynamics progressively shift away from criticality - a dynamical regime poised between order and chaos, associated with maximal computational flexibility and sensitivity - across the same timeframe. Finally, we find that a criticality-based analysis of accelerometry data reveals dramatic simplification of motor behavior in patients two weeks post-ischemic stroke. These proof-of-concept data raise the possibility that similar methods could detect early disease in ALS patients, and criticality-based analysis of wearable sensor data from ALS patients is ongoing.

Conclusion: These findings reframe the presymptomatic phase of ALS - and potentially other neurodegenerative diseases - as a period of active network compensation, wherein subclinical injury maintains performance at a cost of flexible computation, followed by a catastrophic phase of progressive symptoms when network reserves are exhausted.

M329*: Efficacy and Safety of Intravenous Immunoglobulin after One Year of Treatment in Post-Polio Syndrome: Results from the FORCE Trial

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Background: Post-polio syndrome (PPS) is a chronic, progressive neuromuscular condition characterized by new or worsening muscle weakness, fatigue, pain, and decreased functional capacity long after acute paralytic poliomyelitis. Despite substantial burden, no pharmacological treatment mitigating progression is available, underscoring an unmet medical need. Given its broad immunomodulatory properties, intravenous immunoglobulin (IVIG) has emerged as a potential therapeutic option. This study evaluated efficacy and safety of IVIG (Flebogamma® 5% DIF) in participants with PPS.

Methods: This Phase II/III, multicenter, randomized, double-blind, placebo-controlled, two-stage trial enrolled adults with PPS across Europe, Canada, and US. In Stage 1, participants received IVIG 2 g/kg, IVIG 1 g/kg, or placebo every four weeks for 52 weeks to select the optimal dose based on conditional power. Stage 2 randomized participants to the selected dose or placebo. Outcomes were evaluated over one year of treatment using pooled data from both stages. The primary endpoint was changed from baseline (CFB) in physical performance (Two-Minute Walking Distance [2MWD]) at Week 52. Secondary and exploratory endpoints included endurance (Six-Minute Walking Distance [6MWD]), pain (Visual Analogue Scale), health related quality of life (HRQoL; Short Form-36 [SF-36] Physical [PCS] and Mental [MCS] Component Summary scores), muscle strength (Medical Research Council scale), fatigue (Fatigue Severity Scale), and safety.

Results: Across both stages, 191 participants were randomized (IVIG 2 g/kg n=42; IVIG 1 g/kg n=75; placebo n=74). IVIG 1 g/kg was selected for Stage 2. IVIG 1 g/kg significantly improved 2MWD versus placebo at Week 52 (p=0.0469), confirmed by sensitivity analysis (LSMD +6.07 m; p=0.0147). Endurance improved numerically: CFB in 6MWD favored IVIG (LSMD +15.8 m; p=0.1205). SF-36 PCS improved by +4.8 points with IVIG versus +2.8 with placebo (LSMD +1.98; p=0.1615), reflecting clinically meaningful benefit. Manual muscle strength increased with IVIG and declined with placebo (LSMD +0.61; p=0.0220). Fatigue improved modestly (LSMD –0.35; p=0.0803). Pain improved similarly in both groups. IVIG 1 g/kg was well tolerated. Treatment-emergent adverse events (TEAE) incidence was comparable (98.7% IVIG; 93.2% placebo), mostly mild/moderate; headache (52.0% IVIG; 31.1% placebo) and fatigue (29.3% IVIG; 27.0% placebo) were most common. Serious TEAEs were similar (9.3% IVIG; 12.2% placebo). No deaths occurred. Discontinuations due to AEs were low (6.7% IVIG; 5.4% placebo).

Conclusion: Monthly IVIG 1 g/kg for one year demonstrated statistically significant benefits in functional walking capacity in PPS, with meaningful improvement in walking endurance, muscle strength, and physical HRQoL, alongside a favorable safety profile. IVIG represents the first pharmacological intervention to show efficacy in a large, randomized, placebo-controlled PPS trial.

M330: Assessment of the Burden of Constipation in Amyotrophic Lateral Sclerosis and its Relationship to Dysautonomia

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Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of upper and lower motor neurons leading to progressive muscle weakness and devastating neurodegeneration. Symptoms include weakness, fasciculations, atrophy, cramping, and swallowing and speech difficulties. Involvement of respiratory muscles can lead to respiratory failure, which is sadly an extremely common complication in people with ALS (Niedermeyer et al., Chest, 2019). Though ALS is considered a motor system disorder, there is growing evidence that ALS is a multisystem disease. Many patients report at least one non-motor symptom such as sleep disturbance, dysautonomia, or constipation (Niu et al., Frontiers in Neurology, 2022). While autonomic dysfunction continues to be described in ALS, there is minimal research on the burden of constipation in the disease; nearly 50% of people with ALS suffer from constipation at some point in their disease process (Weise et al., European Journal of Neurology, 2022; Yamamoto et al., Heliyon, 2024). There is a lack of consensus on how to address the severity of constipation in ALS patients and the mechanism at which it develops.

Methods: This study uses three pre-established patient assessments of constipation questionnaires- PAC-QOL, PAC-SYM and SCOPA-AUT- as a tool for assessing the severity of patient-reported symptoms of constipation in ALS and help identify and explore its relationship with possible ALS-related dysautonomia. Questionnaires were administered to 83 patients with ALS (PALS) in the ALS clinic at SLUcare SSM/Saint Louis University Hospital in St. Louis, Missouri, and the data was analyzed for statistical significance against disease-free controls.

Results: Percentage of PALS reporting dysfunction on SCOPA-AUT scale was significantly higher than disease-free control (p-value<0.001). PALS were also found to have significantly higher rates of constipation symptoms and negative effects on quality of life (reported on PAC-SYM & PAC-QOL). A significant negative correlation was observed between PALS' ALS-FRS score and autonomic dysfunction scores in all three questionnaires (p-value<0.01).

Conclusion: This report highlights the weight of constipation symptoms on PALS' quality of life and calls the need for more studies to explore the mechanistic relationship between constipation and autonomic dysfunction in ALS.

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M331: Clinical Characteristics of Late-Onset Pompe Disease: A 15-Year Single-Center Experience

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Co-Author(s): *Mansoureh Mamarabadi, Hershey, PA*

Background: Late-onset Pompe disease (LOPD) is a rare lysosomal storage disorder characterized by progressive skeletal and respiratory muscle involvement and frequently delayed diagnosis. This study aims to characterize the clinical presentation, diagnostic pathways, and treatment patterns of patients with LOPD evaluated at a tertiary neuromuscular center.

Methods: Retrospective review of adults with confirmed LOPD evaluated at Penn State Health Hershey Medical Center from January 2010 to May 2025, with descriptive analysis of demographic, clinical, diagnostic, and treatment data.

Results: This ongoing study includes approximately 44 patients evaluated over a 15-year period; preliminary analysis included 24 patients. The cohort was predominantly female (16/24) and White (22/24). Mean age at symptom onset was 38.7 $\pm$ 12.4 years and mean age at diagnosis was 44.8 $\pm$ 13.1 years, corresponding to a diagnostic delay of 8.6 $\pm$ 7.9 years. Twenty-one patients (87.5%) received disease-specific therapy (11 alglucosidase alfa, 8 avalglucosidase alfa, and 2 cipaglucosidase alfa plus miglustat), while 3 (12.5%) remained untreated. Among treated patients, the mean delay from diagnosis to therapy initiation was 1.86 $\pm$ 2.46 years. Mean FVC change from baseline was -0.44 in treated patients versus -0.89 in untreated patients; cardiac function remained stable (mean EF change $+2.43\%$). Muscle biopsy was performed in 15 patients and genetic testing in 14 patients. At last follow-up, 21 patients were alive and 3 had died.

Conclusion: This single-center study highlights diagnostic delays in LOPD, describes real-world clinical presentation and treatment patterns, and compares available enzyme replacement therapies and their effects on muscle strength and respiratory function.

M332: Sporadic Late-Onset Nemaline Myopathy: A Diagnostic Challenge in Adult-Onset Myopathy

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Background: Sporadic late-onset nemaline myopathy (SLONM) is a rare, acquired myopathy causing progressive proximal and axial weakness, often with head drop, dysphagia, and respiratory involvement. It has been associated with conditions such as monoclonal gammopathy of undetermined significance (MGUS) and HIV infection. Creatine kinase levels are often normal, which may delay diagnosis.

Methods: Clinical history, neurologic examination, laboratory studies, electrodiagnostic testing, imaging, genetic testing, and muscle biopsy findings were reviewed.

Results: A 57-year-old man developed progressive proximal, axial, and neck extensor weakness beginning in 2024, resulting in head drop, dysphagia, impaired ambulation, and 20-lb weight loss. The patient was referred to a neuromuscular clinic in May 2025, where examination revealed proximal weakness with preserved distal strength and normal sensation. Electromyography showed myopathic changes with spontaneous activity in proximal and axial muscles. Creatine kinase was normal (77 U/L). MRI of the brain and cervical spine was unrevealing, and genetic testing for inherited neuromuscular disorders was negative. Muscle biopsy demonstrated chronic myopathy with nemaline rods and chronic active neurogenic change consistent with SLONM. Serum immunofixation identified an IgG-kappa monoclonal protein. IVIg therapy was initiated in August 2025 with subsequent improvement in head control, swallowing, and ambulation.

Conclusion: SLONM is a rare but potentially treatable myopathy that can occur with conditions like MGUS. Awareness and evaluation for associated conditions enable accurate diagnosis and timely treatment, leading to meaningful clinical improvement.

M333: Guillain-Barré Syndrome: A Complication of Metapneumovirus Infection

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Background: Guillain-Barré syndrome (GBS) is a rapidly progressing, immune-mediated neuropathy that represents a major cause of acute flaccid paralysis. A significant proportion of cases are precipitated by infections, most commonly Campylobacter jejuni and Haemophilus influenzae, which trigger pathogenic autoimmune processes via molecular mimicry. Here, we present a case of GBS triggered by Metapneumovirus infection.

Methods: A 56-year-old female with a medical history of hypothyroidism presented to the emergency department with complaints of shortness of breath and progressive weakness in both upper and lower extremities. Neurological manifestation of the patient began with acute progressive weakness of the distal lower extremity, 2 days before admission. At that time, her symptoms progressed from the lower extremity to the upper extremity, and she had been quadriplegic 1 day before admission. She denies any urinary or fecal incontinence. A few days prior to her admission, the patient suffered from cough, fever, and dyspnea; however, she did not seek medical advice. On physical exam, the patient was afebrile, hemodynamically stable, and saturating on room air. She was conscious with mild dyspnea. Her muscle strength was weak in the bilateral upper and lower limbs, with 2/5 proximally and 3/5 distally. Deep tendon reflexes were intact throughout, and vibration and fine touch sensation were intact throughout. The respiratory viral panel was positive for Metapneumovirus infection. Routine lab was unremarkable except for B12 at 288 pg/mL. Lumbar puncture revealed elevated protein (129 mg/dL), glucose of 83 mg/dL (with a

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corresponding blood glucose of 130 mg/dL), and no cells. MRI of the entire spine with and without contrast was negative for a cord or root lesion. The patient was started on intravenous immunoglobulin (IVIG) at 0.4 g/kg/day for 5 days. She showed significant improvement over the following days and returned to her baseline functional status.

Conclusion: GBS is most frequently triggered by infections such as Haemophilus influenzae, but it may also arise as a complication of Metapneumovirus infection. Early recognition and prompt initiation of immunotherapy are critical for optimizing recovery outcomes.

M334: Decades in Disguise: Bulbar-Onset Spinal and Bulbar Muscular Atrophy Misdiagnosed as Parkinsonism

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Background: Spinal and bulbar muscular atrophy (SBMA), or Kennedy disease, is a rare X-linked recessive motor neuron disorder caused by CAG repeat expansion in the androgen receptor (AR) gene. It is characterized by slowly progressive lower motor neuron degeneration, bulbar involvement, and androgen insensitivity features. Due to its indolent course and phenotypic overlap with other neurologic conditions, SBMA is frequently under recognized, leading to delayed diagnosis.

Methods: A 66 year-old right handed male with a history of gynecomastia and inguinal hernia presented for evaluation of chronic dysarthria. Symptoms began over 20 years prior with facial twitching and progressive hoarseness, for which he underwent extensive but unrevealing evaluations and was previously labeled as having Parkinson's disease (PD). He declined treatment at that time. Over the past 4 years, he developed progressive proximal limb weakness, fatigue, difficulty with activities such as tennis and opening bottles, as well as cold induced cramps and worsening balance. Neurologic review was notable for fatigable ptosis and blurred vision later in the day, without dysphagia, dyspnea, or sensory symptoms. Examination revealed bilateral facial weakness (cranial nerve VII), hoarseness (cranial nerves IX/X), and tongue fasciculations (cranial nerve XII). There was symmetric proximal weakness (4/5) involving deltoids, triceps, and hip flexors, distal hand weakness greater than feet, diminished reflexes, and intact sensation. Additional findings included bilateral scapular winging, calf hypertrophy, postural tremor, and long-standing gynecomastia. Laboratory studies demonstrated elevated creatine kinase and aldolase. MRI of the cervical spine showed stenosis, and prior electromyography was unremarkable. Genetic testing confirmed SBMA with androgen receptor CAG repeat expansion of 43 repeats (pathogenic ≥39).

Results: This case highlights the overlooked features of SBMA, including bulbar symptoms, lower motor neuron signs, tremor, and endocrine manifestations. The patient's prolonged course, early bulbar involvement, and tremor contributed to misdiagnosis as PD. Androgen insensitivity features such as gynecomastia, combined with proximal weakness and bulbar findings, should prompt consideration of SBMA. While electromyography often supports a motor neuronopathy, findings may be initially nondiagnostic, contributing to delayed recognition. The absence of a clear family history does not exclude SBMA, as under recognition and variable expression may obscure inheritance patterns.

Conclusion: SBMA should be considered in male patients with chronic bulbar symptoms, lower motor neuron findings, tremor, and endocrine features. Early recognition and genetic confirmation are essential to avoid misdiagnosis, guide management, and enable appropriate genetic counseling. This case underscores the importance of maintaining a broad differential in slowly progressive neuromuscular disorders with atypical features.

M335: Stepping into Rarity: Late-Onset Distal Myopathy Revealing PHKA1-Related Glycogen Storage Disease IXd

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Background: Glycogen storage disease type IXd (GSD IXd) is a rare X-linked metabolic myopathy caused by pathogenic variants in the PHKA1 gene, which encodes the muscle isoform of the α-subunit of phosphorylase kinase. This enzyme regulates glycogen metabolism via activation of glycogen phosphorylase. Fewer than 20 cases have been reported worldwide, and the phenotype is often mild or asymptomatic, leading to underrecognition.

Methods: A 73-year-old Chinese male with hypertension, diabetes, and gout presented with a 2 year history of progressive bilateral foot drop. Symptoms began insidiously, with decline in daily ambulation from 10,000 to 4,000 steps, and were symmetric with mild left-sided predominance. He reported ankle heaviness, intermittent plantar paresthesias, and difficulty navigating stairs, but denied myalgia, exercise intolerance, myoglobinuria, or oculobulbar symptoms. He remained independently ambulatory without falls. Examination revealed intact cognition and cranial nerves. Motor testing demonstrated distal lower extremity weakness (4-/5 dorsiflexion and plantarflexion), with preserved proximal strength sufficient to stand unassisted. Bilateral calf hypertrophy and quadriceps prominence were noted. Sensation and reflexes were intact. He had difficulty with heel and toe walking. Laboratory evaluation demonstrated persistently elevated creatine kinase (340–420 U/L) with normal liver function tests and normal serum neurofilament light chain. Electromyography revealed a distal myopathy with membrane irritability and mild superimposed neurogenic features, along with a mild length-dependent sensory polyneuropathy. MRI showed fatty atrophy of the gastrocnemius and tibialis anterior muscles, left greater than right. Genetic testing identified a pathogenic PHKA1 variant, confirming GSD IXd.

Results: This case illustrates an atypical presentation of GSD IXd, characterized by late-onset distal weakness and fatty muscle replacement without classic features such as exercise intolerance or myoglobinuria. The presence of calf hypertrophy, mild CK elevation, and myopathic EMG changes supported a primary muscle process, while normal

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neurofilament light chain argued against a neurodegenerative etiology. Distal-predominant involvement and minimal systemic symptoms may contribute to diagnostic delay or misclassification as neuropathic or degenerative disease. Recognition of this rare metabolic myopathy is important, particularly as genetic testing becomes more accessible.

Conclusion: PHKA1-related GSD IXd should be considered in patients with unexplained distal myopathy, mild CK elevation, and characteristic imaging findings, even in the absence of classic metabolic symptoms. This case expands the phenotypic spectrum and highlights the importance of genetic evaluation in atypical myopathies.

M336: Social Vulnerability Is Associated With Reduced Use of First-Line Therapy in Amyotrophic Lateral Sclerosis: A Real-World EMR Cohort Study

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Background: Disparities in access to disease-modifying therapies in amyotrophic lateral sclerosis (ALS) remain poorly characterized despite expansion of available treatments. Riluzole remains the standard first-line disease-modifying therapy for ALS, yet real-world differences in access to treatment persist. The objective of this work is to evaluate the association between neighborhood-level social vulnerability and utilization of disease-modifying therapies in ALS.

Methods: We conducted a retrospective cohort study using de-identified electronic medical record data from a tertiary academic center (2012–2026). Adults with ALS (ICD-10 G12.21) and ≥2 ALS-related encounters were included. The primary exposure was Social Vulnerability Index (SVI) quartile; The primary outcome was riluzole use.

Multivariable logistic regression assessed the association between SVI and therapy utilization, adjusting for age, sex, race, ethnicity, and language. This study used a fully de-identified dataset and was determined not to constitute human subjects research by the UCLA Institutional Review Board.

Results: Among 1,085 patients with ALS, riluzole use decreased across SVI quartiles from 60.6% to 40.0% ($p<0.001$). In adjusted analyses, higher social vulnerability was associated with lower odds of riluzole use in a graded fashion: Q2 (OR 0.90, 95% CI 0.68–1.18; $p=0.44$), Q3 (OR 0.65, 95% CI 0.48–0.88; $p=0.005$), and Q4 (OR 0.48, 95% CI 0.33–0.69; $p<0.001$). Edaravone showed a similar but non-significant trend.

Conclusion: Higher neighborhood-level social vulnerability is independently associated with reduced utilization of first-line ALS therapy in dose-response pattern. These findings suggest structural barriers to equitable care delivery and highlight opportunities for targeted health system and policy interventions to improve access for all patients.

Limitations include potential residual confounding from unmeasured factors such as disease severity and healthcare access, use of medication orders as a proxy for actual treatment, limited power for newer therapies, and reliance on neighborhood-level SVI.

M337: Sex-Specific Genetic Architecture and Liability Thresholds in Amyotrophic Lateral Sclerosis

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Background: Amyotrophic lateral sclerosis (ALS) exhibits a male predominance and an earlier age of onset in men compared to women, yet the biological mechanisms underlying these sex-based differences remain poorly understood.

Genetic factors are known to play a significant role in ALS susceptibility and disease course, raising the possibility that sex-specific differences in genetic architecture may contribute to the observed epidemiological patterns. Elucidating these differences could provide important insights into ALS pathogenesis and identify novel targets for therapeutic intervention.

Methods: Three complementary approaches were employed. First, rare variant burden was compared between sexes in a large Italian ALS cohort, with replication in the independent AnswerALS cohort. Second, polygenic risk score (PRS) analysis was conducted in 42,448 individuals (8,016 cases; 34,432 controls) using ProjectMinE GWAS summary statistics, with a formal PRS-by-sex interaction term. Third, genome-wide partitioned heritability analysis was performed using the Gene Environment Interaction Estimator (GENIE), followed by pathway annotation of sex-differential heritability signals.

Results: In the Italian cohort, TARDBP variant carriers showed a significant male predominance (male-to-female ratio 2.1:1; $p < 0.0001$), consistent with sex-modifier effects. Females were more likely than males to carry rare damaging variants in ALS genes (23.2% vs. 18.3%; OR 1.38; $p = 0.011$), replicated in AnswerALS (18.9% vs. 12.4%; OR 1.58; $p = 0.013$). PRS analysis revealed a significant PRS-by-sex interaction ($\beta = +0.308$; $p = 3.05\times10^{-10}$): each standard deviation increase in PRS conferred ∼36% greater ALS odds in females than males, indicating that females require higher polygenic burden to exceed the liability threshold. GENIE identified a significant sex-differential genetic component ($h^2_gxe = -0.25$), with larger genetic effects in males. Sex-differential heritability was enriched in midbrain dopaminergic ($Z = 6.72$) and GABAergic neurons ($Z = 8.12$), IFNγ-activated microglia ($Z = 4.70$), and regulatory T cell signatures ($Z = 4.07$). Female-specific buffering localized to RORA and PPARA transcription factor targets; male-enriched signals converged on DAX1-regulated androgen-axis genes and the p53 pathway.

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Conclusion: ALS shows a sex-differential genetic architecture in which females require a higher rare variant burden and greater polygenic load than males to exceed the liability threshold for disease, suggesting a relative biological resilience in women. This female buffering appears to involve IFNγ-activated microglial regulation, regulatory T cell immunosuppression, and RORA/PPARA transcription factor networks, while androgen-axis signaling and the p53 pathway amplify genetic risk in men. These findings offer a biological basis for sex-stratified risk prediction and highlight candidate pathways for targeted therapeutic intervention.

M338: Motor Neuron Disease Preceded by Facial Sensory Deficits: A Case Report Highlighting Diagnostic Challenges in Amyotrophic Lateral Sclerosis Spectrum Variants

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Background: Facial onset sensory and motor neuronopathy (FOSMN) is a rare motor neuron disease and an atypical variant overlapping with amyotrophic lateral sclerosis (ALS). It presents with trigeminal sensory symptoms followed by progressive bulbar and spinal motor involvement, reflecting rostrocaudal neurodegeneration. Prominent trigeminal sensory involvement can divert early diagnostic reasoning toward cranial neuropathies or brainstem processes, placing FOSMN outside traditional ALS frameworks that emphasize progressive motor involvement. Although sensory abnormalities are not typical of classic ALS, emerging evidence suggests shared pathophysiology, including TAR DNA binding protein-43 (TDP-43) related pathways and association with motor neuron disease linked genetic variants (Yu et al., Cell, 2020). Recognizing this overlap is critical, as early consideration of FOSMN in patients with progressive trigeminal sensory symptoms may reduce diagnostic delays, unnecessary interventions, and prompt evaluation for motor neuron disease.

Methods: A 75-year-old woman with diabetes and hereditary hemochromatosis presented with a 6-month history of progressive, painless left-sided facial numbness beginning in the maxillary distribution and later involving the mandibular and ophthalmic divisions of the trigeminal nerve. Initial examination showed isolated left facial sensory loss without motor involvement, and an unenhanced brain MRI was normal. Over two years, the facial numbness spread to the contralateral face in a similar distribution. This raised concern for structural, inflammatory, or infiltrative processes affecting the brainstem, skull base, or leptomeninges, prompting repeat brain MRI with gadolinium and cerebrospinal fluid evaluation, which were unrevealing. She subsequently developed facial weakness, dysarthria, and dysphagia two years after symptom onset, followed by upper limb weakness and gait instability one year later. Examination demonstrated bilateral trigeminal sensory deficits, lower facial weakness, tongue fasciculations, mixed flaccid-spastic dysarthria, and diffuse upper and lower motor neuron signs. The emergence of bulbar and limb involvement along with negative autoimmune/paraneoplastic testing shifted concern toward a motor neuron disorder with cranial sensory features. Electrodiagnostic studies revealed a diffuse active and chronic motor neuron disease with a superimposed trigeminal neuropathy confirming a likely diagnosis of FOSMN.

Conclusion: This case highlights the importance of lesion localization in clinical neurology, including integrating temporal progression with anatomic localization. It also stresses the importance of maintaining a broad differential diagnosis in complex neurological cases. Early trigeminal sensory symptoms can complicate the recognition of atypical motor neuron disease presentations such as FOSMN and contribute to its misdiagnosis. Attention to symptom sequence and electrodiagnostic findings is essential to refine the differential, guide evaluation, and reduce diagnostic delays.

M339: Prognostic Value of Anti-Ganglioside Antibodies in Guillain-Barré Syndrome: A Systematic Review and Meta-Analysis

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Background: Early prognostic stratification in Guillain-Barré syndrome (GBS) is essential for guiding treatment intensity and counseling patients, yet validated biomarkers for functional recovery remain limited. Anti-ganglioside antibodies are routinely measured and implicated in complement-mediated nerve injury, but whether they independently predict outcomes has not been systematically evaluated. No prior meta-analysis has pooled prognostic data for specific anti-ganglioside antibodies in GBS.

Methods: PubMed, Scopus, and the Cochrane Library were searched from inception through 2025. We included observational cohorts of GBS patients tested for anti-ganglioside antibodies with reported functional outcomes or ventilation data. The primary outcome was inability to walk independently (Hughes Functional Grading Scale/GBS Disability Score ≥3) at ≥6 months. Risk of bias was assessed using the Newcastle-Ottawa Scale.

DerSimonian-Laird random-effects models estimated pooled odds ratios (ORs). Pre-specified sensitivity analyses included leave-one-out, restriction to low risk-of-bias studies, and cumulative meta-analysis.

Results: Twenty-four studies (3,632 patients; published 1992–2025) met inclusion criteria. Anti-GM1 positivity was significantly associated with poor functional outcome (k=8; 1,542 patients; OR 2.19, 95% CI 1.56–3.06; p<0.00001; I^2=0%). Event rates were 26.5% (antibody-positive) versus 14.9% (antibody-negative). The association was fully stable on leave-one-out analysis (worst-case OR 2.08, p=0.0001) and persisted when restricted to low risk-of-bias studies (k=5; OR 2.23, p<0.00001). Anti-GQ1b predicted mechanical ventilation (k=2; OR 3.79, 95% CI

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1.84–7.83; p=0.0003), while anti-GM1 did not (k=3; OR 0.98; p=0.97). Cumulative meta-analysis showed a stable effect estimate since 1992 with narrowing confidence intervals.

Conclusion: Anti-GM1 antibodies confer two-fold increased odds of poor walking recovery in GBS with zero heterogeneity across 33 years of international evidence. A biologically coherent dissociation emerged: anti-GM1 (concentrated on limb motor neurons) predicts motor disability but not respiratory failure, while anti-GQ1b (cranial nerve distribution) predicts ventilation requirement. These findings support incorporating antibody specificity into GBS prognostic models, though the absence of poolable adjusted estimates warrants cautious causal interpretation.

M340: A Comparative Systematic Review and Meta-Analysis of Unilateral Biportal Endoscopic Procedure Versus Micro-Endoscopic Discectomy in Lumbar Spinal Stenosis and Related Neuromuscular Dysfunction

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Background: Lumbar spinal stenosis is the narrowing of the lumbar spine, characterized by leg numbness, back pain, and mobility limitations. Microscope endoscopic discectomy (MED) is the most commonly used surgery to treat lumbar spinal stenosis. Despite being effective, a newer minimally invasive technique, Unilateral Biportal Endoscopic (UBE) surgery, has emerged, potentially reducing tissue damage and recovery time. Although both techniques are beneficial, outcomes such as pain relief, postoperative function, and complication rates remain unclear. This study aims to investigate which surgical technique is most optimal for treating patients with lumbar spinal stenosis.

Methods: A comprehensive literature search was conducted across 3 databases, PubMed, Cochrane Library, and Google Scholar. We identified 6000 records; after removing duplicates and screening, 22 comparative studies were included. The MeSH terms used to identify records were "unilateral bipolar endoscopic discectomy", "microscopic discectomy", and "lumbar spinal stenosis". Effect measures used for dichotomous outcomes were risk ratio, and for continuous outcomes, mean difference and standard deviation. Quality assessment was conducted using the Cochrane Risk of Bias tool for randomized trials and Newcastle-Ottawa Scale for observational studies, with reporting in accordance with PRISMA guidelines.

Results: Primary outcomes, including ODI, VAS leg and back pain scores, were evaluated using subgroup analyses across 3, 6, 12, and 24-month follow-up durations. Pooled analysis of 22 studies demonstrated no significant difference in ODI between UBE and MED (MD −0.78, 95% CI −1.63 to 0.08; p=0.07; I^2=95%); leave-one-out sensitivity analysis showed consistent findings. VAS back pain (13 studies) favored UBE (MD −0.26, 95% CI −0.44 to −0.09; I^2=88%). VAS leg pain scores (15 studies) demonstrated a significant reduction with UBE versus MED (MD −0.29, 95% CI −0.47 to −0.11; I^2=88%), with sustained improvement across follow-up intervals. Postoperative adverse events (14 studies) were significantly lower with UBE (RR 0.55, 95% CI 0.37–0.80; I^2=0%), with subgroup analysis demonstrating a reduction in surgical site infections, urinary retention, motor weakness, and hematoma. Secondary outcomes, including intraoperative parameters, with subgroup analyses, significantly favored UBE p<0.000001, incidental durotomy, and radiological outcomes exhibited no significant difference between the two groups.

Conclusion: UBE shows comparable functional outcomes in lumbar spinal stenosis, with better pain control, fewer complications, and improved recovery, supporting its role in managing neurogenic dysfunction and neuromuscular impairment.

M341*: A Motor Neuron-Intrinsic MTMR5/SBF1 Dysfunction Drives Early Lysosomal Trafficking Defects and Mitochondrial Stress in CMT4B3

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Background: Charcot-Marie-Tooth disease type 4B3 (CMT4B3) is a devastating, early-onset disease that manifests with length-dependent weakness, muscle atrophy, and gait impairment due to axon degeneration in peripheral nerves. CMT4B3 is caused by loss-of-function mutations in SBF1, which encodes MTMR5, a key regulator of phosphoinositide turnover and autophagy initiation. Although recent work has begun to define the role of MTMR5 in neuronal autophagy, the mechanisms by which loss of SBF1/MTMR5 contributes to axon degeneration in CMT4B3 remains incompletely defined.

Methods: To enable faithful cellular modeling of this disease, we engineered a motor neuron (iMN) model of CMT4B3 derived from a iPSCs donated by a human patient. We previously showed that our model successfully recapitulates many aspects of disease, including loss of MTMR5 expression and marked cell death in CMT4B3 iMNs. Given that

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mitochondrial turnover and lysosomal homeostasis are regulated by autophagy and integral to motor neuron health, we sought to define how and to what extent these processes are affected in CMT4B3.

Results: Compared to WT control cells, we found that CMT4B3 iMNs demonstrate impaired lysosomal trafficking and mislocalization on live-cell imaging. CMT4B3 iMNs also harbor abnormal accumulation of mitochondria on live-cell imaging and Western analysis, and increased levels of depolarized mitochondria, pointing to toxic disruption of mitophagy with loss of SBF1/MTMR5. Ongoing studies include rescuing these mitochondrial and lysosomal phenotypes with exogenous reconstitution of SBF1 by AAV-delivered gene therapy, or CRISPR-mediated overexpression of MTMR2 and MTMR13, which are paralogs of MTMR5 with functional overlap. We are also confirming the generalizability of these disease phenotypes by expanding our model system to include iMNs engineered from additional patient iPSC lines.

Conclusion: Overall, these studies will establish relevant mechanisms of endolysosomal dysregulation amenable for therapeutic targeting to facilitate translational therapy designs and advance pathobiological understanding of CMT4B3 and related axonal neuropathies.

M342: ANCA-Associated Vasculitic Neuropathy Mimicking Aggressive Axonal GBS: A Case of MPO-Positive Microscopic Polyangiitis

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Background: Microscopic polyangiitis (MPA) is an ANCA-associated small-vessel vasculitis that rarely presents as an acute polyradiculoneuropathy. Vasculitic neuropathy is typically asymmetric and painful, whereas Guillain-Barré syndrome (GBS) classically manifests as symmetric, ascending weakness. Acute vasculitic neuropathy mimicking GBS is uncommon and poses significant diagnostic challenges, particularly when early electrophysiology demonstrates an aggressive axonal process. We report a case of MPO-ANCA positive MPA presenting as a GBS-like syndrome.

Methods: We report a 77-year-old woman with hypertension who presented with 5 weeks of rapidly progressive bilateral upper and lower extremity weakness and severe distal sensory loss following a febrile illness. Examination demonstrated marked vibration and proprioceptive impairment in all extremities, and weakness, most pronounced in the distal lower extremities, and diminished reflexes at the ankles. Electrodiagnostic testing on hospital day one showed a progressive sensorimotor axonal inflammatory neuropathy. MRI of the neuroaxis was unrevealing, and CSF showed normal cell count and protein (31 mg/dL). Despite five sessions of plasma exchange, neurological improvement was minimal.

Results: Extensive autoimmune and infectious workup revealed positive p-ANCA, markedly elevated MPO antibodies, and uptrending creatinine, raising concern for MPA. Renal biopsy confirmed vasculitis, and pulse-dose steroids and rituximab were initiated with stabilization of the patient's neurological symptoms.

Conclusion: This case highlights MPA presenting as an acute axonal GBS-like neuropathy, underscoring the clinical and electrophysiologic overlap between vasculitic neuropathy and inflammatory polyradiculoneuropathies. Normal CSF protein and early axonal changes on EMG should prompt consideration of vasculitis when GBS-directed therapy is ineffective. Early recognition of ANCA-associated neuropathy is critical, as timely immunosuppression may prevent irreversible neurological and renal injury.

M345: Synthetic VHH-TRIM21 RING degraders reduce TDP-43 C-terminal domain aggregates while preserving an endogenous TDP-43 functional readout

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Background: TDP-43 aggregation and cytoplasmic mislocalization are central pathological features of ALS, FTD, and inclusion body myositis, but therapeutic strategies must spare functional nuclear TDP-43. We therefore sought intracellular synthetic VHH-based degraders that reduce TDP-43 aggregate burden while preserving endogenous TDP-43 function.

Methods: A yeast surface display synthetic VHH library was enriched against recombinant SUMO-tagged TDP-43. Binders were then counter-screened as TRIM21 RING-VHH fusion constructs, in which the VHH TDP-43 binder was coupled to the TRIM21 RING E3 ubiquitin ligase domain to promote target degradation. The fusion library was screened in lentivirally transduced HEK293T FRET biosensor cells stably propagating aggregates of the TDP-43 C-terminal domain (CTD) fused to eCFP and eYFP, such that aggregate presence could be
monitored by FRET signal. FRET-negative cells were isolated by FACS and sequenced to identify effective RING-VHH candidates. Top candidates were validated by measuring effects on aggregate burden, viability, and cryptic exon inclusion by qPCR, and were further tested in iPSC-derived cell models harboring TDP-43 CTD aggregates.

Results: Two rounds of enrichment reduced the starting library from ~20 million VHHs to ~100,000 TDP-43-binding candidates. Functional screening identified 15 unique TRIM21 RING-VHH degraders that reduced CTD aggregate burden in cells. VHH6 and VHH85 were the most active, decreasing aggregate-positive cells by ≥70% within 3 days at a lentiviral MOI of 1, without detectable cytotoxicity in this biosensor system. These constructs did not increase cryptic exon inclusion associated with TDP43

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dysfunction, indicating preservation of endogenous TDP-43 splicing function. In iPSC-derived aggregate models, optimized constructs reduced aggregate burden and increased nuclear TDP-43 localization.

Conclusion: This functional screening strategy identified synthetic VHH-TRIM21 RING degraders that potently reduce TDP-43 CTD aggregate burden while sparing a key readout of endogenous TDP-43 function. VHH6 and VHH85 emerge as lead candidates for further mechanistic studies and testing in animal models. They represent promising therapeutic candidates for diseases caused by TDP-43 aggregation.

M346: From Clinical Observation to Neuromuscular Junction Disorder: The Early European Development of Myasthenia Gravis

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Background: Myasthenia gravis (MG) is an autoimmune neurological disorder affecting the neuromuscular junction (NMJ). Its earliest descriptions can be traced back to as early as 17th century and later in late 19th and early 20th centuries.

Methods: Information was gathered through literature review using PubMed, ClinicalKey, OVID, and primary texts. A narrative historical literature review was conducted, focusing on early European medical literature from late 19th to mid-20th centuries. Foundational clinical descriptions, pharmacological testing and subsequent developments in neuromuscular physiology were examined, along with early therapeutic interventions. The aim of this literature review is to examine the historical development of myasthenia gravis within early European neurology and highlight key contributions that established it as a distinct autoimmune neurological disorder.

Results: Earliest descriptions of MG can be traced back to Thomas Willis in his book 'De Anima Brutorum', published in London in 1672. In late 19th century Wilhelm Erb laid down foundational work by describing most important characteristics of disease including oculo-bulbar symptoms and clinical course characterized by remissions and exacerbations. Shortly thereafter Samuel Vulfovitsj Goldflam described key diagnostic, and prognostic features of disease. Their work was so significant that MG at that time was referred to as Erb-Goldflam syndrome, distinguishing it from other neuromuscular disorders and establishing it as distinct clinical entity. Despite this, its underlying mechanism remained uncertain, with competing theories including muscular, neurological, and functional etiologies. A major breakthrough occurred with discovery of acetylcholine (Ach) as chemical transmitter in NMJ. Observations that agents such as prostigmine and physostigmine led to transient but marked improvement in muscle strength provided critical insight into disease mechanism. This pharmacologic response suggested that MG was not primary muscle disorder but rather defect in neuromuscular transmission. Subsequent use of longer-acting agents, including neostigmine, demonstrated reproducible clinical improvement, reinforcing role of impaired synaptic transmission. This further propelled understanding and identification of specific receptors in NMJ, ultimately leading to recognition of autoimmune mechanisms targeting acetylcholine receptor in MG.

Conclusion: Early European history of MG illustrates pivotal process in field of neurology starting from careful clinical observation to understanding the underlying pathophysiological insight and driving therapeutic interventions. Contributions from European neurologists were instrumental in defining MG as distinct disorder and laid groundwork for its later classification as an autoimmune disease. This progression highlights the importance of careful clinical characterization in advancing neurological knowledge. Revisiting this history provides valuable perspective on how foundational observations can shape modern understanding and therapeutic innovations.

M347*: Alternative Polyadenylation Determines Ataxin-3 deubiquitinase-mediated TDP-43 Cleavage and Aggregation to Modify ALS/FTD Disease Risk and can be Modulated by Polyadenylation Site Blocking ASOs

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Background: Genetic variants impacting alternative polyadenylation (APA) of the ataxin-3 (ATXN3) gene represent a novel genetic risk factor for amyotrophic lateral sclerosis (ALS). Specifically, ALS-associated variants increase the use of a distal polyadenylation (polyA) site, resulting in expression of ATXN3 RNA isoforms containing a lengthened 3'untranslated region (3'UTR). ATXN3 RNA isoforms with lengthened 3'UTRs are more unstable than ATXN3 RNA isoforms with shorter 3'UTRs, resulting in a decreased half-life and consequently reduced levels of ATXN3 protein expression. Reduced ATXN3 protein expression enhances the aggregation and stability of exogenous TDP-43 C-terminal fragments (CTFs) in immortalized cells, implicating ATXN3 in the regulation of TDP-43 proteostasis.

Methods: To determine the physiological relevance of ATXN3 protein expression level change to ALS/FTD disease pathogenesis, we generated human iPSC-derived cortical neurons and motor neurons, and found that ATXN3 knockdown promotes cleavage of endogenous TDP-43, inducing key molecular hallmarks of TDP-43 dysfunction, such as cryptic exon inclusion in the stathmin-2 (STMN2) gene and decreased STMN2 protein expression. Moreover, we found that ATXN3 protein levels are reduced in postmortem frontal cortex of ALS/FTD patients and that ATXN3 is inversely correlated with the levels of phosphorylated TDP-43 in the same samples. Given prior evidence linking ATXN3 to endoplasmic reticulum-associated degradation (ERAD), we examined neuronal protein quality control pathways and found that reduced ATXN3 perturbs ERAD and unfolded protein response signaling, supporting a role for ATXN3 in maintaining neuronal proteostasis. To define the mechanism by which polyA site selection influences ATXN3 function,

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we performed CRISPR/Cas9-mediated genome editing to derive isogenic iPSCs in which the distal polyA signal of ATXN3 is inactivated by mutation.

Results: We found that inactivation of the ALS-associated distal polyA signal yielded increased ATXN3 RNA expression and promoted a shift in ATXN3 protein localization to neurites relative to soma, suggesting that APA regulates both ATXN3 mRNA stability and subcellular localization in human neurons. Finally, as APA can be modulated by antisense oligonucleotides (ASOs), we designed and screened a panel of ASOs to block the distal ATXN3 polyA signal, identifying candidate ASOs capable of reducing expression of the long-3'UTR ATXN3 isoform and rescuing ALS disease phenotypes.

Conclusion: Taken together, these results demonstrate that ATXN3 regulates TDP-43 proteostasis in human neurons and that ALS-associated genetic variants in the ATXN3 3'UTR mediate disease risk by impacting the stability and subcellular localization of the ATXN3 transcript. Furthermore, we have documented that ATXN3 APA can be successfully modulated by ASOs, revealing a candidate therapy for ALS/FTD.

M348: Dietary Nutrients Associated with Odds and Progression of Amyotrophic Lateral Sclerosis

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Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder with limited treatment options. We aimed to identify dietary nutrients associated with odds of ALS and disease progression.

Methods: Data from the ARREST and COSMOS studies were analyzed. The Modified Block Food Frequency Questionnaire (FFQ) was collected at enrollment and follow-up. Nutrients and food intake were compared between ARREST healthy controls (HC) vs. ARREST and COSMOS participants with ALS (PALS), adjusting for age, sex, body mass index (BMI), and total caloric intake using linear and logistic regression analyses. The association between nutrient intake or blood metabolite levels with baseline revised ALS functional rating scale (ALSFRS-r) total score and decline in ALSFRS-r from baseline to 6-month follow-up were examined using linear regression models, adjusted with covariates. Blood metabolites levels were measured by liquid chromatography/mass spectrometry (LC/MS) and neurofilament light chain (NfL) was measured with Ella™ from plasma samples of COSMOS PALS (n=101).

Results: A total of 88 PALS and 102 HC in ARREST and 304 PALS in COSMOS were included. Compared to HC, PALS had higher intake of riboflavin, retinol, arginine, methionine, cystine, lactose, sucrose (nutrients associated with milk intake) while consumption of lutein/zeaxanthin (nutrient associated with dark green vegetables) and alcohol were lower (all p-value<0.001). When the highest tertile was compared to lowest tertile group, milk intake was associated with higher odds (OR 3.6, 95% CI 1.9, 7.0) while dark green vegetable intake was associated with lower odds of ALS (OR=0.3, 95% CI 0.15, 0.57). High lutein/zeaxanthin, dark green vegetable intake and blood lutein/zeaxanthin isomer levels were associated with higher baseline ALSFRS-r total score (all p-values<0.05). High blood lutein/zeaxanthin isomer levels were associated with lower baseline NfL levels adjusted for age (p=0.01). Higher baseline milk intake was associated with lower baseline ALSFRS-r score and larger ALSFRS-r decline at 6- month follow-up, mediated by lower glycemic index.

Conclusion: Higher lutein/zeaxanthin intake through dark green vegetables is associated with lower odds of ALS and higher baseline function. Additionally, higher blood lutein/zeaxanthin isomer levels are associated with higher function and lower rate of neuronal degeneration. In contrast, higher milk intake is associated with higher odds of ALS, lower baseline function, and faster functional decline. Further confirmative studies including mechanistic studies and clinical trials are needed.

M349: Efficacy and Safety of Efgartigimod Treatment for Patients with Myasthenia Gravis: A Systematic Review and Meta-analysis

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Background: Efgartigimod, a neonatal Fc receptor (FcRn) antagonist, has emerged as a targeted therapy for myasthenia gravis (MG), a chronic autoimmune neuromuscular junction disease. We conducted a systematic review and meta-analysis to evaluate its efficacy and safety across diverse study designs and patient subgroups.

Methods: A comprehensive literature search identified 50 studies comprising 5,446 patients with MG. Outcomes included pooled response rates and adverse events (AEs). Subgroup analyses were performed based on study design, antibody status, and route of administration. Random-effects models were used to calculate pooled estimates with 95% confidence intervals (CI).

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Results: The overall pooled response rate was 0.755 (95% CI 0.700–0.803, I2 = 77.9%). Observational studies demonstrated a response rate of 0.760 (95% CI 0.693–0.817), while randomized controlled trials (RCTs) showed a slightly lower rate of 0.715 (95% CI 0.658–0.767). Subgroup analyses revealed higher efficacy in acetylcholine receptor antibody-positive MG (AChR Ab+) patients (0.798, 95% CI 0.733–0.851) than in group that did not differentiate auto-antibody types (0.696, 95% CI 0.606–0.773). Intravenous administration showed a response rate of 0.758 (95% CI 0.701–0.807), whereas subcutaneous administration demonstrated a lower rate of 0.691 (95% CI 0.558–0.798).The pooled incidence of overall adverse events was 0.246 (95% CI 0.164–0.352).

Common AEs included infections (0.085, 95% CI 0.055–0.130) and headaches (0.093, 95% CI 0.065–0.131). Mild AEs occurred in 0.122 (95% CI 0.076–0.191), while serious AEs were relatively infrequent (0.040, 95% CI 0.025–0.063). Myasthenic crisis occurred in 0.030 (95% CI 0.019–0.046).

Conclusion: Efgartigimod demonstrates robust efficacy and a favorable safety profile in MG, particularly among AChR Ab + patients. Intravenous administration appears more effective than subcutaneous delivery. These findings support its growing role as a targeted immunotherapy in MG management.

M350-K: Characterizing Energy Metabolism Among People With ALS And Pathogenic Gene Carriers

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Background: Hypermetabolism is common among person with Amyotrophic Lateral Sclerosis (PALS). We leveraged PALS with C9orf72 hexanucleotide repeat expansion (C9-ALS) and asymptomatic gene carriers (C9-carriers) to understand the relationships between energy metabolism alteration, neuronal degeneration, and disease progression.

Methods: C9-ALS, C9-carriers, disease controls with mitochondrial DNA defects (DC) and healthy controls (HC) were included.

Demographics and blood samples were collected at enrollment. We measured total energy expenditure (TEE) with doubly labeled water (DLW), resting energy expenditure (REE) and respiratory exchange rate (RExR) with metabolic chamber, and fat mass (FM) with dual-x-ray-absorptiometry (DXA) or quantitative magnetic resonance (QMR). Fat-free mass (FFM) was calculated from body weight and FM. Plasma neurofilament light (NfL) and growth differentiation factor-15 (GDF-15) were measured with ELLA and ELISA, respectively. ANOVA and linear regressions (reference HC) were used for group comparisons, adjusted for age, sex and FFM as covariates.

Results: Total 55 participants were included, 8 C9-ALS, 16 C9-carriers, 10 DC, and 21 HC. C9-ALS was older than C9-carriers, DC and HC (65 vs 46 vs 46 vs 46, $p<0.01$). Sex, height, weight, body mass index (BMI), FM and FFM were not significantly different between groups. REE was 203 kcal/day higher in C9-ALS compared to HC, adjusted for covariates, $p<0.05$. TEE was 182 kcal/day higher in C9-carriers compared to HC adjusted for covariates, $p<0.05$. RExR was lower in C9-ALS compared to HC (0.72 vs 0.78), $p<0.01$.

Compared to HC, NfL was higher in C9-ALS and GDF-15 was higher in both C9-ALS and DC, adjusted for age (all $p<0.01$).

Discussion: High REE with low RExR, high blood NfL and GDF-15 levels are features of C9-ALS, signifying hypermetabolism with increased fatty acid oxidation, neuronal degeneration and cellular stress. The utility of these features as prognostic and predictive biomarkers in C9-ALS and gene-carriers is being evaluated in the ongoing study.

M351: Machine-Learning Triage of Suspected Guillain-Barré Syndrome Reports in VAERS Using Physician-Adjudicated Data

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Background: Effective post-marketing vaccine surveillance depends on timely identification of true Guillain-Barré syndrome (GBS) cases within the Vaccine Adverse Event Reporting System (VAERS). The high volume of incomplete or ambiguous submissions creates a needle-in-a-haystack problem for clinical reviewers. Whether structured clinical variables alone can support reliable machine-learning triage of suspected GBS reports has not been established.

Methods: VAERS reports from 1990 onward containing the terms "GBS" or "Guillain-Barré Syndrome" were extracted. A subset of 495 reports was manually adjudicated by physicians using Brighton Collaboration criteria, with each report assessed for clinical symptoms, diagnostic findings, and treatments. Cases were assigned to five categories (Confirmed, Probable, Possible, Not GBS, Insufficient Information) and collapsed into a binary outcome: GBS-Consistent (n=156, 31.5%) versus Non-Consistent (n=339, 68.5%). Structured features covered demographics, vaccine type, clinical indicators, and treatments; adjudication-derived variables (Brighton_Criteria_Met, Outcome_30d) were excluded to prevent label leakage. Median imputation with missingness flags was performed within a scikit-learn pipeline to prevent cross-fold leakage. Three gradient-boosted models (XGBoost, LightGBM, CatBoost) were trained and evaluated under 5-fold stratified cross-validation, with balanced accuracy, F1 score, and AUC reported as primary metrics given the 68.5% class imbalance.

Results: All three models demonstrated strong and consistent classification performance. CatBoost achieved the best overall result, with a balanced accuracy of 84.5%, AUC of 0.906, and F1 score of 0.792. XGBoost and LightGBM both reached a balanced accuracy of 82.6%, with AUCs of 0.893 and 0.895 and F1 scores of 0.768 and 0.765, respectively. Cross-model agreement supports that the discriminative signal reflects underlying clinical structure rather than algorithmic artifact.

Conclusion: Despite a modest sample size, gradient-boosted machine-learning models achieve strong and reproducible classification of VAERS GBS reports against physician adjudication. These findings support the feasibility of a physician-led, AI-assisted triage framework to prioritize higher-likelihood cases for detailed expert review.

External validation, dataset expansion, and prospective evaluation are required before integration into pharmacovigilance workflows.

M352*: AI-Assisted Classification and Phenotyping of Guillain-Barré Syndrome Reports in VAERS: Implications for Neuromuscular Surveillance

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Background: Guillain-Barré syndrome (GBS) is a rare immune-mediated neuropathy of significant pharmacovigilance interest following vaccination. The Vaccine Adverse Event Reporting System (VAERS) accumulates large volumes of suspected cases that require expert adjudication using established frameworks such as the Brighton Collaboration criteria, but reviewer capacity is limited and reports are clinically heterogeneous. Whether artificial intelligence can support both prioritization and phenotypic characterization of these reports has not been systematically evaluated.

Methods: VAERS reports adjudicated by clinical experts using Brighton-aligned criteria into five certainty levels (Confirmed, Probable, Possible, Not GBS, Insufficient Information; n=495) were collapsed into a binary outcome: GBS-Consistent (Confirmed + Probable + Possible; n=156, 31.5%) versus Non-Consistent (n=339, 68.5%). For classification, structured features including demographics, vaccine type, clinical indicators, and treatments were used; adjudication-derived variables (Brighton_Criteria_Met, Outcome_30d) were excluded to prevent leakage. Median imputation with missingness indicators was performed within a scikit-learn pipeline to prevent cross-fold leakage. Three gradient-boosted tree models (XGBoost, LightGBM, CatBoost) were trained under 5-fold stratified cross-validation, with balanced accuracy and AUC as primary metrics given class imbalance. For phenotyping, free-text narratives were encoded with BioClinicalBERT embeddings (768 dimensions), reduced to 5 via UMAP, and clustered with HDBSCAN without prespecified cluster number.

Diagnostic labels were not used during clustering. Cluster quality was assessed using silhouette score and bootstrap-stability adjusted Rand index (ARI).

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Results: CatBoost achieved the best classification performance, with a balanced accuracy of 84.5%, AUC of 0.906, and F1 score of 0.792. XGBoost (balanced accuracy 82.6%, AUC 0.893) and LightGBM (balanced accuracy 82.6%, AUC 0.895) performed comparably, indicating that the discriminative signal is reproducible across algorithms. Unsupervised analysis identified two clusters with no points classified as noise, excellent separation (silhouette 0.828), and very high reproducibility (median ARI 0.979, 95% CI 0.487–1.000). Notably, the two clusters had nearly identical median ages (59 and 60 years) and similar onset latencies (10 and 13 days), yet differed sharply in GBS-Consistent rate: Cluster 1 (n=347) showed 40.1% GBS-consistency versus 11.5% in Cluster 0 (n=148). The clustering signal therefore reflects clinical narrative content rather than demographic confounding.

Conclusion: AI-based analysis of VAERS reports enables accurate classification of suspected GBS cases and recovers reproducible phenotypic subgroups that align with physician adjudication without using diagnostic labels. The age- and onset-matched cluster separation supports the interpretation that narrative-based representations capture genuine clinical signal beyond demographic structure. These findings support a physician-led, AI-assisted triage and phenotyping framework for GBS pharmacovigilance, pending external validation, dataset expansion, and prospective evaluation.

M353: Timing Matters: Patient, Caregiver, and Clinician Perspectives on Optimizing Palliative Care in ALS

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Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease associated with substantial psychological and existential distress. While early palliative care (PC) is recommended in ALS to improve quality of life for patients and caregivers, specialty PC access remains limited. Leveraging patient, caregiver, and clinician perspectives, more research is needed to better understand barriers to timely, optimized PC implementation.

Methods: We conducted a mixed-methods study at the UCSF ALS Clinic. Semi-structured interviews were conducted with 25 participants: patients/caregivers within 0–12 months of diagnosis (n=10), patients/caregivers 12–48 months post-diagnosis (n=10), and bereaved caregivers (n=5). Interviews examined PC timing, initial understanding of PC, and unmet supportive-care needs. Neurologist (n=5) and PC clinician (n=5) interviews were conducted pertaining to referral decision-making, optimal timing of PC introduction and referral, and patient readiness. Interview transcripts were analyzed using inductive thematic coding and rapid qualitative summary matrices to compare themes across groups.

Results: Qualitative analysis identified three key themes: (1) early awareness versus active involvement, (2) an unmet need for anticipatory guidance, and (3) readiness- and needs-responsive engagement. Patients generally valued early awareness of PC, but readiness for active involvement varied. Slow progressors with robust supports were more likely to perceive early PC involvement as unnecessary, whereas rapid progression, psychological distress, caregiver burden, and emerging medical decisions increased its perceived value. Across cohorts, limited understanding of PC and associations with hospice persisted, while generic descriptions of PC often failed to convey its practical role. Participants identified an unmet need for a "roadmap" describing potential future physiological needs, decisions, and resources, while simultaneously describing "information overload" immediately following diagnosis. Neurologists similarly emphasized information overload and patient readiness, while PC clinicians favored early awareness before crises arose.

Conclusion: This study will identify actionable, stakeholder-informed strategies to support earlier integration of PC in ALS and expand patient-centered PC access. Qualitative findings will identify best practices for early referral and introduction to PC, strengthening ALS clinicians' confidence in psychosocial/existential support, and improving implementation strategies that support consistent PC across the ALS disease course.

M355: A Rare Case of Late-Onset Myotonia

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Background: Paramyotonia congenita (PMC) and Potassium-aggravated myotonia (PAM) are rare, autosomal dominant skeletal muscle channelopathies that exist on a spectrum and are caused by SCN4A gene mutations on chromosome 17q, which prolong the opening of voltage-gated sodium channels. Hallmark features include paradoxical muscle stiffness after exercise and cold exposure. Genetic testing is considered the gold standard for diagnosis, with supporting evidence via clinical presentation and electromyography (EMG). While the condition typically presents within the first decade of life, this case highlights a rare form with later presentation. Current treatment includes symptomatic management with various sodium channel blockers and with cold exposure avoidance.

Results: We report a case of a 43-year-old female who was referred for further workup of muscle issues starting seven years prior, with symptoms initially progressing then eventually stabilizing. She complained of proximal muscle weakness, although the physical exam revealed 5/5 strength throughout. She endorsed worsening with overuse but denied any worsening with cold temperatures. She had already been evaluated by several physicians, leading to a diagnosis of polymyositis by her rheumatologist based on elevated CK, proximal muscle weakness, myalgias, and arthralgias. She was subsequently treated with repository corticotropin/ACTH injection after not tolerating corticosteroids and also with intravenous immunoglobulin (IVIG). After one year without signs of clinical improvement, a muscle biopsy was completed for

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further investigation. Biopsy of quadriceps revealed neurogenic atrophy and rare necrotic fibers with a lack of inflammation, inclusions, or vasculitis, raising concern for misdiagnosis. An initial EMG interpretation two years prior stated "myopathic discharges" were present.
Retrospectively, the discharges were almost certainly actually myotonic in nature. Repeat EMG revealed diffuse myotonic charges. Genetic work-up was positive for a heterogenous mutation of G1306V in SCN4A, narrowing down the diagnosis. A taper for the ACTH injections was initiated, and IVIG was discontinued and replaced with mexiletine. However, the patient endorsed worsening joint pain with lower frequencies of ACTH injections, so they were reinitiated. Following a facial rash, mexiletine was discontinued and lamotrigine was started with improvement in motor symptoms.
Conclusion: This case highlights the importance of considering late-onset neuromuscular disorders in patients with treatment-resistant muscle weakness, as well as the appropriate use of diagnostic EMG, with muscle biopsy and genetic testing as supplementary information for more difficult diagnoses. Attention to detail in EMG interpretation and early identification of neuromuscular disorders can avoid the complications of unnecessary treatments and improve disease management.

M356: A Slowly Progressive MYOT-Related Myofibrillar Myopathy Misdiagnosed as Multilevel Radiculopathy: A 66-Year-Old Woman with Long-Standing Distal Weakness

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Background: Myofibrillar myopathies (MFMs) are a heterogeneous group of protein-aggregate myopathies that often present with slowly progressive weakness and are frequently misdiagnosed due to overlapping features with neuropathic disorders. MYOT-related MFM (MFM3) commonly manifests with distal-predominant weakness but may show nonspecific or misleading electrodiagnostic findings.
Methods: Case Presentation: A 66-year-old woman presented with decades-long, slowly progressive lower-extremity weakness beginning with difficulty toe walking and later involving challenges rising from the floor and ambulating. Neurological examination demonstrated mildly asymmetric, distal-predominant weakness in both upper and lower extremities, with additional mild proximal weakness in the legs, reduced ankle reflexes, and minimal distal sensory loss. Multiple outside electromyography (EMG) studies over several years showed persistent spontaneous activity without chronic neurogenic changes and were interpreted as multilevel radiculopathy. Repeat EMG at our center demonstrated widespread spontaneous activity, polyphasic motor unit potentials of borderline-to-normal duration, early recruitment, and no evidence of chronic denervation-findings more consistent with a myopathic process. Muscle MRI could not be obtained due to insurance limitations. Comprehensive neuromuscular gene panel testing identified a pathogenic heterozygous MYOT variant, confirming a diagnosis of autosomal dominant MFM3.
Results: Discussion: This case illustrates how MYOT-related MFM can masquerade as radiculopathy or other neurogenic disorders when EMG shows persistent spontaneous activity without definitive chronic denervation. Longitudinal misinterpretation of electrophysiology may delay diagnosis in slowly progressive phenotypes.
Conclusion: Conclusion: In adults with chronic distal-dominant weakness and inconclusive or misleading EMG findings, myofibrillar myopathy-particularly MYOT-associated disease-should remain in the differential. Early genetic testing may prevent years of diagnostic uncertainty and guide appropriate long-term surveillance.

M357: Homozygous RFC1 AAGGG Repeat Expansions Are Common in Idiopathic Peripheral Neuropathy

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Background: Biallelic intronic AAGGG repeat expansions in RFC1 cause cerebellar ataxia with neuropathy and vestibular areflexia syndrome and may also contribute to isolated sensory neuropathy. The clinical significance of both heterozygous and homozygous (biallelic) RFC1 expansions in more diverse patient populations remains unclear-partly due to the absence of accurate, user-friendly computational pipelines specifically tailored for tandem repeat analysis.
Methods: To discern the relationship between RFC1 expansions and idiopathic peripheral neuropathy (iPN), we performed whole-genome sequencing (WGS) followed by polymerase chain reaction (PCR)-based confirmation in a

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large, well-characterized US cohort consisting of 788 patients with iPN (369 pure small fiber neuropathy (SFN), 266 sensorimotor, 144 pure sensory, and 9 pure motor). We developed an integrative pipeline combining ExpansionHunter Denovo and Expansion Hunter coupled with unsupervised clustering to reliably detect and genotype RFC1 expansions from short-read WGS data, achieving 97.2% concordance with repeat-primed PCR-based validation.

Results: Biallelic RFC1 expansions were present in only 1 out of 778 controls but present in 18 out of 788 (2.3%) patients with iPN (Fisher's exact $p = 7 \times 10-5$), including 6.9% (10/144) of pure sensory, 1.1% (4/369) of SFN, and 1.5% (4/266) of sensorimotor neuropathy. These data indicate that motor nerve involvement should not exclude patients from RFC1 repeat screening. Monoallelic expansions were observed at a nominally higher frequency in iPN than in controls (9.1% vs 7.2%), but this difference did not reach statistical significance (Fisher's exact $p = 0.17$). We also found no evidence of second mutations or expansions on the other allele among monoallelic carriers.

Conclusion: Our approach provides a robust, cost-effective method for detecting RFC1 expansions from WGS data. Our findings indicate that homozygous (biallelic) AAGGG repeat expansions in RFC1 contribute to development of iPN. Heterozygous expansions may also confer disease risk, but future studies are needed to assess this observation and explore any phenotypic differences with biallelic cases.

M358: Feasibility Study of Non-Invasive Assessment of Emotional Responsiveness in Patients with ALS

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Background: Amyotrophic Lateral Sclerosis (ALS) presents with heterogeneous emotional and behavioral responses that are difficult to quantify in clinical settings. Current assessments rely on subjective clinician judgment, limiting scalability, reproducibility, and consistency. Objective, non-invasive measures of emotional responsiveness could improve and support personalized care. The reliability of widely available artificial intelligence tools for this purpose remains unclear.

Methods: We analyzed 28 ALS patient visits using speech recordings obtained during routine clinical encounters. Audio was transcribed into text and processed using natural language processing (NLP) to quantify emotional content and linguistic markers of concern. Patient-reported emotional status was assessed using the Hospital Anxiety and Depression Scale (HADS). In parallel, we evaluated large language models (LLMs) such as ChatGPT, Claude, Gemini using standardized prompts to assess patient concern levels, and compared outputs for agreement, variability, and reproducibility. We developed a classification framework integrating clinician-rated emotional concern with functional impairment measured by the ALS Functional Rating Scale (ALS-FRS). Patients were categorized as Congruent, Muted, or Excessive based on proportionality between emotional expression and disease severity. Acoustic features (loudness, sharpness, roughness, fluctuation strength) were extracted to identify objective correlations of these phenotypes.

Results: LLMs demonstrated low agreement and poor reproducibility in unsupervised assessment of patient concern, with substantial variability across models and prompt iterations. Emotional classifications showed limited concordance with physiological measures, including forced vital capacity. The proposed framework identified distinct behavioral phenotypes. The Excessive group, more frequently male, required increased clinician time and exhibited heightened concern relative to functional status. The Muted group, more frequently female, showed reduced expressed concern despite comparable functional impairment. The Congruent group demonstrated proportional alignment between emotional expression and functional status. These phenotypes were associated with distinct acoustic signatures. Muted responses demonstrated higher loudness and sharpness with lower roughness and fluctuation strength, whereas Excessive responses showed lower loudness and sharpness with higher roughness and fluctuation. Although partial overlap with early ALS-related speech changes is recognized, this was mitigated through cohort selection.

Conclusion: Speech-derived digital biomarkers provide objective, non-invasive measures of emotional responsiveness in ALS. When integrated with clinician assessment, functional status, and patient-reported outcomes, these measures can support more accurate categorization of patients and support earlier identification of individuals who may benefit from targeted interventions. However, current-generation LLMs demonstrate limited reliability in unsupervised clinical emotional assessment, underscoring the need for rigorous validation prior to clinical use.

M359*: Sex-Dependent Remodeling of Langerhans Cell Morphology and Transcriptional Profiles in Painful Diabetic Neuropathy

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Background: Neuropathic pain affects over 20 million people in the United States, with painful diabetic neuropathy (PDN) representing one of the most prevalent and treatment-resistant forms. Although PDN is characterized by nociceptor dysfunction, the upstream peripheral mechanisms remain incompletely understood. Beyond dorsal root ganglion (DRG) nociceptor hyperexcitability, we have previously demonstrated that skin-resident Langerhans Cells (LCs) contribute to PDN via CCL2/CCR2-dependent neuro-immune signaling. Notably, genetic depletion of LCs prevented mechanical allodynia and spontaneous pain-like behavior in male, but not female, PDN mice, revealing a sex-dependent role. Single-cell and interactome analyses further revealed male-specific inflammatory LC programs, including upregulation of chemokine signaling pathways. However, the mechanisms underlying these sex differences and their persistence during later PDN stages remain unclear.

Methods: We employed a high-fat diet (HFD,42% fat) mouse model of PDN in which male and female mice are fed HFD for 10- or 20- weeks. Single-cell RNA sequencing (scRNAseq) was performed on paw skin cells of male and female mice to identify sex-specific transcriptional profiles and LC features. LC morphology was analyzed using ImageJ SNT plugin, quantifying dendrite number, total dendritic length and arborization complexity.

Results: At 10 weeks of HFD, male mice exhibited increased LC density in the paw epidermis, which correlated with mechanical allodynia, whereas no significant changes were observed in females. Morphological analysis revealed increased dendritic complexity in LCs from HFD female mice, while LCs from HFD males displayed reduced soma size and decreased dendritic arborization. Comparative scRNA-seq analysis identified sexually dimorphic patterns of differentially expressed genes (DEGs), with pathway analysis highlighting sex-dependent alterations in inflammatory and signaling programs. At 20 weeks of HFD, analysis of LC density and morphology suggested that disease progression alters LC activity in females, indicating also time-dependent sex-differences.

Conclusion: Collectively, our research establishes LCs as key contributors to PDN and identify sexually dimorphic changes in LC morphological and transcriptional profile. These findings provide new insights into sex-specific neuro-immune interactions in metabolic neuropathy and highlights potential implications for the development of novel diagnostic and therapeutic strategies.

M360*: Brain Structure, Cognition, and Fluid Biomarkers in Myotonic Dystrophy Type 2: A Multimodal Analysis

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Background: Nearly two-thirds of myotonic dystrophy type 2 (DM2) patients report cognitive symptoms as a major source of disability. Limited brain imaging studies suggest cerebral white matter (WM) is primarily affected in DM2; however, the mechanisms underlying these symptoms remain poorly understood.

Methods: 3T brain MRIs were acquired from 35 adults with DM2 and 30 age-and sex-matched controls. Brain morphometry and white matter integrity were assessed using T1-MPRAGE and diffusion tensor imaging (DTI). DTI metrics, including fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD), and regional gray matter (GM) volumes were compared between groups using linear regression models. Comprehensive assessment of cognitive (NIH-Toolbox and UDS V.3) and motor measures was correlated with MRI using partial Pearson correlation (r), while fluid biomarkers (plasma and cerebrospinal fluid [CSF]) were analyzed with false discovery rate (FDR) correction. All statistical analyses were adjusted for age and sex.

Results: Among 65 participants (58% female), mean age (DM2=57.5±8.2 vs. controls=60.2±8.6 years) and education level (DM2=16.2±1.8 vs. controls=17.0±1.7) did not differ between groups. Compared to controls, widespread disruptions in cerebral WM integrity, characterized by lower FA and higher RD, were the most prominent abnormalities in DM2 (mean difference [DM2-controls]: FA = −0.035, P<0.0001; RD = 0.00005, P<0.0001), suggesting WM microstructural pathology. Cortical GM volume loss was also observed across multiple lobes (mean DM2-controls = -0.014, P<0.0001). The DM2 group demonstrated significant deficits in executive function (P<0.003), working memory (P=0.05), and episodic memory (P<0.017). Strong correlations were observed between superior frontal FA and executive function (r=0.44, P = 0.008), and between superior frontal and parietal GM volume and working memory (r=0.40, P=0.024). Frontal RD was also significantly correlated with the 10-meter gait speed (r = −0.41, P=0.015) and the step test (r=0.46, P=0.008), demonstrating a relationship between WM abnormalities and motor endpoints. Plasma biomarkers showed significant elevation in P-tau 181 (logFC=1.03, PFDR=0.006), P-tau 231 (logFC=0.8, PFDR=0.016), Total-tau (logFC=0.56, PFDR=0.03), and NfL (logFC=0.63, PFDR=0.02) levels in the DM2 group, whereas P-tau 217 did not reach statistical significance (logFC=0.6, PFDR=0.06).

Conclusion: Our study demonstrates strong associations between WM microstructure, regional gray matter volume, and cognitive dysfunction in DM2. Plasma biomarkers support tau-related mechanisms, potentially secondary to RNA splicing abnormalities. Longitudinal studies and validation of plasma biomarkers against CSF are required to better understand disease mechanisms and progression in DM2. Additional CSF analyses will be presented at the ANA meeting.

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M361-LB: Development of Quantitative Muscle Imaging as a Biomarker of Disease Endpoints in Myotonic Dystrophy (DeQoDE-DM)

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Background: Myotonic dystrophy (DM), the most common form of muscular dystrophy in adults, is associated with progressive muscle weakness and heterogeneous muscle involvement. Past and current clinical trials in DM have relied on muscle biopsies to evaluate disease burden and therapeutic response. However, this method is invasive and may be inefficient for long-term monitoring. Reliable and non-invasive biomarkers that capture regional muscle pathology are needed for natural history studies and clinical trial design. Dixon magnetic resonance imaging (MRI) enables muscle fat fraction (MFF) estimation and may serve as a sensitive imaging biomarker of disease severity.

Methods: In preliminary analyses, the DM group included 14 participants (9 DM2, 5 DM1), age 52±10 years, 36% females. The control group included 11 participants, age 46±13 years, 73% females. Mean differences in MFF between groups were significantly higher in the DM group in all regions: lower back 17.8% (p-value=0.003), hip 15.3% (p-value=0.008), thigh 15.8% (p-value=0.001), and calf 12.3% (p-value=0.005). In the DM group, higher average thigh MFF was strongly associated with slower gait speed (ρ=-0.70, p-value=0.005), reduced step test performance (ρ=-0.76, p-value=0.002), weaker grip strength (ρ=-0.59, p-value=0.027), and weaker strength of knee extensors (ρ=-0.88, p-value<0.0001) and knee flexors (ρ=-0.71, p-value=0.006), while higher average MFF in the anterior compartment of the calf was significantly correlated with weaker ankle dorsiflexors strength (ρ=-0.83, p-value=0.0005). Additional participants and STIR analyses will be presented at the ANA meeting.

Results: Our interim findings suggest that Dixon-derived MFF captures regional heterogeneous muscle involvement and disease severity in both DM types and correlates with clinically relevant motor endpoints. The robust associations further support longitudinal evaluation of MFF as a candidate biomarker for disease progression in DM.

Conclusion: For an ongoing study, 3T MRI scans (Siemens Cima.X) covering the lower back, hip, thigh, and calf muscles were acquired in 14 participants with DM and 11 controls. Two-point Dixon and short-tau inversion recovery (STIR) sequences were obtained. To quantify MFF (%), individual muscles were segmented automatically using an AI-based automated segmentation software (MuscleMap). Clinical outcome assessments (COAs), including quantitative grip and lower extremity muscle strength testing, and motor endpoints (6-minute walk test, 10-meter gait speed [m/s], step test, sit-to-stand, timed up and go) were collected in all participants. Groups were compared with a Mann-Whitney U test. Spearman's rank correlation (ρ) was used to measure the associations between regional MFF and COAs. Muscle segmentation and MFF analyses were performed by an analyst blinded to diagnostic group and DM subtype.

M362: Refractory Chronic Cough as an Early Prodrome of Cerebellar Ataxia-Neuropathy-Vestibular Areflexia Syndrome (CANVAS): A Case Report

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Background: RFC1-related disease spans a spectrum from full cerebellar ataxia-neuropathy-vestibular areflexia syndrome (CANVAS) to isolated sensory or autonomic neuropathy. CANVAS is due to AAGGG repeat expansion in the second intron of replication factor C subunit 1 (RFC1) gene. In addition to autonomic dysfunction symptoms as the most prevalent, sensory neuropathy/ neuronopathy manifestations with and without overt vestibular dysfunction vary in presentation and severity. Two-thirds of individuals affected by CANVAS report a dry spasmodic cough that may antedate neurologic signs by decades, highlighting cough as an overlooked prodrome.

Methods: We describe index patient with CANVAS and present a review of recent literature (2000–2026) concerning RFC1-related clinical conditions.

Results: A 57-year-old woman had a refractory dry cough from young adulthood. In her 5th decade she developed cold feet with paraesthesias, unsteady gait and orthostatic lightheadedness. Autonomic review revealed heat intolerance, anhidrosis and mottled acral skin. Exam was notable for length-dependent loss of light touch, vibration and proprioception. NCS demonstrated absent SNAPs in legs and reduced in arms, with H-reflexes and motor sparing. Brain MRI showed mild parenchymal atrophy and nonspecific periventricular FLAIR hyperintensities without cerebellar and brainstem abnormality. Patient's mother had undifferentiated neurodegenerative disorder. Repeat-primed PCR detected biallelic RFC1 AAGGG expansions, establishing an RFC1-related disorder in the spectrum of CANVAS. Chronic cough was therefore recognized as the inaugural symptom, preceding neuropathy by 3 decades.

Conclusion: Refractory cough underpinned by neuronally mediated hypersensitivity can be the sole clinical manifestation of CANVAS. Sensory ganglionopathy, with both central and peripheral axonopathies, is the core component of RFC1-associated conditions. In cases where SNAPs are either absent or low, tibial SSEP can be useful diagnostic step. Autonomic dysfunction encountered in 50% of patients may be related to primary ganglionopathy. Prevalence of vestibular dysfunction is reported in up to 98% of cases. There is no specific treatment. Neurologists should query for a lifetime chronic cough in late-onset progressive sensory ataxia with and without overt vestibulo-ocular reflex (VOR) dysfunction. Timely recognition enables targeted genetic testing and counselling, and appropriate management of symptoms including avoidance of unnecessary immunotherapies. Genetic testing with repeat-primed PCR to detect intronic

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expansions in RFC1 should be performed in cases with suspicion of CANVAS and/or in case of whole-exome sequencing negative hereditary sensory and autonomic neuropathy.

M363: Nanopore Long-read Sequencing for Profiling Genomic Rearrangements in Neuromuscular Disorders: A Resource For All

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Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease marked by the rapid degeneration of both upper and lower motor neurons, usually leading to death within 3 to 5 years after symptom onset. Nearly 40 genes have been associated with ALS, accounting for approximately 68% of familial cases and 11% of sporadic cases. However, a portion of heritability remains unexplained, which may be attributed to structural variants, such as deletions, insertions, duplications, and inversions. While short-read sequencing has traditionally been used in genetic studies due to its affordability, it has a limited ability to detect structural variants, particularly in repetitive genomic regions.

Methods: We used the Oxford Nanopore long-read sequencing platform to analyze DNA from autopsied brain tissue in 135 ALS cases and analyzed them against 393 controls (including both blood and brain samples). Analyses pipeline employed Sniffles2 for SV detection, Straglr for short tandem repeat profiling across approximately 900,000 loci, Clair3 for SNV calling, and pepper-deepvariant for phasing.

Results: By using this approach, we cataloged 159,093 high-confidence structural variants and genotype approximately 900,000 tandem repeat loci. Our analysis identified pathogenic variants in established ALS-associated genes, including SOD1, TARDBP, and FUS, and long-read sequencing enabled us to resolve these variants into specific haplotypes. We also detected pathogenic repeat expansions in known ALS genes, such as C9orf72 and HTT. Additionally, long-read sequencing enabled precise determination of repeat numbers and methylation patterns on expanded alleles.

Conclusion: Together, these results demonstrate the value of long-read genome sequencing for comprehensive profiling of structural variants and provide new opportunities for genetic research in ALS.

M364: Artifact-Aware AI-Assisted Identification of Myasthenia Gravis-Consistent Reports in VAERS Using Physician-Adjudicated Anomaly Detection

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Background: Myasthenia gravis (MG) is often incompletely captured in passive surveillance narratives. The Vaccine Adverse Event Reporting System (VAERS) is essential for rare signal detection but constrained by unverified, variable narratives and stimulated reporting. Conventional MedDRA- or keyword-based approaches conflate true MG with mimics or nonspecific symptoms. We redefined the analytic target as narrative consistency with MG-specific features, treating information incompleteness ("information poverty") as a primary analytic variable.

Methods: VAERS reports (1990–2025) were identified via MedDRA and narrative screening. A nine-domain physician adjudication instrument captured clinical features and diagnostics. Diagnostic certainty was assigned using a hierarchical MGFA-aligned framework (Confirmed to Insufficient Information). To address extreme class imbalance (826 Not MG vs 19 MG), an unsupervised autoencoder was trained exclusively on 800 adjudicated Not MG reports to learn the latent

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structure of typical non-MG narratives. MG-consistent reports were operationalized as deviations from this distribution. Performance was evaluated on an enriched test set (26 Not MG, 19 MG) using a reconstruction error threshold (mean + 2 SD).

Results: The model achieved an AUC-ROC of 0.779, accuracy of 80.0%, and balanced accuracy of 77.0%. It correctly classified 25/26 Not MG reports (specificity 96.2%) and identified 11/19 MG-consistent reports (sensitivity 57.9%), with 8 false negatives. No cases met criteria for confirmed MG; positive cases were limited to Probable and Possible classifications, reflecting substantial information incompleteness in VAERS narratives. Metrics reported here are not expected to be significantly affected by the enriched test set composition, as the detection threshold is calibrated on training reconstruction errors independently of class prevalence, and should therefore

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remain stable under real VAERS proportions (∼2%). Missed cases likely reflect sparse or non-specific narratives, consistent with the dependence of detection on feature availability. The reconstruction error threshold will be recalibrated when more training data becomes available.

Conclusion: An artifact-aware anomaly detection framework trained on physician-adjudicated non-MG reports provides a transparent and methodologically aligned approach to identifying MG-consistent narratives in highly imbalanced surveillance data. High specificity supports utility for signal refinement, while reduced sensitivity reflects both narrative sparsity and the structural constraints of anomaly detection in incomplete data environments. This work formalizes a principled separation between signal detection and diagnosis in passive surveillance and establishes a generalizable framework for rare disease signal extraction under conditions of information poverty. Future work will incorporate medical-record validation, mimic-focused negative controls, and advanced narrative representations to improve sensitivity and define the clinical meaning of high-consistency signals.

M365: Beyond Demographics: Narrative-Based Phenotyping of Suspected Guillain-Barré Syndrome Reports in VAERS Recovers Physician-Adjudicated Diagnostic Structure

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Background: Guillain-Barré syndrome (GBS) is a vaccine-pharmacovigilance signal of standing clinical interest, yet identification of true cases within the Vaccine Adverse Event Reporting System (VAERS) is constrained by report heterogeneity, incomplete documentation, and the high cost of expert adjudication. Free-text clinical narratives represent the most information-dense component of VAERS reports but remain underexploited. Whether modern clinical language models can recover diagnostic structure from these narratives, independent of demographic confounding, is unknown.

Methods: Of 495 VAERS reports flagged as suspected Guillain-Barré syndrome, all were adjudicated by clinical experts using Brighton Collaboration–aligned criteria. Free-text narratives were encoded using BioClinicalBERT (768-dimensional embeddings), projected to 5 dimensions via UMAP, and clustered with HDBSCAN without prespecified cluster number. Diagnostic labels and structured demographic variables were not used at any stage of the clustering pipeline. Cluster quality was assessed using silhouette score and bootstrap-stability adjusted Rand index (ARI). Clusters were characterized post hoc by physician-adjudicated GBS consistency, age, and onset latency.

Results: HDBSCAN identified two clusters (n=347 and n=148) with all 495 reports assigned (no noise points), excellent separation (silhouette 0.828), and very high reproducibility (median ARI 0.979, 95% CI 0.487–1.000). Post hoc characterization showed that clusters differed markedly in physician-adjudicated GBS consistency, with one cluster enriched for GBS-consistent reports and the other for non-consistent reports. The clusters were well matched on demographic and temporal features-median ages 60 and 59 years, median onset latencies 10 and 13 days-indicating that separation reflects narrative clinical content rather than age- or latency-driven confounding.

Conclusion: Unsupervised analysis of VAERS Guillain-Barré syndrome narratives using a clinical language model recovers physician-adjudicated diagnostic structure with excellent separation and stability, despite never accessing diagnostic labels or demographic variables. The age- and onset-matched cluster contrast indicates that narrative-based representations capture genuine clinical signal beyond demographic confounding. These findings support the development of a physician-led, narrative-aware AI framework for GBS pharmacovigilance, with potential application to other neuromuscular adverse

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events. External validation, larger labeled cohorts, and prospective evaluation are warranted.

M366: Age-Dependent Vulnerability in TDP-43 Pathology: Investigating Immunological and Molecular Determinants of Early Mortality in Mice Models

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Background: TAR DNA-binding protein 43 (TDP-43) pathology, characterized by cytoplasmic mislocalization, aberrant phosphorylation, and aggregate formation, is a hallmark of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and is increasingly observed in subsets of Alzheimer's disease. These pathological events disrupt RNA processing and proteostasis, ultimately driving neuronal dysfunction and cell death. Although aging is the strongest risk factor for neurodegenerative disorders, early-onset diseases often progress more rapidly, suggesting a paradoxical vulnerability of younger brains. Using an adeno-associated virus (AAV)-mediated TDP-43 overexpression model, we have observed decreased survival and increased neurological impairment in young mice when compared to old mice. The immunological and molecular basis of this age-dependent susceptibility remains poorly understood.

Methods: In the AAV-mediated TDP-43 overexpression model, we compare pathological and neuroinflammatory outcomes in young (5-7 months) and aged (20 months) mice expressing equivalent levels of human TDP-43. Neuronal survival and TDP-43 aggregation are quantified across spinal cord regions using immunofluorescence for total and phosphorylated TDP-43 alongside neuronal markers (NeuN, ChAT). Microglial and astrocytic activation are assessed via Iba1 and GFAP staining, and proteostatic stress is evaluated through pan-ubiquitin labeling with colocalization analysis of phosphorylated TDP-43 inclusions. Importantly, molecular pathology is correlated with longitudinal behavioral measures of motor function and overall survival within the same animals, directly linking aggregate burden to functional disease progression.

Results: We hypothesize that younger mice exhibit greater susceptibility to TDP-43 toxicity due to dysregulated neuroinflammatory responses and impaired proteostatic resilience relative to aged counterparts, resulting in accelerated neuronal loss and faster functional decline.

Conclusion: We predict that younger mice will exhibit dysregulated neuroinflammatory responses and impaired proteostasis relative to aged animals, correlating with accelerated motor decline and early mortality. These findings will define how age modulates TDP-43 toxicity and provide a mechanistic foundation for age-specific therapeutic strategies targeting neuroinflammation and proteostasis in early-onset ALS and FTD.

M367: Optimizing Treatment Strategy for Onasemnogene Abeparvovec in Spinal Muscular Atrophy: A Meta-Analysis

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Background: Onasemnogene abeparvovec (OA), an AAV9-mediated SMN1 gene replacement therapy, has profoundly impacted spinal muscular atrophy (SMA) management. Optimal treatment strategies, including monotherapy versus combination regimens, and clinical determinants of safety burden remain incompletely characterized.

Methods: A PRISMA-compliant meta-analysis of 26 studies from 3,224 screened records was conducted. Motor milestone acquisition, safety outcomes, and event-free survival (EFS) were pooled via a Freeman-Tukey double arcsine transformation with DerSimonian-Laird heterogeneity estimation. Subgroup analyses evaluated treatment modality (naïve OA, combination with Nusinersen /Risdiplam, sequential OA), dose, SMN2 copy number, SMA type, symptom status, age (≤12 vs >12 months), and weight (<8.5 vs ≥8.5 kg). EFS was modelled via multiple meta-regressions. Continuous motor function was assessed via CHOP-INTEND (severe infantile SMA) and HFMSE (ambulant, less severe SMA), synthesized as Standardized Mean Change (SMCR) under random-effects models.

Results: Presymptomatic patients achieved near-universal milestone acquisition, sitting without support: 1.00 [1.00-1.00]; standing without support: 1.00 [0.96-1.00], significantly exceeding symptomatic counterparts ($p < 0.001$). Naïve OA monotherapy demonstrated strikingly superior milestone attainment versus combination therapy across all symptom statuses: standing without support (1.00 [0.96-1.00] vs 0.12 [0.00-0.59]; $p < 0.001$) and head control (1.00 [1.00-1.00] vs 0.78 [0.22-1.00]; $p = 0.038$). Three-copy SMN2 patients consistently outperformed two-copy cohorts across all milestones ($p < 0.001$). Hepatotoxicity was elevated in patients >12 versus ≤12 months (0.833 vs 0.26; $p < 0.001$) and in those ≥8.5kg versus <8.5kg (0.71 vs 0.12; $p < 0.001$). Transient thrombocytopenia was significantly dose-dependent ($p = 0.005$) and markedly higher with

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combination versus naïve OA (0.52 [0.23-0.80] vs 0.16 [0.02-0.37]; $p = 0.042$). Cardiac adverse events were elevated with combination versus naïve OA (0.48 vs 0.09; $p = 0.0004$). Serious OA-related TEAEs affected 18% (95% CI [14-23%]), with higher rates in symptomatic patients. Treatment-related mortality was negligible (0.00 [0.00-0.01]). EFS was uniformly preserved across doses, SMA types, and symptom status; meta-regression yielded no significant modifiers, establishing OA's survival benefit as class-wide, dose-independent. OA produced clinically meaningful CHOP-INTEND improvement (SMCR = 1.21 [0.61-1.82]); HFMSE change was non-significant.

Conclusion: OA confers universal survival benefit across SMA types and symptom status, while functional gains are maximized by presymptomatic naïve monotherapy and three-copy SMN2 status. Presymptomatic patients ≤12 months and <8.5kg demonstrate superior efficacy and lower toxicity. Combination therapy showed inferior outcomes and greater adverse events, consistent with ASO bridging delaying gene replacement while disease progresses. These findings support naïve OA monotherapy at earliest opportunity as preferred treatment strategy.

M368: Cutaneous Stigmata Heralds Calamity: A Case Series on Delayed Presentation of Occult Spinal Dysraphism in Adolescents

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Background: Occult spinal dysraphism (OSD) includes a range of closed spinal anomalies which may go unnoticed because of intact outer skin. Skin markers may signify the earliest clues, but the markers themselves are often misinterpreted, causing slow diagnosis, an increasing unsolved case, and a range of prospecting neurological problems, especially in lower and middle income areas.

Methods: The Department of Neurosurgery, Allama Iqbal Medical College / Jinnah Hospital Lahore, conducted this retrospective case series from June 2023 – May 2024. 19 adolescent female patients (ages 9 – 16 years) with cutaneous stigmata and OSD with MRI findings were included. The clinical presentations, types of cutaneous markers, radiological findings, types of surgery, and outcomes after surgery and the analysis were done. All the patients had tethered cord released and the dysraphic lesion excised by the same neurosurgery team, and the patients were followed for 6 months.

Results: All patients had one or more midline lumbosacral cutaneous stigmata, most notably a tuft of hair and a dermal sinus. The most common clinical complaints were lower back pain (83%) and gait problems or weakness of the lower limbs (67%). MRI confirmed tethered cord syndrome and associated anomalies, such as thickened filum terminale, lipomyelomeningocele, and split cord malformation. The mean time between the first appearance of signs and diagnosis was 2.4 years. The most common causes of delayed diagnosis were misinterpretation of the cutaneous findings as benign (58%), lack of knowledge of the condition among primary health care providers (25%), and poor availability of imaging studies (17%). After the surgery, all patients experienced significant improvement in their neurological state and relief of pain, and none suffered surgical complications or worsening of their condition during follow-up.

Conclusion: Skin lesions are important initial signs of occult spinal dysraphism and should lead to rapid MRI investigations. Unfortunately, delays in diagnosis are common. However, important neurological improvement and reorganization after surgery are found for even older children and adolescents. More healthcare professionalism and caregiver sensitization are needed to improve early diagnosis and outcome.

M369: Survival and Cause of Death in Pontocerebellar Hypoplasia: An Individual-Level Meta-analysis to Guide Prognostic Counseling

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Background: Pontocerebellar hypoplasia (PCH) is a rare, heterogeneous group of neurodevelopmental disorders characterized by abnormal development of the pons and cerebellum, typically presenting with severe developmental delay, epilepsy, and early mortality. Prognostic counseling remains challenging due to fragmented survival data from small cohorts and evolving genetic classification. We aimed to characterize overall survival, cause of death, and mortality risk by clinical type and genetic etiology, integrating these findings with a companion clinical and genetic review spanning 1912-2022.

Methods: We conducted a systematic review and individual-level meta-analysis following PRISMA reporting guidelines, including PubMed-indexed studies (January 1993-March 2022) reporting patient-level data for individuals with PCH. Of 559 identified patients, 478 had sufficient data for time-to-event analyses. Survival was estimated using Kaplan-Meier methods and Cox proportional hazards models adjusted for study publication period. Causes of death were extracted as reported and grouped into predefined categories. Findings were contextualized within a companion review of 191 publications (1912-2022) characterizing clinical, genetic, and neuroradiographic features of PCH by type and subtype.

Results: Causes of death were heterogeneous, and 38.4% of decedents lacked a documented cause, highlighting a critical gap in mortality reporting. Among those with a known cause, respiratory failure (20.9%) and infection (14.7%) were most common, followed by cardiorespiratory failure (7.3%) and status epilepticus (6.8%). Time from symptom onset to

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death varied by cause: deaths attributed to status epilepticus (HR 2.48, 95% CI 1.11-5.53) and withdrawal of life-sustaining treatment (HR 5.56, 95% CI 1.53-20.25) occurred earliest. Mortality risk varied by clinical type: PCH1 showed increased hazard of death compared with unspecified PCH (HR 4.33, 95% CI 2.45-7.65), with the PCH1E subtype showing the highest risk (HR 31.65, 95% CI 11.64-86.04). Variants in SLC25A46 (HR 77.29, 95% CI 25.19-237.12) and EXOSC3 (HR 3.36, 95% CI 1.42-7.97) were also associated with increased mortality. The companion review identified TSEN54, RARS2, EXOSC3, and AMPD2 as the most frequently reported pathogenic genes across 26 disease categories and proposed a gene-linked diagnostic algorithm to guide classification.

Conclusion: Respiratory failure and infection are the leading documented causes of death in PCH, with direct implications for anticipatory guidance and supportive care planning. Survival varies widely by clinical type, subtype, and genetic etiology. Integrating cause-specific mortality patterns with clinical and genetic classification provides neurologists with a more individualized, evidence-based framework for prognostic counseling in PCH.

M370: Temporal Trends in Amyotrophic Lateral Sclerosis Mortality in the United States,1999-2024: A CDC WONDER Study

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Background: Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease with a projected rising incidence as populations age. Understanding temporal trends in ALS mortality is critical for health resource allocation and care infrastructure planning.

Methods: We analyzed CDC WONDER mortality data (1999-2024; ICD-10: G12.2) encompassing 186,855 deaths. Joinpoint regression (up to 3 joinpoints; Monte Carlo permutation) calculated annual per cent change (APC) and average annual per cent change (AAPC) in age-adjusted mortality rates (AAMR; per 100,000 population, 2000 US standard).

Results: Overall, AAMR declined from 2.14 to 1.84 (AAPC −0.61%; 95% CI: −0.92, −0.30). Inflexion points in 2014 and 2017 marked a shift from stagnation to sustained decline. Divergent age trajectories emerged: adults ≥65 years showed significant sustained reductions (AAPC −0.98%; 95% CI: −1.28, −0.68; $p < 0.05$), while adults 45–64 years experienced rising mortality through 2013 (APC 1.18%; 95% CI: 0.72, 1.64; $p < 0.001$) before stabilization. Sex disparities persisted, favouring females (2024 rates: 2.21 vs. 1.50). Non-Hispanic Whites demonstrated sharp post-2014 declines (APC −5.29%; 95% CI: −7.12, −3.44) absent in minority populations. Geographic heterogeneity was pronounced: the Northeast showed sustained reductions (AAPC −0.67%; 95% CI: −0.98, −0.36; $p < 0.001$), while the Midwest maintained elevated rates until 2014.

Conclusion: ALS mortality has shifted from plateau to sustained decline, likely reflecting improved multidisciplinary care and disease-modifying pharmacotherapy. However, the widening survival gap between older and middle-aged adults, coupled with persistent racial and geographic disparities, demands urgent targeted interventions to ensure equitable access to specialized ALS care.

M371: Serum Protein Profile Predicts Antiretroviral Response in Amyotrophic Lateral Sclerosis

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Background: A subset of individuals with Amyotrophic Lateral Sclerosis (ALS) have activation of an endogenous retrovirus, HML-2 in the brain and spinal cord. Antiretroviral therapies (ART), developed for human immunodeficiency virus (HIV), have demonstrated activity against HML-2 in vitro. This study investigates the effects of ART in ALS and identifies proteomic features associated with treatment response.

Methods: Serum samples for 17 individuals with ALS with high levels of HML-2 in the serum who received ART for 24 weeks (clinicaltrials.gov Indentifier: NCT024337110)

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were analyzed at baseline and week 20 using targeted proteomics, quantifying 132 proteins involved in neurological and immune function. Longitudinal changes in protein levels and their relationship to changes in HML-2 expression were assessed.

Results: Ten participants demonstrated a reduction in HML-2 levels over the treatment period. Proteomic analysis identified 14 proteins, whose levels significantly changed at 20 weeks. Of these, 3 proteins increased following treatment. In addition, levels of seven proteins at baseline correlated with change in HML-2 expression with treatment. A composite score was developed from five of these proteins (markers of neurodegeneration and neuroinflammation) which showed a strong correlation with a decrease in HML-2 levels following treatment ($r = 0.881$, $p = 2.9 \times 10^{-6}$)

Conclusion: A drop in HML-2 levels with ART in ALS is associated with a significant change in specific markers of neurodegeneration and neuroinflammation. Levels of another subset of proteins strongly predicted individuals most likely to respond to ART. A composite score from these proteins can be used to identify candidates for future studies. Validation in a larger cohort is needed to confirm these observations.

M372: Neuronal Caveolin-1 overexpression preserves motor neuron and neuromuscular junction integrity in female TDP-43 A315T mouse model of Amyotrophic Lateral Sclerosis (ALS)

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Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive degeneration of motor neurons (MN), ultimately leading to paralysis and death. Our lab previously demonstrated that neuronal Caveolin-1 (Cav-1) overexpression (SynCav1) extends survival and improves neuromuscular function in a SOD1 model of ALS [Wang, Theranostics, 2022; Sawada, FASEB Journal, 2019]. However, SOD1 mutations account for less than ~5% of ALS cases, while ~95% of cases are related to dysfunction of TAR DNA-binding protein 43 (TDP-43). Thus, this study aims to determine the effect of SynCav1 in the TDP-43 A315T mice.

Methods: Mice were divided into three groups: transgene-negative (TgN), TDP-43-SynNull, and TDP-43-SynCav1. AAV-PHP.eB containing either SynCav1 or SynNull (2×10^{11} v.g) was delivered retro-orbitally to 3-month-old female TDP-43A315T mice. Cav-1 overexpression was validated by immunofluorescence (IF) and immunoblot (IB).

Lower MN and gastrocnemius neuromuscular junction (NMJ) integrity were assessed at week 24 (symptomatic) and week 30 (late symptomatic). Transmission electron microscopy (TEM) was used to evaluate MN ultrastructure.

Results: Immunoblot confirmed ~5-fold Cav-1 overexpression in the spinal cord. At week 24, ventral horn MN soma size was decreased in both cervical (455 μm^2 vs 559 μm^2, $p < 0.0001$) and lumbar (615 μm^2 vs 726 μm^2, $p < 0.0001$) regions of TDP-43-SynNull mice compared to TgN with no change in MN count. This morphological change was accompanied by a decrease in NMJ innervation percentage (46% vs 63%, $p = 0.0003$) in TDP-43-SynNull mice compared to TgN group. In contrast, TDP-43-SynCav1 mice preserved MN size (cervical: 524 μm^2; lumbar: 748 μm^2) and NMJ innervation (69%) at levels comparable to TgN. TEM revealed increased mitochondrial damage in TDP-43-SynNull motor neurons, which was attenuated by SynCav1. At week 30, TDP-43-SynNull mice exhibited a significant reduction in lumbar MN count compared to TgN (13.7 vs 19.7, $p = 0.0004$), whereas TDP-43-SynCav1 mice showed partial preservation compared to TDP-43-SynNull (16.4 vs 13.7, $p = 0.03$). Similarly, NMJ innervation declined in both groups, with TDP-43-SynCav1 mice showing only a modest, non-significant trend toward preservation compared to TDP-43-SynNull mice (47% vs 38%, $p = 0.09$).

Conclusion: Together, these findings suggest that neuronal Caveolin-1 overexpression may provide neuroprotective effects and delay TDP-43-induced neurodegeneration in the early stages in this mouse model, but this effect was not enough to prevent MN death and NMJ denervation in later stages. Future studies should evaluate whether SynCav1 combined with TDP-43–targeting therapies provides synergistic benefit.

M373: Impersonating Congenital Myopathy: A Case of GFPT1-related Congenital Myasthenic Syndrome

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Background: Biallelic mutations in GFPT1 encoding Glutamine-fructose-6-phosphate-transaminase 1 cause autosomal recessive congenital myasthenic syndrome (CMS) type 12. Disease onset can vary from birth to adulthood. Patients typically present with limb-girdle pattern of weakness without significant respiratory, ocular or bulbar involvement. CK elevation up to 3 times the upper limit of normal has been reported. GFPT1 mutations disrupt protein glycosylation, impairing the neuromuscular transmission and can also lead to accumulation of tubular aggregates in muscle biopsies. Patients respond to acetylcholinesterase inhibitors, 3,4-diaminopyridine and albuterol.

Methods: A 33-year-old woman with a history of motor delay presented with chronic muscle cramps. She was born at 38 weeks with respiratory distress, feeding difficulties and arthrogryposis. She walked at the age of 2.5 years and lost ambulation by 8 years. Weakness further worsened after scoliosis correction surgery around the age of 15 and she started requiring nocturnal noninvasive ventilatory support. There was no family history of neuromuscular conditions.

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Neurological examination demonstrated normal mental status, diffuse contractures, muscle atrophy with narrow facies with facial weakness as well as a mild head drop. Distal upper extremities strength was MRC grade 2/5 while distal lower extremities strength was MRC grade 1/5. Proximal muscle groups had no functional strength (1/5).

Results: Muscle biopsy at age 3 years demonstrated marked fiber size variability, fiber splitting and internal nuclei. Some fibers were necrotic and contained macrophages. Prior genetic testing revealed a heterozygous pathogenic variant in DYSF, and two heterozygous variants of uncertain significance in COL6A1 and COL6A3. None were deemed diagnostic. Subsequently, whole genome sequencing revealed biallelic loss of function variants in GFPT1 (c.686-2A>G and c.686dup, p.R230*). Asymptomatic parents were heterozygous carriers of the GFPT1 variants. Her cramps responded to lamotrigine and her fatigability and muscle strength improved with pyridostigmine and albuterol.

Conclusion: This case demonstrates the importance of considering GFPT1-related CMS as a potential mimicker of congenital myopathies and congenital muscular dystrophies. GFPT1 mutations are often not included in the commonly available congenital muscular dystrophy or congenital myopathy gene panels and may be only detected by more sensitive testing such as comprehensive neuromuscular disorders panels or whole genome sequencing. An accurate diagnosis enables optimal symptomatic treatment while helping to avoid unnecessary immunosuppressive therapy, used for seronegative myasthenia gravis. Additionally, lamotrigine may be used as a potential treatment for severe cramps in this type of CMS.

M374: Acute Flaccid Paralysis Uncovering Novel Mutation in a Paediatric Alkaptonuria

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Background: Introduction: Alkaptonuria is a rare autosomal recessive metabolic disorder caused by homogentisate 1,2-dioxygenase deficiency, leading to homogentisic acid accumulation, dark urine, ochronosis, and progressive joint disease. Early pediatric recognition is critical, yet South Asian genetic data remains limited. Objectives: To characterise the clinical, biochemical and genetic spectrum of Alkaptonuria in pediatric patients.

Methods: This case series evaluated four male children (1 month to 13 years) diagnosed with AKU based on clinical presentation, urinary HGA screening via gas chromatography-mass spectrometry, and HGD gene sequencing. In-silico tools predicted variant pathogenicity.

Results: Darkening urine upon standing was the hallmark finding. One 13-year-old patient presented with Alkaptonuria co-occurring with intellectual disability and acute flaccid paralysis; genetic testing identified a pathogenic TAF1 variant. Molecular analysis identified four HGD variants, including two novel homozygous missense mutations: c.87T>A (p.MetLys) in exon 13 and c.7G>T (p.AspTyr) in exon 7. Management included Vitamin C, E, and nitisinone. Notably, a significant decrease in urinary HGA excretion was observed after just a single dose of nitisinone.

Conclusion: This study expands alkaptonuria's molecular spectrum with novel HGD variants. The rapid reduction in HGA excretion after one dose of nitisinone highlights its potential as an effective disease-modifying therapy when initiated early to reduce long-term systemic complications.

M375*: System-wide RNA processing disruption and compensation by EXOSC3 p.G191 variants in pontocerebellar hypoplasia 1B reveal candidate therapeutic targets

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Background: Pontocerebellar hypoplasia 1B (PCH1B) is characterized by hypotonia, progressive cerebellar atrophy, and motor neuron dysfunction, and is caused by pathogenic variants in the EXOSC3 gene. EXOSC3 is a subunit of the RNA exosome, a protein complex that degrades/processes multiple species of RNA. PCH1B shows genotype-phenotype

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correlation: patients harboring specific EXOSC3 variants do not survive beyond one year of age, while patients with other variants can live into the second decade of life. The molecular mechanisms contributing to disease severity among patients carrying different EXOSC3 variants remain poorly understood.

Methods: We investigated the functional consequences of EXOSC3 p.G191 variants, which are associated with milder and more heterogeneous PCH1B phenotypes, using CRISPR/Cas9-engineered human HEK293T cell models harboring G191C and G191D variants in heterozygosity and homozygosity. We applied multi-omics approaches including ultra-deep total RNA sequencing, global proteomics, and Protein Integral Solubility Assay (PISA) thermal stability with computational structural analyses. To assess the reversibility of observed changes, we performed EXOSC3 overexpression experiments in variant cell lines followed by global proteomics.

Results: RNA sequencing revealed extensive changes in transcript abundance across all EXOSC3 G191 genotypes, with homozygous G191D/G191D cells showing the most pronounced effects, including significant alterations in cerebellar-enriched transcripts and AU-rich element-containing RNAs. Alternative splicing analysis revealed that EXOSC3 G191 variants promote increased skipping of exon 3, generating a short isoform predicted by molecular dynamics simulations to be fully unstable, unique to G191 variants among PCH1B-associated alleles. At the protein level, all full-length EXOSC3 G191 proteoforms showed substantial thermodynamic destabilization (ΔΔG_fold of 4-6 kcal/mol) by λ-dynamics simulations, consistent with approximately 50% reductions in EXOSC3 protein abundance across all genotypes. Coordinated decreases in all nine RNA exosome core subunits and the exonuclease EXOSC10 were observed, consistent with orphan protein decay driven by the unstable short EXOSC3 isoform. PISA measurements confirmed significant destabilization of EXOSC3, EXOSC1, and MPP6 in G191D/G191D cells, with MPP6 and EXOSC1 destabilization extending to heterozygous genotypes. In contrast, DIS3 and multiple independent RNA processing pathways, including the Integrator complex and DEAD-box helicase DDX59, were significantly upregulated, suggesting compensatory recalibration of RNA metabolism. EXOSC3 overexpression confirmed that RNA exosome subunit and compensatory factor levels are inversely responsive to EXOSC3 abundance.

Conclusion: EXOSC3 p.G191 variants disrupt RNA exosome integrity through alternative splicing, protein destabilization, and orphan decay, partially offset by compensatory upregulation. Overexpression rescue suggests antisense oligonucleotide or small molecule therapies targeting exon 3 skipping are viable for PCH1B.

M376: Unmasking Myasthenia Gravis in a Patient with Post-ACDF Horner Syndrome

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Background: Horner syndrome is a recognized but uncommon complication of anterior cervical discectomy and fusion (ACDF), resulting from intraoperative injury to the cervical sympathetic chain. It classically presents with ipsilateral ptosis, miosis, and anhidrosis. Myasthenia gravis is an autoimmune neuromuscular junction disorder characterized by fatigable weakness, commonly affecting ocular and bulbar musculature. Although uncommon, the co-occurrence of these two distinct neurological conditions may complicate clinical assessment when overlapping features are present.

Methods: We present a case of postoperative Horner syndrome that initially masked an underlying diagnosis of myasthenia gravis. Written informed consent and institutional approval were obtained.

Results: Initial encounter: A 78-year-old woman with hypertension, hyperlipidemia, and hypothyroidism, who underwent C3–C5 ACDF three months prior, presented with right-sided ptosis and miosis. She developed mild right-sided ptosis immediately postoperatively, which initially improved over the first month but subsequently progressed, prompting referral by her neurosurgeon. Neurological and ophthalmological workup performed at presentation, including MRI and vascular imaging, excluded ischemic, compressive, and vascular etiologies. Horner syndrome was confirmed clinically and further supported by phenylephrine-responsive ptosis. Given the atypical clinical course, a myasthenia gravis antibody panel was obtained, with plans for outpatient follow-up. Follow-up: Over the following month, she developed new bulbar symptoms including dysarthria and dysphagia, along with diplopia and worsening bilateral ptosis. Acetylcholine receptor (AChR) binding antibody was elevated at 27.7 nmol/L, with MuSK antibody undetectable, consistent with AChR-positive myasthenia gravis. CT chest revealed no thymoma. The patient was treated with pyridostigmine 30 mg every 6 hours, intravenous immunoglobulin, and prednisone 40 mg with taper. Respiratory status was closely monitored with negative inspiratory force measurements. The patient demonstrated gradual clinical improvement and was discharged with outpatient neurology follow-up. Concurrent diagnoses of post-ACDF Horner syndrome and myasthenia gravis were established.

Conclusion: This case highlights the diagnostic complexity that arises when two neurological conditions share overlapping clinical features. Clinicians should maintain a broad differential even after an initial diagnosis is established, particularly when symptoms progress beyond the expected trajectory of a surgical complication. In patients with postoperative ptosis, failure to improve or emergence of bulbar symptoms should prompt evaluation for concurrent neuromuscular disorders.

M377*: Early Intervention with RKER-065 Mitigated Disease Progression in an Amyotrophic Lateral Sclerosis Mouse Model

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Background: Skeletal muscle is increasingly recognized as an active contributor to amyotrophic lateral sclerosis (ALS) pathogenesis rather than a passive target of denervation. In ALS, muscles exhibit impaired regenerative capacity accompanied by local inflammation, which is closely linked to "dying-back" neurodegeneration. Chronic inflammation in muscle further impairs neuromuscular junction (NMJ) integrity and exacerbates disease progression. Activin A and myostatin are potent factors that suppress muscle growth, inhibit myogenesis, and promote catabolic signaling. Activin A has also been associated with increased expression of pro-inflammatory cytokines and muscle fibrosis. RKER-065 is the research version of the modified type II activin receptor ligand trap, rinvatercept, which was designed to inhibit myostatin and activins. Our prior studies showed that RKER-065 preserved muscle function, reduced inflammatory signaling, and improved muscle environment in dystrophic animals. This study aims to investigate the potential efficacy of RKER-065 in the SOD1-G93A (SOD1) mouse model of ALS.

Methods: Six-week-old male SOD1 mice were intraperitoneally injected with vehicle (Veh mice) or RKER-065 (10mg/kg, QW) for 5 weeks. Vehicle-treated B6SJL/J mice served as controls (WT). Lean mass was assessed by nuclear magnetic resonance at baseline and week 4. Muscle function was determined by weekly grip strength measurements and evoked force assay at week 4. Terminal NMJ function for signaling transduction was evaluated by compound muscle action potential (CMAP) and repetitive nerve stimulation (RNS) tests at week 5.

Results: We observed significant weight loss and muscle weakness in vehicle-treated SOD1 mice. Compared with WT controls, Veh mice exhibited reduced body weight gain and decreased lean mass, impaired muscle contractile performance under evoked force stimulation, and declined action potential amplitude in CMAP and RNS assays. In contrast, RKER-065-treated SOD1 mice had significantly higher body and lean mass than both WT and Veh mice. Improved muscle function in RKER-065-treated SOD1 mice was reflected as significantly increased grip strength relative to Veh mice. In the assessment of evoked force, SOD1 mice treated with RKER-065 exhibited significantly increased contractile force relative to that of Veh mice under sciatic nerve stimulations. RKER-065 treatment also significantly elevated the action potential amplitude of the tibialis anterior muscle in CMAP and RNS assessments under different stimulation frequencies, indicating improved neuromuscular transmission and enhanced fatigue resistance.

Conclusion: We found that early intervention with RKER-065 preserved muscle mass, improved muscle function, and maintained NMJ integrity in SOD1 mice. These findings suggest that inhibition of myostatin and activin A with RKER-065 has the potential to slow ALS progression.

NEURO-ONCOLOGY

M378: First Seizure Unmasks Endometrioid Adenocarcinoma Brain Metastases

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Background: To report the exceptionally rare presentation of seizures as the first sign of multifocal brain metastases from endometrioid adenocarcinoma years after hysterectomy. Background: Brain metastases as the first clinical finding in endometrial carcinoma occur in well under 1% of cases, with published estimates around 0.1–0.2%. In a Mayo Clinic cohort of 1,632 patients with endometrial cancer, only 2 cases (0.12%) presented with brain metastases at the time of initial diagnosis.

Methods: Case Report

Results: A 45-year-old woman with hypertension, hyperlipidemia, and hypothyroidism, status post total hysterectomy in 2021 for benign heavy menstrual bleeding, presented with a generalized tonic–clonic seizure and transient bowel incontinence. Neurologic examination was initially non-focal. MRI revealed 17 enhancing lesions in supratentorial and infratentorial regions, with the largest in the right posterior temporal–occipital junction, associated with vasogenic edema but no mass effect. Work up to differentiate infectious vs malignancy was done. She underwent right temporal craniotomy for resection of the dominant lesion. Histopathology demonstrated adenocarcinoma with papillary/micropapillary architecture, moderate nuclear atypia.

Immunoreactivity for PAX8, CK7, and vimentin, consistent with metastatic endometrioid adenocarcinoma of Müllerian origin. CT-guided liver biopsy showed similar histology, confirming systemic metastatic disease. Infectious workup was negative. Follow-up in 3 months she developed left-sided hemiparesis and MRI revealed progression of multifocal metastases with perilesional edema and multiple acute and subacute cortical infarctions, largest in the right parietal lobe with. Management included dexamethasone, antiepileptic therapy (Keppra transitioned to Lacosamide), therapeutic anticoagulation, systemic chemotherapy (carboplatin, paclitaxel, pembrolizumab), and whole-brain radiation therapy.

Conclusion: This case is unique for seizure as the sole initial symptom, absence of focal neurological deficit, and delayed multifocal CNS presentation years after benign hysterectomy. Subsequent discovery of systemic metastases highlights the

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diagnostic complexity and clinical significance. Most reported cases involve focal deficits, rapid progression, and poor prognosis, underscoring the rarity and educational value of this presentation.

M379*: Siglec-15 and PD-1 checkpoint blockade in combination with oncolytic Zika virus infection confers protection against immune-resistant gliomas

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Background: Glioblastoma (GBM) is an aggressive brain tumor; most patients die within two years. There are two major challenges to treatment: (1) cancer stem cells are resistant to chemoradiation and (2) the immunosuppressive tumor microenvironment renders immune checkpoint blockade ineffective. We are developing oncolytic Zika virus (ZIKV) as a new therapy. ZIKV has specificity against cancer stem cells and stimulates CD8+ T-cell-mediated anti-tumor immunity. We have demonstrated our genetically engineered ZIKV, which cannot be transmitted by mosquitos, is safe in non human primates. ZIKV extends survival in preclinical GBM models (Nair et al., JCI Insight, 2021), but myeloid cell-driven immunosuppression persists. An antagonist of Siglec-15, a myeloid immune checkpoint molecule (Wang et al., Nat Med, 2019), is in a phase II trial for non-small cell lung cancer, but its role in CNS malignancies is still unclear.

Methods: We evaluated Siglec-15 expression in human GBM using flow cytometry and immunofluorescence microscopy. Using syngeneic glioma models (CT2A, SB28), we tested a blocking antibody against Siglec-15, and Siglec-15 knock out mice, alongside ZIKV and anti-PD-1 therapies. We performed survival studies and analyzed immune responses via flow cytometry, T-cell proliferation and phagocytosis assays, and tumor rechallenge.

Results: Siglec-15 was expressed by human GBM myeloid (16-22%) and tumor cells (18-19%). In CT2A-bearing mice, ZIKV+anti-Siglec-15 therapy increased long-term survival (60% vs. 40% with ZIKV alone), and this further increased to 83% with anti-PD-1 treatment. Triple therapy in SB28-bearing mice yielded a 76% long-term survivor rate, with higher levels of CD8+ T-cell activation (1.7-fold). Rechallenged mice showed expansion of brain-resident/effector memory CD8+ T-cells (11-fold), with 80% long-term survival rates. Siglec-15 loss augmented tumor cell phagocytosis (CT2A: 25%; SB28: 7%) and T-cell responses (activation: 81%; proliferation: 86.8%) compared to wild-type.

Conclusion: Targeting Siglec-15, combined with PD-1 blockade and oncolytic ZIKV overcomes myeloid immunosuppression and enhances cytotoxic T-cell activation in GBM, promoting durable anti-tumor immunity. These findings support further investigation of this combination therapy.

M380: ALK-Positive Histiocytosis Presenting with Diffuse Leptomeningeal Disease and

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Background: Refractory headaches with elevated intracranial pressure (ICP) require evaluation for secondary causes. While idiopathic intracranial hypertension is common in young adults, atypical features such as progressive neurologic deficits or leptomeningeal enhancement should prompt consideration of inflammatory, infectious, vascular, or neoplastic etiologies. ALK-positive histiocytosis is a rare neoplasm most often presenting with focal CNS mass lesions; diffuse leptomeningeal disease without a mass is uncommon.

Methods: We report a young woman with prior diagnosis of HaNDL syndrome who presented with progressive headaches, papilledema, diplopia, and elevated ICP. She underwent serial neuroimaging, cerebrospinal fluid (CSF) analysis, ophthalmologic evaluation, systemic malignancy workup, and neurosurgical biopsy.

Results: Initial workup showed markedly elevated CSF opening pressure with lymphocytic pleocytosis and MRI findings of intracranial hypertension (optic nerve sheath distension and venous sinus narrowing) without leptomeningeal enhancement, with symptomatic improvement on acetazolamide. She later developed worsening papilledema, diplopia, and abducens nerve palsy. Repeat MRI demonstrated new diffuse leptomeningeal enhancement throughout the brain and spinal cord with cranial and spinal nerve root involvement, along with progression of venous sinus stenosis and cerebellar tonsillar descent. CSF studies showed persistent ICP elevation with evolution from lymphocytic to macrophage-predominant pleocytosis. Extensive infectious, inflammatory, and neoplastic evaluations were negative.

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Given refractory ICP elevation and progressive leptomeningeal disease, an external ventricular drain was placed and brain/dural biopsy performed. Pathology showed perivascular CD68-positive, ALK-positive histiocytic infiltration without mass formation, consistent with ALK-positive histiocytosis. Symptoms improved with CSF diversion, steroids, and supportive care, with targeted therapy planning initiated.

Conclusion: ALK-positive histiocytosis may present as diffuse leptomeningeal disease with refractory intracranial hypertension in the absence of a mass lesion. New leptomeningeal enhancement, progressive cranial neuropathies, and evolving CSF profiles should prompt tissue diagnosis to avoid delay in recognition and treatment.

M381: Geographical and Demographic Disparities in Pediatric Brain Tumor Mortality in the United States from 1999 to 2023: A Nationwide Joinpoint Regression Analysis

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Background: In the United States, brain tumors remain the leading cause of cancer-related deaths in children. Despite advances in diagnosis and therapies that result in better outcomes, the increases in survival rates may not be evenly distributed across different demographic and geographic groups.

Methods: The CDC WONDER Multiple Cause of Death database for 1999-2023 was used to calculate death rates for malignant brain and other central nervous system tumors (ICD-10 C70-C72, D32, and D33). We estimated crude death rates per 100,000 people and segmented them by age, gender, race, census region, and metropolitan status. Joinpoint regression models analyzed Annual Percent Change (APC) and Average Annual Percent Change (AAPC), with p-values < 0.05 indicating significance.

Results: Pediatric brain tumour mortality decreased slightly but significantly (APC = -0.31%; p = 0.009). Children aged 1–4 years experienced the greatest decline (APC = −2.08%; 95% CI −2.72 to −1.43; p < 0.001), with older groups remaining stable. Males experienced a progressive reduction (APC = -0.41%; p = 0.04), while females showed a biphasic pattern, with an initial decrease (APC = -0.47%; p = 0.0016) followed by a nonsignificant rebound (APC = +8.82%) until 2021. Regionally, mortality decreased significantly in the West (APC = -0.94%; p < 0.001) but remained stable in the Midwest and Northeast, with varying patterns in the South. Racial disparities were negligible, with only minor nonsignificant reductions among White and Hispanic youngsters. Mortality decreased similarly in urban areas (APC ≈ -0.3%), whereas rural rates remained consistently higher.

Conclusion: While the national death rate for pediatric brain tumors has decreased significantly, the benefits of development remain variable. Children aged 1-4 and those living in western states had the greatest survival gains, whereas southern, rural, and female groups exhibited stagnation or reversal. Targeted investments in pediatric neuro-oncology infrastructure, timely access to specialized care, and equity-oriented surveillance metrics are critical to ensuring that future discoveries translate into uniform survival improvements for all children in the United States.

M382: Physical Exercise in Brain Tumor Patients: A Systematic Review

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Background: Brain tumors – both primary and metastatic – are a leading cause of mortality and disability among cancer patients. While physical exercise has proven effective in the management of multiple cancer- and treatment-related symptoms in patients with systemic cancers, it remains poorly studied in patients with brain tumors. This systematic review aims to evaluate the available evidence on the safety, feasibility, and potential clinical effects of physical exercise in patients with brain tumors.

Methods: PubMed and the Cochrane Library were systematically searched through December 2025 using the PRISMA guidelines for a systematic review; protocol registered in PROSPERO (CRD420251111272), to identify studies assessing the role of physical exercise in patients with primary or metastatic brain tumors. Studies were screened according to predefined inclusion and exclusion criteria. Non-English studies, protocols and ongoing studies, and those strictly focusing on symptom-targeted rehabilitation interventions or behavioral therapies were excluded. Overall study quality was assessed using the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence, while risk of bias in randomized trials was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool. Data were extracted using a structured approach and included the brain tumor type, the FITT(frequency, intensity, time, type) principle of exercise interventions, timing with tumor treatment, main outcomes, and adverse events.

Results: Thirty-one studies (23 clinical trials, 4 observational studies, 2 qualitative analyses, 1 case report and 1 case study) met the inclusion criteria. Due to heterogeneity in study designs and reported outcomes, results were synthesized descriptively. Participation in aerobic, resistance, and combined exercise interventions was feasible for patients with brain tumors. The majority of studies reported improved physical fitness, cognition, and tumor-specific symptoms, with heterogeneous findings for fatigue and quality of life. Reported adverse events were rare and consistent with

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exercise-related adverse events reported for individuals without cancer.

Conclusion: Physical exercise appears safe and feasible in patients with brain tumors, with emerging evidence suggesting potential benefit. However, current findings are largely based on small studies with heterogeneous designs, structured interventions, and a high risk of bias, which limit broader generalizability. Larger prospective trials are needed to inform exercise guidelines for patients with brain tumors.

M383: Intraoperative Stimulation Mapping in Pediatric Supratentorial Brain Tumor Resection: A Systematic Review and Meta-Analysis of Neurological Outcomes and Extent of Resection

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Background: Surgical resection of pediatric supratentorial brain tumors demands a careful balance between maximal tumor removal and neurological preservation. Unlike in adults, where IONM indications and techniques are well-established, evidence in children remains sparse, compounded by the unique functional and developmental complexities of the pediatric brain. This systematic review and meta-analysis evaluate the impact of intraoperative stimulation mapping on extent of resection and postoperative neurological deficits in pediatric supratentorial brain tumor surgery

Methods: A systematic review of studies was conducted according to PRISMA guidelines (PROSPERO ID: CRD420251101609). Studies published between January 1990 and June 2025 were included. Data were pooled using a random-effects model, and heterogeneity was assessed with I^2 statistics.

Results: The analysis included 41 studies encompassing 1,908 pediatric patients. Pooled GTR rates were significantly higher in the monitored group (76.9%; 95% CI: 69.1–82.6) compared to the unmonitored group (52.8%; 95% CI: 45.2–60.4). Postoperative neurological deficits occurred less frequently with IONM use (15.1%; 95% CI: 8.7–22.8) than without (23.1%; 95% CI: 12.4–38.8). Stratified analyses demonstrated that eloquent cortex involvement was associated with reduced GTR rates and greater neurological morbidity; notably, IONM use mitigated this effect.

Conclusion: This meta-analysis provides convincing evidence for the routine use of IONM in pediatric supratentorial tumor resection, underscoring its value in maximizing tumor removal while safeguarding neurological function, especially in eloquent cortex. Furthermore, it identifies a critical need for prospective comparative studies and standardized pediatric IONM protocols to better preserve long-term function in this population.

M384: Socioeconomic Predictors of Diagnostic Delay in Nonfunctioning Gonadotroph Adenomas

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Background: Nonfunctioning gonadotroph adenomas (NFGAs) are a common subtype of pituitary tumors that typically present with visual or endocrine symptoms from mass effect but lack hormonal hypersecretion. This indolent course often leads to diagnostic delay. While comorbidities have been implicated, broader socioeconomic contributors remain poorly defined. The objective of this study was to identify socioeconomic predictors influencing time to diagnosis in patients with NFGAs, focusing on Area Deprivation Index (ADI), presence of a primary care provider (PCP), and presentation pathway (emergency department [ED] vs outpatient).

Methods: A retrospective cohort included adults who underwent resection of histologically confirmed NFGAs at our institution. Patients with functional tumors, recurrent disease, or uncertain symptom onset were excluded, leaving 110 for analysis. A negative binomial hurdle model explained days from symptom onset to diagnosis using ADI, PCP, and presentation for both the zero portion and the count portion.

Results: Incidental diagnosis accounted for 61% of cases and was more frequent among ED presentations (84%) than outpatient evaluations (51%; p=0.001). ED presentation had higher ADI (55.9 vs 46.2; p=0.03), reflecting lower socioeconomic status (SES). ADI did not differ between incidental and symptomatic presentations (p=0.28).

Diagnosis within 1 month of symptom onset occurred in 46 (42%) patients. In the hurdle model, outpatient presentation had a sixfold higher likelihood of delayed diagnosis (>1 month) compared to no delay (within the same month) (OR 6.1, 95% CI 2.38–15.49, p<0.001). Each unit increase in ADI decreased odds of delay by 2.3% (95% CI 0.3–4.4%, p=0.02). Among those with delay, having a PCP shortened diagnosis time by 4.6 months (p=0.054).

Conclusion: Patients from lower SES (higher ADI) were more likely to present through the ED and receive earlier diagnoses, likely reflecting greater reliance on emergent care. However, ADI was not associated with incidental tumor detection, suggesting that SES affects the route of presentation rather than the manner of diagnosis. Higher-SES patients more often pursued outpatient evaluation, which correlated with diagnostic delay, while having a PCP modestly reduced time to diagnosis.

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M385: Tumor Treating Fields in Glioblastoma: A Systematic Review of Quality of Life and Functional Outcomes Across Randomized and Prospective Studies

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Background: Glioblastoma is associated with profound neurologic morbidity and limited survival. Tumor Treating Fields prolong survival in randomized trials, yet concerns persist regarding the impact of continuous device use on patient-reported quality of life and functional independence. Objective:- To synthesize evidence on health-related quality-of-life and functional outcomes associated with Tumor Treating Fields therapy in adults with glioblastoma.

Methods: A systematic search of PubMed, Embase, and Cochrane CENTRAL was performed from inception through January 2026 following Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. Eligible studies included randomized controlled trials and prospective observational studies in adults with histologically confirmed glioblastoma reporting validated quality-of-life or functional outcomes, including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, Brain Cancer Module-20, Karnofsky Performance Scale, or Mini-Mental State Examination. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the Cochrane Risk-of-Bias 2 tool and Newcastle-Ottawa Scale. Narrative synthesis was pre-specified given anticipated heterogeneity in outcome instruments and assessment timepoints.

Results: Six studies including 1,243 patients met inclusion criteria: two phase III randomized trials and four prospective observational cohorts. In the EF-14 Trial, global health-related quality-of-life scores did not differ significantly between Tumor Treating Fields plus temozolomide and temozolomide alone despite the survival benefit associated with device therapy; Mini-Mental State Examination scores remained stable across arms. The EF-11 Trial demonstrated comparable quality-of-life outcomes between Tumor Treating Fields and physician's-choice chemotherapy, with fewer systemic toxicities including nausea and hematologic adverse effects in the Tumor Treating Fields arm. Across prospective cohorts, device-related scalp irritation occurred in 43–52% of patients and rarely resulted in treatment discontinuation. Karnofsky Performance Scale scores generally remained above 70 among patients continuing therapy beyond six months. Caregiver burden associated with device management was inconsistently measured across studies.

Conclusion: Tumor Treating Fields therapy does not meaningfully compromise health-related quality of life, cognitive function, or functional independence compared with standard chemotherapy, while offering reduced systemic toxicity. Caregiver burden and device-related dermatologic outcomes remain undercharacterized and warrant prospective investigation. Future neuro-oncology trials should incorporate standardized patient-reported and caregiver-reported outcome measures to fully define the patient-centered value of Tumor Treating Fields in glioblastoma management.

M386: A Novel Case of ARID1A Mutation in Pediatric Choroid Plexus Tumor

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Background: Choroid plexus papillomas and choroid plexus carcinomas represent the two most common subtypes of choroid plexus tumors. Various genetic alterations have been characterized in these tumors. We describe a 9-year-old male with recurrent atypical choroid plexus papilloma, WHO Grade 2, who required three surgeries, highlighting management complexities.

Methods: Molecular analysis of tumor tissue was performed. Analysis revealed an ARID1A frameshift mutation, p.-Phe1848LeufsTer3, with 42% variant allele frequency. No other pathogenic variants were identified in TP53, SMARCB1, or SMARCA4. Due to aggressive recurrent behavior and the ARID1A alteration, the tumor was managed using a carcinoma-directed approach. The patient received chemotherapy with carboplatin, etoposide, and vincristine per Head Start III protocol. Radiation oncology was consulted.

Results: Despite initial gross total resection, the tumor recurred locally at 4 months, necessitating two additional resections. Following identification of the ARID1A mutation, a multidisciplinary team recommended adjuvant therapy. The patient completed 4 cycles of chemotherapy with stable disease on MRI. He subsequently underwent CT simulation and received focal proton radiotherapy, 54 Gy in 30 fractions. Therapy was tolerated without grade 3+ toxicity.

Conclusion: This is a unique case of an ARID1A mutation in a pediatric choroid plexus tumor. ARID1A mutations occur in atypical teratoid/rhabdoid tumors and adult carcinomas but have not been described in pediatric CPTs [Thomas C, Acta Neuropathol, 2023]. The aggressive recurrence pattern suggests ARID1A alterations may be associated with atypical behavior in CPTs and may warrant carcinoma-directed therapy [Merker M, Neuro-Oncology, 2022]. This case underscores the importance of molecular profiling in pediatric CPTs to guide multidisciplinary management. Further research is needed to determine the prevalence and prognostic significance of ARID1A mutations in CPTs, as no established protocols exist for recurrent ARID1A-mutated tumors.

M387: Glioblastoma in Patients with Multiple Sclerosis: A Natural History Analysis of Inflammatomas

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Health Brown University, Providence, RI Eric T Wong, MD, Department of Neurology and Medicine, Rhode Island Hospital & Brown University Health, Providence, RI

Background: Glioblastoma (GBM) is the most common primary malignant brain tumor, marked by aggressive growth, angiogenesis, and invasion, with limited survival despite multimodal therapies. Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disorder of the central nervous system characterized by blood–brain barrier disruption and lymphocytic infiltration. Both are disorders of the white matter and optimal patient management remains undefined.

Methods: A systematic review was conducted using PubMed, Scopus, and Web of Science to identify cases of co-existing GBM and MS. Clinical characteristics, imaging findings, and survival outcomes were extracted from eligible cases. Survival outcome was estimated using Kaplan-Meier statistics and hazard ratio of prognostic factors was computed using penalized Cox regression modeling. A large real-world database (TriNetX) was also queried to estimate outcome from disease co-occurrence.

Results: Twenty-one patients were identified with concurrent GBM and MS. Most had relapsing-remitting MS (57%) with a median disease duration of 18 years prior to GBM diagnosis, and median age at the time of glioblastoma diagnosis was 55 years. Median overall survival (OS) was 3.0 months (95% CI 1.0-8.0). MS subtype, age, EDSS, or duration of the disease, were not associated with OS (all $p>0.05$). Longer progression-free survival (PFS) was significantly associated with improved OS (HR 0.3, $p=0.036$). patients with no or unknown DMT had a HR of 10.4 (95%CI 1.3–86.4, $p=0.030$) compared to the high-efficacy group. No differences in PFS were observed across DMT groups.

Higher baseline disability (Expanded Disability Status Scale, EDSS) showed a trend toward worse survival, with shorter median OS in patients with EDSS ≥6 compared to those with <6 (0.5 vs 4.0 months, $p=0.081$). MS subtype was not significantly associated with OS ($p>0.05$), though relapsing-remitting MS had the longest median survival numerically. Among patients with available imaging (n=19), Multiple sclerosis involvement in the brainstem or pons was associated with significantly shorter OS (log-rank $p=0.009$) and HR 4.5 (95%CI 1.4–15.0) ($p=0.015$).

Cerebellar involvement also indicated a trend for worsened survival HR 2.6 (95%CI 0.9–7.6) ($p=0.079$). Conversely, patients with periventricular lesions exhibited a better prognosis, HR 0.2 (95%CI 0.1–0.7) ($p=0.011$). GBM tumor location and MS–GBM spatial co-localization were not associated with survival. TriNetX was queried to estimate the frequency of co-occurrence. Only 33 cases were identified from 177-million patients (0.00002%) in this real-world database.

Conclusion: Co-occurrence of GBM and MS is rare and associated with poor patient outcomes. Higher EDSS and brainstem involvement appear to be adverse prognostic factors, whereas prior exposure to high-efficacy DMT is associated with improved survival, supporting a potential role for negative immune modulation of GBM outcome. Further validation in larger cohorts is warranted.

M388: Progressive Multifocal Glioblastoma in a Patient with Multiple Sclerosis: Case report

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Background: Multiple sclerosis is a chronic immune-mediated demyelinating disorder of the central nervous system characterized by blood-brain barrier disruption and lymphocytic infiltration. Glioblastoma is the most common primary malignant brain tumor, marked by aggressive growth, angiogenesis and invasion, with limited survival despite multimodal therapies.

Methods: Clinical data were obtained through review of the electronic medical record (Epic)

Results: Case Presentation: A 65-year-old woman with a 40-year history of relapsing-remitting multiple sclerosis presented with a new-onset focal seizure characterized by speech arrest and left-sided motor activity.

Neuroimaging revealed three homogeneously enhancing lesions in the right frontal and temporal white matter with surrounding edema and elevated relative cerebral blood volume, initially suggestive of lymphoma.

However, biopsy confirmed multifocal glioblastoma, IDH-wildtype and MGMT-unmethylated, with lymphocytic perivascular cuffing. Her multiple sclerosis had been managed with long-term glatiramer acetate for 20 years, with reduced relapse frequency before discontinuation one year before presentation. She underwent hypofractionated radiotherapy with

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concurrent temozolomide, followed by adjuvant therapy, demonstrating a mixed radiographic response. Despite further surgical resection and confirmation of temozolomide sensitivity on ex vivo testing, her clinical status progressively declined with worsening cognitive and motor deficits.
Subsequent treatments included corticosteroids, bevacizumab, and attempted initiation of everolimus, a novel approach. Cerebrospinal fluid analysis showed persistent oligoclonal bands without malignant cells, consistent with ongoing inflammation. The disease continued to progress, and she was transitioned to hospice care, ultimately succumbing 10.5 months after diagnosis.
Conclusion: Discussion: This case highlights the rare coexistence of multifocal glioblastoma and multiple sclerosis, both involving white matter pathology and associated with poor prognosis. The patient's tumor demonstrated atypical imaging features suggestive of lymphoma, potentially reflecting an underlying B-cell–mediated inflammatory response characteristic of multiple sclerosis. Long-term glatiramer acetate exposure may have contributed to a pro-tumorigenic microenvironment, although current evidence does not support an increased risk of malignancy
. Therapeutically, temozolomide offers potential dual benefit in glioblastoma and multiple sclerosis, while modified hypofractionated radiotherapy was utilized to minimize treatment-related neurotoxicity. Everolimus was selected as a second-line agent for its theoretical combined antineoplastic and immunomodulatory effects. Conclusion: Interpretation is limited by the single-patient design, multifocal disease burden, and non-standardized treatment approach. The off-label and late use of everolimus further restricts assessment of efficacy. Overall, this case underscores the complex interplay between neuroinflammation and tumor biology and should be considered hypothesis-generating for future studies, including consideration of Everolimus and other drugs, such as dimethyl fumarate, which may also provide dual activity through metabolic and immune pathway modulation.

M391: Levetiracetam Use and Survival Outcomes in Glioblastoma: A Systematic Review and Meta-Analysis

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Background: Levetiracetam (LEV) is widely used for seizure management in glioblastoma and has also been investigated for its potential antiproliferative effects; however its impact on overall survival (OS) and progression-free survival (PFS) remains uncertain. We evaluated whether LEV use is associated with improved OS and PFS in adults with histologically confirmed glioblastoma receiving standard-of-care surgery and temozolomide-based chemoradiotherapy.
Methods: We conducted a systematic review and meta-analysis of randomized and observational studies. Eligible studies evaluated perioperative or adjuvant LEV exposure and included a comparator group (no antiepileptic drugs or alternative agents). Adjusted hazard ratios (HRs) were pooled using a random-effects model. OS was the primary outcome; secondary outcomes included PFS, seizure control, and safety.
Results: Seventeen studies comprising 11,313 patients met inclusion criteria. LEV use was not associated with a statistically significant improvement in OS (pooled HR 0.88, 95% CI 0.76–1.01; $p = 0.08$; $I^2 = 73.8\%$). Pooled analyses likewise did not demonstrate a consistent benefit in PFS, although some individual studies reported longer median PFS with LEV. In observational cohorts, LEV was associated with improved seizure control and fewer adverse effects compared with enzyme-inducing antiepileptic drugs.
Conclusion: LEV use was not associated with a statistically significant improvement in OS or PFS in glioblastoma populations. Its favorable safety profile and seizure control support its continued use for tumor-related epilepsy rather than as a survival-modifying therapy.

M392-LB: Epimedin A Prevents Glioblastoma Growth and Invasion

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Background: Glioblastomas (U87) are an aggressive brain tumor that arises from glial cells and invades surrounding parts of the brain. The prognosis for glioblastoma is poor, with a median survival rate of 15 months with treatment. Treatments are aggressive with severe side effects. Molecular therapeutics are required to control U87 cell growth with a better safety profile. Several plant-derived compounds were tested for chemo preventive effects against glioblastoma. However, the role of Epimedin A, isolated from the genus of low-growing plants known as Epimedium (Horny Goat Weed), in preventing cancer growth is not clear. We examined the chemo preventive effects of Epimedin A in U87 cells. We specifically investigated the effects it has on cell proliferation, apoptosis, oxidative signaling, and migration.
Methods: Our results suggest that Epimedin A prevents the growth of U87 cells in a dose-dependent manner, with 60μM producing the greatest reduction in cell proliferation under EGF stimulation. Furthermore, Epimedin-A also prevented the invasion and migration of U87 cancer cells. Additionally, Epimedin A increased caspase-3 expression, as measured by PARP cleavage under EGF stimulation, and

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reduced the formation of reactive oxygen species. Epimedin A also regulates the expression of various pro- and anti-apoptotic proteins such as Bcl-x, HIF-1alpha, Bad, Bax, cleaved Caspase-3, Cytochrome C, SMAC/Diablo.

Results: Epimedin A has displayed inhibitory effects on U87 cells' viability. Specifically, studies showed inhibitory effects on proliferation, migration, and ROS. Further, Epimedin A regulates the expression of various pro- and anti-apoptotic factors and inflammatory markers in cancer cells. We next planned to examine its in vivo efficacy using nude mice xenografts. Thus, our results indicate that Epimedin A inhibits the growth of U87 cells and may act as a chemo preventive agent.

Conclusion: U87 cells obtained from ATCC were treated with an increasing concentration of Epimedin A (0-100 uM) ± EGF. Cell viability was examined using the MTT assay, while invasion and migration were assessed by scratch and transwell migration assays, respectively. Expression of various apoptotic proteins was measured by an antibody array. Reactive oxygen species levels were measured using fluorescence-based assay. Statistical comparisons were performed using one-sided t test for a prespecified directional hypothesis and reported using mean ± standard deviation.

M393: Case of Posterior Reversible Encephalopathy Syndrome or Leptomeningeal Disease? Exploring the diagnostic difficulty of AMS in advanced gastrointestinal malignancy

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Background: Altered mental status (AMS) is a frequent and diagnostically challenging presentation, particularly in patients with advanced malignancy. The differential diagnosis in this population is broad and includes metabolic derangements, medication or chemotherapy-related toxicity, infectious etiologies, paraneoplastic syndromes, and central nervous system involvement such as brain metastases or leptomeningeal disease. Leptomeningeal disease (LMD) is the dissemination of malignant cells within the leptomeninges and cerebrospinal fluid, a known but rare complication of solid tumors.

Leptomeningeal disease (LMD) is most commonly associated with breast cancer, lung cancer, and melanoma. Its occurrence in esophageal adenocarcinoma is exceedingly uncommon, with reported incidence rates of less than 1%. We present a diagnostically challenging case of AMS in a patient with esophageal malignancy.

Methods: A 65-year-old male with a metastatic esophageal adenocarcinoma, hypertension, and paroxysmal atrial fibrillation presented with subacute worsening of balance issues and acute onset of altered mental status. He had been having balance issues for two weeks before admission but per wife, was more confused and had speech changes over the last two days. On admission, systolic blood pressure was in the 190s. CT head, CTA, and EEG were unremarkable except for generalized edema. During his hospital stay, the patient developed visual disturbances and the leading diagnosis at that time was posterior reversible encephalopathy syndrome (PRES). However, symptoms persisted despite BP control, which raised concern for an alternative or concurrent diagnosis.

Results: An MRI was done and showed leptomeningeal enhancement concerning for cancer involvement. Lumbar puncture was completed, which confirmed malignant cells on cytology. He was treated with steroids and whole brain radiation with minimal improvement and was discharged on hospice.

Conclusion: This case expands the recognized clinical spectrum of leptomeningeal disease by illustrating its presentation in a patient with metastatic esophageal adenocarcinoma mimicking posterior reversible encephalopathy syndrome. It contributes to the limited body of literature documenting LMD in gastrointestinal malignancies and emphasizes the need for maintaining a broad differential diagnosis when evaluating altered mental status in cancer patients. Early consideration of atypical etiologies of AMS, even in the setting of seemingly classic presentations, is essential, as it has significant implications for prognosis, management, and goals of care discussions.

M394: Pain Outcomes in Patients With/Without Volumetric Tumor Response: Post Hoc From the ReNeu Trial of Mirdametinib in Adults & Children With Neurofibromatosis Type 1-Associated Plexiform Neurofibroma

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Background: Patients with NF1-PN commonly experience pain, which often negatively impacts health-related quality of life. In the pivotal trial of mirdametinib (ReNeu; NCT03962543), adults and children with NF1-PN reported significant improvements in worst tumor pain severity and pain interference at Cycle(C)13, the prespecified endpoint for pain outcomes in ReNeu. As MEK inhibitor–associated pain alleviation may be multifactorial, driven by target PN volume reduction and/or direct modulation of nerve pain signaling, target PN response may not solely determine pain improvement. This post hoc analysis evaluated pain changes from baseline in adults and children treated with mirdametinib who achieved a target PN confirmed response (responders) and those who did not (non-responders), at select time points.

Methods: In ReNeu, confirmed objective response was defined as a ≥20% reduction from baseline in target PN volume on

≥2 consecutive MRI scans within 2 to 6 months. Patient- or parent proxy-reported pain outcomes were assessed at baseline and during the 28-day treatment cycles using Numeric Rating Scale-11 (NRS-11) and Pain Interference Index (PII) total scores. Change from baseline to C5, C9, and C13 for NRS-11 and PII are reported (1) vs target PN volume change and (2) by responder status, in both adults and children.

Results: Of 58 adults and 56 children who received mirdametinib, 41% (n=24) and 52% (n=29), respectively, achieved a confirmed objective response during the 24-cycle treatment phase. Mirdametinib significantly improved pain outcomes for adults (NRS-11 and PII, both P<.001) and children (NRS-11 and PII [patient- and parent proxy-reported], all P<.05) at C13 relative to baseline. Weak to moderate correlation (Spearman rank) was found between percentage change in target PN volume and change in NRS-11 or PII total scores from baseline to C13 in adults (NRS-11, ρ=.418; PII, ρ=.092, respectively) and children (NRS-11, ρ=.128; PII, patient-reported ρ=.138, parent proxy-reported ρ=-.108). There was no significant difference between responders and non-responders in the magnitude of reduction from baseline (ie, improvement) to C13 in mean NRS-11 or PII total scores in adults or children. C5 and C9 results were consistent with C13.

Conclusion: Patients with NF1-PN previously reported pain improvement with mirdametinib, but the contribution of target PN response was unknown. This analysis demonstrates that adults and children may derive symptomatic benefit in pain outcomes with mirdametinib treatment independent of radiographic response.

M395: Transcriptomic Meta-Analysis and Functional Validation Identify a Long Non-Coding RNA Network that Governs Zika Virus Oncolysis in Glioblastoma Multiforme

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Background: Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor, with a median survival under two years despite maximal therapy. Zika virus has emerged as a candidate oncolytic agent due to its selective tropism for rapidly proliferating neural progenitor-like cells, including GBM stem cells. While Zika-mediated GBM cell killing is reproducible, the molecular mechanisms governing oncolytic efficacy, especially the role of long non-coding RNAs (lncRNAs), remain poorly defined.

Methods: We performed a transcriptomic meta-analysis of four publicly available RNA-sequencing datasets from Zika-infected GBM and neuroblastoma (NBM) models, with NBM serving as a comparator outgroup. Differential gene expression (FDR ≤ 0.05) and pathway enrichment analyses identified conserved molecular signatures. Candidate lncRNAs were prioritized through hypothesis-free screening. Four candidates (MELTF-AS1, TIPARP-AS1, NR2F1-AS1, SLC9A3-AS1) underwent functional validation through siRNA-mediated knockdown in GBM cell lines (U87 and A172), with and without Zika infection, assessed by CellTiter-Glo viability assay (6-8 biological replicates).

Results: Meta-analysis identified a shared transcriptional response in Zika-infected GBM cells, including upregulation of TNF, NF-κB, and p53 signaling pathways, and 31 consistently dysregulated lncRNAs unique to GBM, with no overlap in NBM. Zika infection alone reduced cell viability in both lines in a time-dependent manner. Silencing MELTF-AS1 reduced baseline viability by ∼70% in both cell lines at 96 hours and further enhanced Zika-induced cytotoxicity, consistent with its oncogenic pro-survival role. In contrast, knockdown of TIPARP-AS1 increased A172 viability to 314% of control at 120 hours under Zika infection, while SLC9A3-AS1 silencing increased viability by 126-303% across cell lines, suggesting context-dependent roles that diverge from predicted oncogenic function. NR2F1-AS1 silencing produced more modest, cell line-dependent attenuation of oncolysis.

Conclusion: These findings identify MELTF-AS1 as a pro-survival lncRNA whose silencing enhances Zika-mediated cytotoxicity, and TIPARP-AS1, NR2F1-AS1, and SLC9A3-AS1 as facilitators of viral oncolysis whose loss attenuates cell death. Together, these results refine the mechanistic understanding of Zika oncolysis and highlight lncRNA targets for further investigation as adjuncts to oncolytic virotherapy in GBM.

M396: Trends in mortality from Primary Malignant Brain Neoplasms in the United States from 1999-2024: A CDC WONDER analysis

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Background: Primary malignant brain neoplasms are aggressive, often fatal central nervous system tumors, with prognosis remaining dismal despite therapeutic advances. Demographic and geographic mortality patterns, however, remain incompletely characterized. This study analyzes CDC WONDER data to assess malignant brain neoplasm mortality trends in the United States from 1999 to 2024.

Methods: We conducted a retrospective CDC WONDER analysis (1999–2024) using ICD-10 followed by C71.0 to C71.9 (Malignant neoplasm of the brain). Age-adjusted mortality rates (AAMR) were stratified by sex, race, census region, and urbanization. Joinpoint regression calculated Annual Percent Change (APC) and Average Annual Percent Change (AAPC) with $p<0.05$.

Results: From 1999 to 2024, 594,618 deaths were reported. The overall age-adjusted mortality rate (AAMR) decreased non-significantly from 1999 to 2024, with an AAPC of -0.1107 (95% CI: -0.2913 to 0.0703). Males exhibited higher mortality than females (8.21 vs. 5.54 per 100,000 population) in 2024. Males showed a significant overall decrease (AAPC: -0.2916*, $p = 0.0247$), with a significant decrease from 1999–2006 (APC: -1.4339*, $p = 0.00007$), followed by a significant increase from 2006–2020 (APC: 0.4553*, $p = 0.0002$), then a non-significant decrease from 2020–2024 (APC: -0.8839, $p = 0.1212$).

Females showed a non-significant overall decrease (AAPC: -0.1138, $p = 0.2415$), with a significant decrease from 1999–2006 (APC: -1.3665*, $p = 0.0002$) followed by a significant increase from 2006–2024 (APC: 0.3776*, $p = 0.00001$). Among White individuals, AAMR increased non-significantly across the full study period (AAPC: 0.0181, $p = 0.8304$). Regionally, the Midwest showed a non-significant decrease from 1999–2024 (AAPC: -0.0953, $p = 0.3594$). In the South, the overall trend was significant and decreasing (AAPC: -0.2215*, $p = 0.0297$). By urbanization, large central metro areas showed a non-significant overall decrease from 1999–2020 (AAPC: -0.3664, $p = 0.0795$), whereas medium metro areas demonstrated a non-significant decrease (AAPC: -0.3342, $p = 0.3589$). Adults aged 75–84 years exhibited the highest mortality (22.81 per 100,000 in 2024) and showed a significant increase from 1999–2024 (AAPC: 0.4338*, $p = 0.000003$).

Conclusion: Primary malignant CNS neoplasms reveal stark mortality disparities across age, sex, race, and geography. These findings expose critical gaps in equitable access to surgical resection, molecular diagnostics, and targeted therapies. Urgent, coordinated neuro-oncologic and health systems interventions are needed to address this underrecognized public health crisis

M397*: Heterogeneity in Tissue Modeling for Tumor Treating Fields Dosimetry: Implications for Field Distribution in the Brain

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Background: Tumor Treating Fields (TTFields) therapy is a validated treatment for glioblastoma, used alongside surgery, radiotherapy, and chemotherapy. A fundamental question in TTFields computational modeling involves whether assigning distinct conductivity values to gray and white matter affects electric field distributions, or whether simplifying these tissues as a homogeneous medium would suffice.

Methods: T1-weighted MR datasets from n=56 models (28 patients) were segmented. Three experiments were conducted: (1) swapping gray matter (GM) and white matter (WM) conductivities (n=42), (2) assigning WM conductivity to all soft tissue, and (3) assigning a singular conductivity value at $\sigma=0.2$ S/m to all soft tissue. Plan quality metrics (PQMs) for electric field intensity (E), specific absorption rate (SAR), and current density (CD) were evaluated at 95%, 50%, and 5% coverage levels for gross tissue volume (GTV), scalp, GM, and WM. Paired t-test was used to determine statistical significance.

Results: Modifying soft tissue conductivity produced statistically significant changes in all PQMs compared to homogeneous modeling (all $p<0.001$). E coverage at GTV increased 130-176% (E95%), while SAR increased 380-559% depending on conductivity assumption. SAR95% at the scalp increased up to 21,170% with $\sigma=0.2$ S/m and 8,959% with $\sigma=$WM. Current density showed similar increases of 109-145% at the GTV and up to 4,350% at the scalp. Swapping GM and WM conductivities produced minimal changes at the GTV (<10%, mostly non-significant, $p>0.05$), indicating target dose predictions are robust to GM/WM segmentation uncertainty. Local tissue effects were observed: GM tissue showed 14-19% increased E-field when assigned WM conductivity, while WM tissue showed 15-20% decreased E-field when assigned GM conductivity.

Conclusion: While GM/WM property swapping produces modest but statistically significant metric variations, assigning

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all soft tissue with a homogeneous conductivity value dramatically overestimates field intensities across all structures. These findings underscore the importance of personalized tissue conductivity assignment in computational TTFields modeling for treatment planning.

M398: The Natural History of Lymphomatosis Cerebri: An Analytical Assessment

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Background: Lymphomatosis cerebri (LC) is a rare manifestation of primary central nervous system lymphoma characterized by diffuse white-matter infiltration. LC is often misdiagnosed as demyelinating disease or other inflammatory conditions because of its diffuse neuroimaging appearance. Given its rarity, prognostic factors and optimal treatment remain unclear. We performed an analytical assessment of published LC cases.

Methods: Case reports and series published from 1995 through 2024 were identified in PubMed using the search term "lymphomatosis cerebri." Demographic, clinicopathologic, cerebrospinal fluid, treatment, and survival data were extracted. Overall survival (OS), time from first treatment to progression, symptom onset to diagnosis, and symptom onset to death were analyzed using Kaplan–Meier and log-rank methods. Prognostic factors were evaluated by age, lymphoma subtype (B- vs T-cell), duration of corticosteroid use, and cerebrospinal fluid parameters. Survival outcomes from various treatment regimens were assessed by Kruskal-Wallis testing, and post-mortem trends over time were fitted to Poisson models.

Results: Ninety-one LC cases from 56 publications were identified. Median age at presentation was 57 years. Among 78 cases with analyzable survival data, median OS was 4.0 months (95%CI 1.1–11.0). Median intervals from symptom onset to diagnosis and death were 4.0 and 11.0 months, respectively. The median symptom-onset-to-diagnosis interval declined numerically from 6.8 months in 1995–2000 to 3.5 months in 2021–2024 (R^2=.794, P=.109). OS showed no significant temporal trend (R^2=.813, P=.098). Patients aged ≤57 years had
longer OS than those aged >57 years (13.5 vs 1.3 months, P=.012). Compared to cases with corticosteroid use only after diagnosis, cases with corticosteroid exposure prior to diagnosis had shorter OS (13.5 vs 1.3 months, P=.001) and a longer symptom-onset-to-diagnosis interval (4.0 vs 6.0 months, P=.010). Age-adjusted Cox model revealed prediagnosis corticosteroid exposure was associated with a higher mortality (HR 3.77, 95%CI 1.65–8.61, P=.002). Post-mortem diagnosis was identified in 22 of 90 cases (24.4%).

Conclusion: Patients with LC have poor survival, but those with younger age at diagnosis have a better outcome. Documented corticosteroid exposure before diagnosis is associated with shorter survival and a longer symptom-onset-to-diagnosis interval. Corticosteroid use prior to LC diagnosis may delay initiation of effective treatment.

Neuro-Opthalmology and Neuro-Vestibular Disease

M399: Safety and Efficacy of Intravenous Recombinant Tissue Plasminogen Activator in Acute Central Retinal Artery Occlusion: A Systematic Review and Meta-Analysis

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Background: Central retinal artery occlusion (CRAO) is a neuro-ophthalmological emergency characterized by vision loss attributable to obstruction of blood flow through the central retinal artery (Schrag, 2015; Dagra, 2024). An effective treatment for CRAO remains lacking, despite a relatively broad therapeutic window ranging from approximately 4.75 to 23.43 hours (Schumacher, 2010). Therefore, we performed a systematic review and meta-analysis to compare the safety and efficacy of intravenous recombinant tissue plasminogen activator (rt-PA).

Methods: A systematic review of PubMed, Embase, and Cochrane library was conducted through March 2026 to identify studies comparing r-tPA versus standard therapy in patients with acute CRAO. Meta-analysis inclusion criteria followed Cochrane guidelines. Two reviewers independently extracted data and assessed study quality. Risk of bias was determined using the ROBINS-1 and ROB-2 tools. We calculated pooled rates and odds ratio (OR) for clinical recovery, defined as a final logMAR ≤0.7, with corresponding 95% confidence interval (CI). Mean difference (MD) with 95% CI were used to compare best-corrected visual acuity (BCVA) between groups. Risk ratio (RR) with 95% CI were employed to assess adverse events. A random-effects model was applied for all analyses.

Results: We included a total of 4 studies (2 observational and 2 RCTs) comprising 310 patients. Intravenous rt-PA was associated with a significant improvement in best-corrected visual acuity compared with standard therapy (MD −0.29; 95% CI −0.51 to −0.06; $p = 0.01$; $I^2 = 0\%$). There was no significant difference in clinical recovery between groups (

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OR 1.88; 95% CI 0.74 to 4.81; p = 0.19; I^2 = 56%). Similarly, the risk of adverse events was comparable between rt-PA and standard therapy (RR 0.80; 95% CI 0.35 to 1.81; p = 0.59; I^2 = 0%).

Conclusion: In acute CRAO, intravenous rt-PA improves visual acuity without increasing adverse events, although no significant benefit in clinical recovery was observed. These results support further investigation in adequately powered randomized trials.

M400: Peduncular Hallucinosis with Palato-Ocular Myoclonus Secondary to Ponto-Mesencephalic Hemorrhage: A Rare Dual-Pathway Brainstem Syndrome

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Background: Peduncular hallucinosis features vivid, complex visual hallucinations with preserved insight, classically linked to midbrain or thalamic lesions.[1,2] Palato-ocular myoclonus arises from disruption of the dentato-rubro-olivary pathway within the Guillain–Mollaret triangle, causing hypertrophic olivary degeneration.[2,3] Their simultaneous occurrence from a single pontine lesion is rarely reported.

Methods: Single case report with clinical, radiological, and neurophysiological correlation.

Results: A man in his 40s with poorly controlled hypertension presented with dorsal ponto-mesencephalic haemorrhage complicated by respiratory failure, ophthalmoplegia, dysarthria, dysphagia, and right-sided weakness. He subsequently developed pendular ocular oscillations and palatal tremor consistent with palato-ocular myoclonus, followed by recurrent vivid hallucinations of unfamiliar individuals working and dancing, predominantly during fatigue and sleep disturbance, with preserved insight throughout.[7] MRI confirmed dorsal pontine haemorrhage without cortical involvement. Primary psychosis, [4] Charles Bonnet syndrome, [5] seizures, delirium, [6] and medication-induced hallucinations were excluded.

Quetiapine 50 mg twice daily significantly reduced hallucination frequency and distress via 5-HT2A antagonism and restoration of thalamocortical gating of the disinhibited ponto-geniculate-occipital pathway.[10] Gabapentin was restarted for tremor via GABAergic modulation of inferior olivary oscillations. [9] References 1. Lhermitte J. Rev Neurol. 1922;38:1359–65. 2. Guillain G, Mollaret P. Rev Neurol. 1931;2:545–66. 3. Goyal M, et al. AJNR. 2000;21:1073–77. 4. Manford M, Andermann F. Brain. 1998;121:1819–40. 5. Ffytche DH. Curr Psychiatry Rep. 2005;7:168–79. 6. Kumral E, et al. J Neurol. 2002;249:1659–70. 7. Benke T. J Neurol. 2006;253:1561–71. 8. Mocellin R, et al. Aust N Z J Psychiatry. 2006;40:742–51. 9. Samuel M, et al. Brain. 2004;127:1248–68. 10. Limousin N, et al. Sleep Med Rev. 2008;12:367–76.

Conclusion: A single ponto-mesencephalic haemorrhage simultaneously disrupted two anatomically convergent brainstem circuits: the dentato-rubro-olivary pathway producing palato-ocular myoclonus,[9] and the pontine–geniculate–occipital pathway generating peduncular hallucinosis through disinhibition of REM-related visual networks.[8,10] Recognising this dual-pathway syndrome prevents misattribution to primary psychiatric illness and guides appropriate management with GABAergic agents and low-dose atypical antipsychotics.

M402: Interocular Microvascular Asymmetry Selectively Associates with Verbal Memory Performance

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Background: The retinal microvasculature mirrors cerebrovascular health and correlates with cognitive performance. Although retinal imaging offers a non-invasive assessment of cerebral structure and function, thus far only inter-eye differences and fair right-left eye correlations have been reported in prior studies. Herein, we evaluated the correlations between single-eye and inter-ocular differences in retinal microvascular measures with cognitive performance in a cohort of cognitively intact individuals.

Methods: Bilateral macula-centered color fundus photographs from 280 cognitively intact participants were analyzed using Automorph. After quality control, 121 left-eye and 138 right-eye images were retained. Six microvascular features (vessel density, tortuosity density, squared curvature tortuosity, distance tortuosity, fractal dimension, and vessel caliber) were automatically quantified across the entire region, zone B and Zone C, for all vessels, arteries and veins. We derived interocular asymmetry as the absolute inter-eye difference (diff[abs] = |left − right|). Cognitive measures included Rey Auditory Verbal Learning Test (AVLT), Trail Making Test-B (TMT-B), WAIS Digit Symbol Substitution (WAIS-DSS), and Complex Figure Test (CFT). Linear regression models evaluated the associations between retinal microvascular features and cognitive scores, adjusted for age, sex, and education (Model 1), and additional cardiovascular risk factors (Model 2).

Results: Among all microvascular features, the interocular difference in squared curvature tortuosity within Zone B (all vessels) showed the strongest and most consistent positive association with AVLT (p = 0.0021, Cohen's d = 0.698, β = 0.105, partial correlation= 0.330, 95% CI [0.039–0.170]), robust to cardiovascular risk factors adjustment (p = 0.0022, unchanged effect estimates). Higher tortuosity was associated with better AVLT, suggesting that reduced squared curvature tortuosity may reflect early verbal memory decline. This feature was not significantly associated with TMT-B (p = 0.425, Cohen's d = -0.176) nor WAIS-DSS (p = 0.664, Cohen's d = -0.096or CFT, indicating selectivity for verbal memory. Across all microvascular features that were significantly associated with AVLT, interocular absolute difference achieved larger effect sizes than their single-eye

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counterparts. Zone B was the most sensitive region for AVLT-related microvascular changes, for both arteries ($p = 0.039$, Cohen's $d = 0.460$) and veins ($p = 0.038$, Cohen's $d = 0.462$).

Conclusion: The interocular asymmetry of squared curvature tortuosity in macula-centered Zone B is a domain-specific biomarker that selectively and robustly associates with verbal memory, outperforming single-eye measurements and independent of executive function, non-verbal memory and processing speed. Interocular retinal microvascular asymmetry is a promising non-invasive approach for verbal memory performance screening and monitoring.

M403: Type 1 Cryoglobulinemia Presenting with Sequential Bilateral Ophthalmoplegia and Ophthalmic Venous Outflow Obstruction

Presenting Author(s): *Julieta Serobyan, BS, Los Angeles, CA*
Co-Author(s): *Irma Zhang, MD, MS, MHS, UCLA Department of Neurology, Los Angeles, CA, Robert del Carlo, Los Angeles, CA, Roger Woods, Los Angeles, CA*

Background: Cryoglobulinemia involves cold-precipitable immunoglobulins that can cause systemic vascular complications. Type I cryoglobulinemia, driven by monoclonal immunoglobulin production, primarily affects the skin and kidneys through hyperviscosity and vascular occlusion. Central nervous system involvement is uncommon (<5%), and cranial neuropathies are rare. Reported neurologic manifestations include ischemic stroke, encephalopathy, and peripheral neuropathy, while orbital and ophthalmic venous involvement is only rarely described. We present an unusual case of cryoglobulinemia with sequential bilateral ophthalmoplegia and orbital venous outflow abnormalities, initially concerning for a primary thrombotic process.

Methods: A 71-year-old woman with a history of Hashimoto's thyroiditis, pulmonary hypertension, irritable bowel syndrome, and fibromyalgia presented with severe headache and diplopia on lateral gaze. She was initially evaluated at an outside hospital for right eye pain and ophthalmoplegia, which improved with corticosteroids. Three weeks later, she developed worsening headache, retro-orbital pain, and diplopia on left gaze.

Results: Examination revealed bilateral impaired eye abduction, diffuse musculoskeletal pain, and non-blanching violaceous patches on the heels and plantar surfaces. Funduscopic examination and lumbar puncture were unremarkable. MRI and CT angiography demonstrated an abnormal vascular structure suggestive of a venous varix. Ophthalmic vein thrombophlebitis was initially suspected, and anticoagulation was started. Further evaluation revealed high-titer antinuclear antibodies (ANA, 1:640), hypocomplementemia (low C3/C4), and positive cryoglobulins. Infectious, antineutrophil cytoplasmic antibody (ANCA)-associated workup, and myasthenia gravis studies were negative. Serum immunofixation demonstrated a faint monoclonal free lambda light chain. Serum IgG was normal and IgM decreased prior to plasma exchange; both were subsequently low post-treatment. Total protein was not significantly elevated. These findings supported type 1 cryoglobulinemia with features raising concern for an underlying monoclonal process. High-dose corticosteroids alone did not result in improvement. The patient underwent five days of plasma exchange with marked improvement in ophthalmoplegia, headache, and cutaneous findings. She was discharged on a prednisone taper and is now on rituximab. She is undergoing further evaluation for an underlying hematologic disorder.

Conclusion: This case highlights a rare presentation of Type 1 cryoglobulinemia with sequential bilateral ophthalmoplegia, likely due to cranial nerve VI involvement and impaired orbital venous outflow. The initial presentation mimicked a thrombotic process; however, systemic findings, hypocomplementemia, and positive cryoglobulins supported the diagnosis of cryoglobulinemia, with suspicion of type I process leading to hyperviscosity that exacerbated flow through a known orbital vascular malformation.

Recognition of this atypical presentation is important, as timely treatment with immunosuppression and plasma exchange can result in significant clinical improvement and prevent unnecessary interventions.

Awards

The Grass Foundation – ANA Award in Neuroscience

The Interictal Network as a Window into Epilepsy

Presenting Author: *Erin Conrad, MD, MA, University of Pennsylvania*

Abstract: How is the epileptic brain network altered in the interictal state—the periods between seizures? Although seizures define epilepsy clinically, patients spend the vast majority of their lives outside of seizures, in a persistent but poorly understood pathological brain state. My laboratory studies this interictal network state as a measurable, dynamic substrate of epilepsy, using quantitative analysis of scalp and intracranial EEG together with electrical stimulation to define its structure, excitability, and capacity for change.

Our lab's first line of work addresses a fundamental limitation in epilepsy surgical planning: the brief EEG monitoring window captures only a subset of seizure onsets, contributing to missed epileptogenic regions and postoperative failure. By characterizing abnormalities in the interictal background, we overcome this temporal sampling bias. Quantitative analysis of interictal spike patterns and network connectivity localizes seizure generators and identifies epileptogenic tissue without relying on seizure capture, offering a more complete picture of the epileptic network.

Our second line of work develops interictal EEG as a biomarker of disease severity and treatment response. Current assessment of antiseizure medication efficacy is largely trial-and-error, with success judged months later by changes in seizure frequency. Medications act continuously on the brain, however, altering the interictal network before seizures change. We demonstrate in children with genetic epilepsies that quantitative EEG features predict functional status, supporting their use as early, objective indicators of

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therapeutic response. Ongoing work extends these models across epilepsy subtypes to enable personalized tracking of seizure burden and medication response.

Our third line of work uses electrical stimulation as a causal probe of interictal network excitability. Stimulation-evoked responses vary substantially over time within individuals, modulated by stimulation history and ongoing network state. These findings establish that interictal excitability is dynamic and measurable, motivating longitudinal tracking of how it evolves as seizures approach and how it can be reshaped by neuromodulation.

Together, these investigations leverage epilepsy as a model system for understanding how human brain networks deviate from—and return toward—stable function.

Wolfe Research Prize for Identifying New Causes or Novel Treatment of Neuropathy and Related Disorders

Past, Present, and Future: The Role of Genomics in Elucidating Peripheral Neuropathies

Presenting Author: *Stephan Zuchner, MD, PhD, University of Miami*

Abstract: Peripheral neuropathies have been transformed by genomic studies, from now classic disease-gene discoveries to today's next-generation sequencing approaches and sophisticated bioinformatics. Work from the Zuchner lab and collaborators illustrates this trajectory, beginning with landmark discoveries such as MFN2 as the major cause of axonal nerve degeneration, through the resolution of the 'common' SORD gene–pseudogene locus, to current structural variant studies using long-read genomes. Together, these advances have profoundly reshaped the diagnosis and classification of inherited neuropathies over the past 20 years. Gene discoveries have revealed convergent mechanisms of axonal degeneration and survival, as well as Schwann cell integrity. Still, a major diagnostic gap remains, and our continued efforts to provide open data platforms and coordinate multi-site research studies will be essential to elucidate genetic and non-genetic forms of neuropathy. Looking forward, we embrace a genomics-to-therapy paradigm that is already creating growing opportunities for therapeutics and clinical trials.

Derek Denny-Brown Young Neurological Scholar Award - Physician-Scientist Clinical

Multiple Sclerosis in Africa: Changing Paradigms and Improving Diagnosis and Access to Care

Presenting Author: *Deanna Saylor, MD, MHS, FAAN, FANA, University of North Carolina Chapel Hill*

Abstract: Multiple sclerosis (MS) has traditionally been considered a rare disease in Africa. However, emerging evidence suggests that MS is instead under-recognized and underdiagnosed in settings with limited neurology workforce capacity, restricted access to neuroimaging, and few disease-specific resources. This lecture will discuss the evolving understanding of MS in Africa and efforts to improve diagnosis and access to care across the continent. This work includes the Zambia Multiple Sclerosis Study, a prospective cohort study and national registry that has characterized disease course, risk factors, comorbidities, outcomes, and contributors to diagnostic delay among people with MS in Zambia. Additional studies across Africa have examined barriers to MS diagnosis and treatment and demonstrated associations between reported MS prevalence and indicators of healthcare access, including health expenditure and MRI availability. The lecture will also highlight collaborative efforts to strengthen MS care infrastructure, including development of the first demyelinating disease registry in Ghana, a multinational study of the impact of HIV on MS, and the development of treatment guidance for resource-limited settings that contributed to inclusion of three MS disease-modifying therapies on the World Health Organization Essential Medicines List.

Derek Denny-Brown Young Neurological Scholar Award - Physician-Scientist Basic

Inflammatory Signaling in the Leptomeninges

Presenting Author: *Adrienne Boire, MD, PhD, FANA, Memorial Sloan-Kettering Cancer Center*

Abstract: The Boire lab studies leptomeningeal metastasis as a means to understand the principles of metastasis as well as the nervous system's relationship to the larger organism. In health, the leptomeninges maintain neural homeostasis and provide a route of biochemical communication between the periphery and the central nervous system. Leptomeningeal metastasis wreaks havoc with the homeostatic capacities of the CSF leading to neurological disabilities and death. We seek to understand neuroanatomically where and mechanistically how cancer cells become competent to enter into the leptomeninges so that we may block leptomeningeal metastasis before it begins. Once within the leptomeninges, cancer cells face profound metabolic challenges including low extracellular iron, hypoxia, and low extracellular lipid. We investigate how cancer cells overcome these metabolic constraints so that we may interrupt this signaling and arrest cancer cell growth in the space. This work is under active translation as a Phase 1 clinical trial, NCT05184816. Recent basic work in the laboratory has focused on understanding the robust, but ultimately futile immune response in this space: We transcriptionally and proteomically interrogated human specimens, identifying Interferon-as a key mediator of leptomeningeal anti-cancer response. We generated immunocompetent mouse models recapitulating human disease and found that interferon-'s anticancer activity in the leptomeninges bypasses the adaptive immune system. Instead,

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interferon-drives maturation of leptomeningeal dendritic cells in an antigen-independent manner through the cytotoxic action of natural killer cells. Leptomeningeal metastasis therefore demands a unique approach to immune therapy. We are currently investigating inflammatory signaling between cancer cells and leptomeningeal fibroblasts as a possible mechanistic bottleneck dictating cancer growth within the leptomeninges.

Derek Denny-Brown Young Neurological Scholar Award – Neuroscientist

TDP-43 Loss of Function as a Convergent Driver of ALS Pathophysiology

Presenting Author: *Evangelos Kiskinis, PhD, Northwestern University Feinberg School of Medicine*

Abstract: Nuclear depletion and cytoplasmic aggregation of the RNA-binding protein TDP-43 are pathological hallmarks of nearly all cases of amyotrophic lateral sclerosis (ALS) and approximately half of frontotemporal dementia (FTD) patients. However, the molecular mechanisms by which TDP-43 dysfunction contributes to neurodegeneration remain incompletely understood. Using human induced pluripotent stem cell (iPSC)-derived neuronal models, postmortem patient tissue, transcriptomics, proteomics, and functional electrophysiology, our laboratory has sought to define convergent disease mechanisms downstream of TDP-43 pathology.

In this presentation, I will discuss recent work demonstrating that TDP-43 loss of function drives widespread defects in RNA processing, neuronal physiology, and neuroimmune signaling. We identified disease-specific mis-splicing of KCNQ2, a voltage-gated potassium channel critical for regulating neuronal excitability, resulting in production of a non-functional channel isoform that triggers intrinsic hyperexcitability in ALS/FTD neuronal models. We have also uncovered disruption of UPF1-dependent RNA surveillance and alternative polyadenylation pathways in TDP-43-deficient neurons. In parallel, I will highlight new findings from integrated single-cell transcriptomic and spatial proteogenomic analyses revealing marked peripheral-to-central immune remodeling in ALS that correlates with TDP-43 dysfunction and motor neuron pathology. Finally, I will discuss how these discoveries are enabling development of targeted RNA-based therapeutic strategies for ALS.

Together, our work supports a model in which TDP-43 dysfunction acts as a convergent driver of ALS pathophysiology by disrupting RNA metabolism, neuronal excitability, proteostasis, and neuroimmune homeostasis.

ANA Rising Star Award

Inducing a Torpor-Like State Through Targeted Preoptic Circuit Activation Protects the Brain After Stroke

Presenting Author: *Eric Landsness, MD, PhD, Washington University in St. Louis*

Abstract: Ischemic stroke remains a leading cause of long-term neurological disability, and despite decades of investigation, no FDA-approved cerebroprotective therapies currently exist. Therapeutic hypothermia has shown robust protection in experimental stroke models but has failed clinically, in part because externally imposed cooling triggers metabolically costly counter-regulatory responses. In contrast, naturally occurring states such as torpor achieve reductions in temperature through coordinated regulation of thermogenesis, metabolism, and behavioral state and are associated with remarkable tolerance to physiological stress.

Our work investigates whether selective activation of genetically defined thermoregulatory circuits can induce a torpor-like state that is associated with acute cerebroprotection after ischemic injury. Using chemogenetic approaches in mice, we selectively activated kappa opioid receptor–expressing neurons within the preoptic area of the hypothalamus ($POAKOR^+$ neurons), a neuronal population involved in regulation of body temperature and energy expenditure. Activation of $POAKOR^+$ neurons after transient middle cerebral artery occlusion induced a sustained hypothermic and hypometabolic state associated with reduced infarct volume and improved early motor outcomes. Importantly, these protective effects were attenuated when body temperature was maintained at normothermia despite neuronal activation, supporting a temperature-dependent component of protection.

To investigate the biochemical organization of this state, we performed untargeted metabolomic and lipidomic profiling of whole brain tissue following $POAKOR^+$ activation. These analyses revealed coordinated remodeling of nucleotide, phospholipid, sphingolipid, and energetic metabolic pathways, suggesting that regulated hypothermia engages broader systems-level metabolic programs beyond passive cooling alone.

Together, these findings support the concept that selective engagement of endogenous thermoregulatory circuitry can induce a regulated torpor-like state associated with cerebroprotection. More broadly, this work highlights the potential translational relevance of neural circuit–based approaches for studying metabolism, hypothermia, and brain resilience after ischemic injury.

Audrey S. Penn Lectureship Award

Health Disparities: A Historical and Contemporary View Through the Lens of Stroke

Presenting Author: *Olajide Williams, MD, MS, FANA, Columbia University*

Abstract: This talk traces the roots of health disparities from 1619 to present day America through the lens of stroke. It examines how structural racism contributes to stroke disparities by shaping social determinants of health and downstream biological risk. The presentation reviews key insights from stroke epidemiology, explores the relationship between

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upstream inequities and social risk factors, and highlights randomized controlled trials that offer potential strategies to improve risk factor control, health literacy, and stroke outcomes.

ANA2026 Plenary Abstracts

Saturday, October 17, 2026 - Opening Symposium: The Role of CAR T-Cells in Changing the Therapeutic Algorithm in Autoimmune Neurology

The Role of CAR T-Cells and Why They Promise to Change the Therapeutic Algorithm in Autoimmune Neurology: Experience from Stiff Person Syndrome and Myasthenia Gravis

Author: *Marinos Dalakas, MD, PhD, FANA, Thomas Jefferson University*

T cells, genetically modified to express Chimeric Antigen Receptors (CAR T), are showing promising benefits in patients with refractory autoimmune neurological diseases 2-3 months after therapy (1). Based on our experience in a series of 26 patients with therapy-refractory antibody-positive SPS and several others with MG, CARs targeting CD19-positive, antibody-secreting, long-lived plasma cells and plasmablasts, demonstrated impressive, long-lasting, and drug-free clinical improvements with signs of immune reset shifting immunity to a healthy state (2). The presentation will elaborate on these results and discuss the future trajectory of CARs as a promising means destined to change the present therapeutic algorithm in all disability-building neuroautoimmunites because, in contrast to currently approved biologics that selectively target one immunoregulatory factor, the CD19 CAR T-cells exert effects even beyond B cells or non-pathogenic antibodies like anti-GAD, as they cross the blood-brain barrier and lymphoid tissues and expand as “living cells” to memory cells ensuring sustained benefits even in two different autoimmune diseases in the same patient, like SPS and MG (1,3). CAR T-cells are likely to be more effective if applied in the early stages of disability development when patients reach early-active/refractory status rather than waiting for very late disease progression when neurological deficits might be irreversible (3).

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CAR-T Cell Treatment in CNS Autoimmunity

Author: *Scott Zamvil, MD, PhD, FAAN, FANA*

Chimeric antigen receptor (CAR)-T cells are rapidly being advanced for treatment of CNS autoimmune diseases and for many other conditions. First, I will describe the development and immunologic basis for CAR-T cell therapy. Anti-CD19 and anti-BCMA CAR-T cells promote depletion of B cells at different stages of B cell differentiation. Anti-CD19 CAR-T cells target and eliminate naive, immature and mature memory B cells whereas anti-BCMA CAR-T cells eliminate antibody-secreting plasmablasts and plasmablasts. I will describe initial studies testing anti-CD19 CAR-T cells, which have shown promise in multiple sclerosis (MS), stiff person syndrome (SPS) and MOG antibody-associated disease (MOGAD). Anti-BCMA shown benefit in initial testing in neuromyelitis optica spectrum disorder (NMOSD) and could have a role in treatment of progressive MS.

Several different types of CAR-T cells are in development or are beginning to be tested in patients with autoimmune conditions. Here, I will describe the features of allo-CAR-T and in vivo CAR-T cells. Other novel CAR-T cell constructs have been tested in models of autoimmunity and may soon be applied to treatment of CNS diseases. Myelin antigen-specific CAR-T cells have been effective treatment of MS models. SynNotch technology provides a method to selectively deliver anti-inflammatory cytokines and other molecules (i.e. a "payload") to one tissue. I will describe how SynNotch has been successfully employed to deliver anti-inflammatory IL-10 in treatment of CNS autoimmunity.

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CAR T-Cell Therapy in Autoimmune Encephalitides and Insights into Neurotoxicity Risk in Oncology Patients

Author: *Josep Dalmau, MD, PhD, FANA, Institute for Biomedical Investigations - CaixaResearch Institute*

CAR T-Cell Therapy in Autoimmune Encephalitides and Insights into Neurotoxicity Risk in Oncology Patients Autoimmune encephalitides (AE) comprise an expanding group of antibody-mediated disorders characterized by marked clinical

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heterogeneity and variable responses to immunotherapy. Approximately 15–20% of patients remain refractory to current treatment strategies, while in anti-IgLON5 disease, many patients experience progressive neurological deterioration leading to irreversible tauopathy despite immunotherapy. For highly selected cases, chimeric antigen receptor (CAR) T-cell therapy is emerging as a promising therapeutic option. Although patient selection criteria have not yet been formally established, key considerations include the specific AE subtype, the patient's potential for neurological recovery based on clinical and paraclinical findings, evidence of treatment refractoriness, and the risk of CAR T-cell therapy–associated complications, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

This presentation will review the current evidence regarding CAR T-cell–associated neurotoxicity, with particular emphasis on the risk factors, clinical manifestations, and management of CRS and ICANS, integrating published data with our experience in a multi-institutional study of 600 patients with hematological malignancies treated with CD19-directed CAR T-cell products. We will also summarize the emerging clinical experience with CAR T-cell therapy in AE and other autoimmune disorders of the CNS, including stiff-person syndrome, DAGLA antibody-associated encephalitis, and autoimmune cerebellar degeneration. Finally, we will present three challenging cases treated with CD19-directed CAR T-cell therapy (one MOGAD and two anti-NMDA receptor encephalitis), illustrating the complexities of patient selection in the setting of severe disease and prolonged disease duration, while highlighting the unresolved questions surrounding treatment refractoriness and the potential for neurological recovery.

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Sunday, October 18, 2026 - Repetitive Sequences in Neurological Diseases and Health

The Ticking DNA Clock: Lifelong Somatic Expansion of Repeated DNA As a Cause Of DNA-repeat Disorders

Author: Steven McCarroll, PhD, Howard Hughes Medical Institute/Broad Institute of MIT and Harvard Medical School

Inherited DNA-repeat disorders such as Huntington's disease and the spinocerebellar ataxias have long presented fundamental challenges to our understanding: Why do patients enjoy decades of good health before symptoms commence? Why do such disorders profoundly affect certain types of neurons while sparing other types of neurons and other cells? I will describe experiments in Huntington's disease that taught us a surprising answer to such questions: the inherited DNA repeat that causes the disease must undergo decades of somatic expansion – in specific types of neurons – and expands to several times its inherited length before it even begins to cause harm1,2. This surprising model is turning out to explain many long-puzzling features of the illness, such as its tendency to affect different brain areas in ways that had long appeared to have different mechanisms. It also helps us understand how common genetic modifiers of the disease3 shape its pathogenic trajectory. Since very many DNA repeats are somatically unstable and tend to expand with age4, an interesting possibility is that a similar dynamic may underlie many different DNA-repeat disorders.

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Understanding Repeat Expansion Diseases Using Population-scale Genomic Data

Author: Arianna Tucci, MD, PhD, Queen Mary University of London

DNA repeat expansions are a common cause of neurological disease, yet their accurate detection using short read genome sequencing has long been considered technically unfeasible. In recent years, the availability of large-scale genomic datasets from patients and population cohorts has enabled the development of bioinformatic tools to address these challenges.

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My lab has helped developed and applied such approaches, leading to three major advances.

First, we demonstrated a clinical-grade pipeline for the detection of pathogenic repeat, enabling the diagnosis of previously unsolved cases and establishing short-read genome sequencing as a first screening tier test for clinical diagnostics in the National Health Service in England.

Second, we applied this approach to over 500,000 individuals and discovered that the carrier frequency of pathogenic repeat expansion is much higher than previously thought. Through disease modelling that combined genetic data with age at onset and survival, we estimate that the actual prevalence of repeat expansion diseases may be two to three times greater than what clinical reports currently suggest, implying substantial underdiagnosis and/or incomplete penetrance..

Third, leveraging data from >10,000 family trios (mother-father-child), we quantified germline mutation rates across polyglutamine disease genes, finding a low but measurable risk of instability among intermediate alleles, clarifying the roles of parental sex, age, and allele size.

Together, these studies redefine repeat expansion diseases by shifting the perspective from rare, clinically ascertained conditions to a spectrum of genetic variation observable at population scale. This work provides a framework to study repeat expansion diseases prevalence, penetrance, and germline instability, with the aim of improving disease classification, risk prediction, and the identification of genetic modifiers that shape clinical outcomes.

D4Z4 Macrosatellite Repeat Rearrangements in Facioscapulohumeral Muscular Dystrophy

Author: Silvère Van der Maarel, PhD, Leiden University Medical Center

Repetitive DNA in the human genome was long regarded as largely nonfunctional, and variation within these regions has therefore been largely overlooked in genomic studies.[1] However, this perspective has changed considerably over recent decades. Among the most understudied classes of repetitive DNA are macrosatellite repeats; highly polymorphic loci composed of variable numbers of near-identical repeat units, each typically exceeding 100 bp in length.

Facioscapulohumeral muscular dystrophy (FSHD), a rare inherited myopathy characterized by progressive and irreversible weakness of the facial, scapular, and upper limb muscles, is caused by epigenetic dysregulation of the D4Z4 macrosatellite repeat located in the subtelomeric region of chromosome 4q.[2] Loss of repression at this locus results in aberrant expression of the embryonic transcription factor DUX4 in skeletal muscle.[3]

In this presentation, I will discuss the genetic and epigenetic mechanisms that lead to DUX4 expression in FSHD, recent insights into population-level variability underlying the disease, and the challenges these complexities pose for routine molecular diagnostics. I will then address the downstream consequences of inappropriate DUX4 activity in muscle tissue and review current therapeutic strategies aimed at suppressing DUX4 as a treatment for FSHD.

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Sunday, October 18, 2026 - Advances in Microscopy for Visualizing Neurologic Disease

Organelle Quality Control in Neuronal Homeostasis, Neurodevelopment, and Neurodegeneration

Author: *Erika L.F. Holzbaur, PhD, University of Pennsylvania Perelman School of Medicine*

Organelle quality control pathways are central to the maintenance of neuronal homeostasis. These pathways involve careful regulation of both biosynthetic and degradative pathways for cellular organelles such as mitochondria. We are interested in the mechanisms that maintain a healthy mitochondrial network in neurons, identifying a novel role for FMRP-dependent local protein synthesis in mitochondrial fission in axons and dendrites [1]. We are also interested in mechanisms regulating the clearance of aging or damaged organelles. Neurons rely on basal autophagy to maintain axonal health and function by clearing aging mitochondria and synaptic vesicles [2, 3], while acute organelle damage triggers organelle turnover via stress-induced pathways such as mitophagy and lysophagy [4–8]. Mutations that disrupt these pathways lead to either neurodevelopmental or neurodegenerative disease, which we are studying in human iPSC-derived neurons.

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NeuroZoom: Super-Resolution for Neurologic Disease Discovery

Author: *Craig Blackstone, MD, PhD, FANA, Massachusetts General Hospital, Harvard Medical School*

Cells are the fundamental unit of both life and disease, and cellular and in vivo models are commonly used to facilitate understanding of disease pathogenesis and to identify and test possible therapies. Experimental assessment of cells and their intracellular organelles and cytoskeleton are a critical part of these studies. However, traditional approaches used to visualize intracellular changes, such as confocal microscopy, are hampered by the optical diffraction limit and lack sufficient temporal resolution in live cell studies. Traditional electron microscopy (EM) can provide high resolution static images in two dimensions but is subject to fixation artifacts and limited in the third dimension by the inability to cut ultra-thin sections.

Over the past decade, several advanced imaging approaches have been developed that provide orders-of-magnitude improvement in spatial and temporal resolution. Dynamics can be identified even at the level of individual molecules within organelles. These approaches have revealed new layers of normal cellular architecture, identifying organellar morphologies and dynamic changes previously unseen (1). Consequently, these tools can be applied to cellular disease models to track protein movement and aggregation, as well as to visualize subtle changes in organelle morphology, contacts, movement and function – thus enabling more precise pathologic insights and therapeutic responses (2).

Advances in imaging have occurred in EM as well. Focused-ion beam scanning EM (FIB-SEM) of cells and tissues permits much higher resolution three-dimensional reconstructions of cells and intracellular organelles (3). FIB-SEM can even be paired with super-resolution microcopy to generate correlative images of unprecedented resolution and detail. Taken together, these new views of cells in normal and disease states permit the identification of disease-related changes previously undetected and labeled "no change" using more traditional approaches, paving the way for improved therapeutic assessments.

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State-of-the-Art Technologies to Generate and Analyze Large Amounts of Imaging and Genetic Data, Including Robotic Microscopy and AI

Author: *Steve Finkbeiner, MD, PhD, FANA, Gladstone Institutes/University of California, San Francisco*

Neurological diseases are difficult to study because their earliest, most tractable biology unfolds at scales and speeds that exceed what human observers can reliably see, count, or compare across the thousands of cells, patients, or postmortem samples needed to draw firm mechanistic conclusions. Robotic microscopy paired with artificial intelligence (AI) is changing this by making it possible to image living cells and postmortem tissue at scale and extract quantitative, reproducible phenotypes that link molecular and cellular events to disease.

In one line of work, we built automated live-cell imaging platforms that repeatedly image individual human induced pluripotent stem cell (iPSC)-derived neurons over days to weeks and track their fate. Deep learning models trained on these images can predict fluorescent markers directly from unlabeled, living cells, reducing the cost and toxicity of conventional labeling.1 Applying this platform to iPSC-derived motor neurons from people with amyotrophic lateral sclerosis (ALS), we used machine learning to decode cellular signatures of disease directly from live imaging, without assuming in advance which features mattered. The resulting models distinguished ALS from control neurons and tracked degeneration in a manner that scaled with genetic penetrance across TDP-43-mutant, C9orf72-mutant, and sporadic lines, and localized the discriminating signal to the nucleus, pointing to a nucleocytoplasmic transport defect we then validated directly. This approach stratifies a clinically heterogeneous disease into mechanistically coherent subgroups and identifies morphological changes that precede degeneration, a potential window for early intervention.2

A second example moves from living cells to human postmortem tissue. Characterizing amyloid and other Alzheimer disease pathologies by eye is slow and variable between observers, which limits how well large brain banks can be mined for insight. We developed a scalable annotation tool and a Mask R-CNN deep learning pipeline that detects, classifies, and segments amyloid pathology in whole-slide digital images with high accuracy and generalizes to samples never seen during training. Applied across nearly 300 samples, the model's quantitative pathology measures correlated with expert neuropathological ratings and with clinical measures of cognitive impairment, showing that automated digital pathology can substitute for, and scale far beyond, manual assessment.3

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Together, these examples show how robotic microscopy and AI can generate disease-relevant data at a scale unattainable by conventional means, reveal mechanisms invisible to the unaided eye, and nominate therapeutic targets and patient-stratification strategies across the neurodegenerative disease spectrum.

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Monday, October 19, 2026 - Emerging Approaches to Enhance Neuronal Resistance Against Neurodegeneration

Using CRISPR-based Functional Genomics in Human Neurons and Glia to Understand Resilience in Tauopathy

Author: *Martin Kampmann, PhD, University of California, San Francisco*

The selective vulnerability and resilience of specific neuronal populations is a hallmark of neurodegenerative diseases [1]. Understanding the underlying molecular mechanisms would not only provide novel insights in the molecular processes driving neurodegeneration, but could also pave the way for novel therapeutic approaches that promote neuronal resilience. The Kampmann lab has developed unbiased CRISPR screening approaches in human iPSC models [2,3] and mouse in vivo models [4] to uncover mechanisms of neuronal vulnerability and resilience, in particular Alzheimer's disease and related tauopathies [5,6]. A mechanistic understanding of endogenous mechanisms of resilience could pave the way for novel therapeutic strategies.

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Identifying Molecular Signatures and the Functional Relevance of Resilience Factors in Alzheimer's Disease

Author: *Inma Cobos, MD, PhD, Stanford University School of Medicine*

Selective neuronal vulnerability is a hallmark of Alzheimer's disease (AD), yet the molecular basis of resilience remains poorly understood. Advances in single-cell omics have been pivotal in characterizing the transcriptomic diversity of the human brain and elucidating selective cell vulnerability in neurodegenerative dementias.1 Single-nucleus transcriptomic profiling has broadly defined highly vulnerable populations that are depleted early in disease pathogenesis, including specific superficial-layer inhibitory interneurons and layer 2/3 excitatory neurons in the neocortex. The early loss of interneuron populations disrupts circuit balance, establishing cortical hyperexcitability as a primary driver of ongoing neurotoxicity. Conversely, other neocortical subtypes remain relatively preserved during advanced AD stages despite residing in the same pathological microenvironments.2 Current spatial and multiomic frameworks are uncovering pathological networks that single-modality analyses often miss, demonstrating that local tissue microenvironments and complex neuronal-glial crosstalk modulate the transition from homeostatic states toward neurodegenerative or resilient phenotypes. Within this context, evaluating specific cellular responses to amyloid and tau proteinopathies reveals complex stress-response and survival dynamics. Coordinated crosstalk between protoplasmic astrocytes and microglia promotes targeted glial chemotaxis toward amyloid-beta (Aβ) plaques. This intercellular communication drives plaque compaction, advancing the progression of diffuse plaques to neuritic or senile plaques. In response to amyloid burden and hyperexcitability, vulnerable neurons exhibit distinct pathological trajectories. To investigate these trajectories, soma-seq multiomic profiling of single somas with or without neurofibrillary tangles

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(NFTs) differentiates molecular alterations specifically associated with NFTs from broader AD-associated changes.3 This resolution highlights both tau-dependent and tau-independent mechanisms of neurodegeneration. These broader analyses indicate that NFTs represent cell-type-specific responses to amyloid pathology and other stressors; while initially protective against hyperexcitability and neuronal death, these compensatory mechanisms progressively fail, becoming toxic to both the tangle-bearing neurons and their microenvironment. Through integrative multiomic characterization and functional validation, the field is now mapping these cascades, from the early depletion of specific neuronal subtypes and cortical hyperexcitability to the ensuing glial and proteinopathic responses. Identifying these inherently resilient subtypes and the mechanisms underlying their preservation provides a critical foundation for therapeutic strategies aimed at slowing disease progression and enhancing broader neuronal resistance against neurodegeneration.

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Understanding Defense Mechanisms and Transport Across the BBB and Move Towards Targeted, Noninvasive Study and Repair of the Brain

Author: *Viviana Gradinaru, PhD, California Institute of Technology*

The brain is protected by the selective blood–brain barrier (BBB), which restricts access from circulating agents. Understanding the molecular mechanisms governing BBB transport could enable precise delivery to specific brain regions—and help anticipate how future pathogens might exploit this gateway.

This talk presents a decade-long effort to develop a platform for mapping the molecular rules that govern movement from the bloodstream into the brain. The goal is to enable rational, noninvasive delivery of therapeutic and experimental agents.

Using protein engineering—including directed evolution—and data science, we created adeno-associated viral vectors (AAVs) and non-viral shuttles capable of crossing the BBB. These vectors now support widespread transgene expression and enable advanced applications, such as in vivo whole-brain genetic screening.

This growing knowledge base—of both disease pathways and BBB entry mechanisms—offers promising strategies for identifying therapeutic targets and delivering safe, targeted interventions to the brain for both discovery and treatment.

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Tuesday, October 19, 2026 - The Menopausal Transition and Brain Health

Menopausal Hormone Therapy and Brain Health: From Controversy to Consensus

Author: *Pauline Maki, PhD, University of Illinois Chicago*

Menopausal hormone therapy (MHT) remains one of the most debated topics in women's health, particularly regarding its effects on cognitive symptoms of menopause and dementia risk. MHT is FDA approved for the treatment of vasomotor symptoms (VMS; hot flashes and night sweats), vulvovaginal symptoms, and prevention of osteoporosis. Following removal of the FDA boxed warning, there is broad consensus that, for most women with moderate to severe VMS, the benefits of MHT outweigh the risks.

More controversially, MHT has been promoted for the treatment of brain-based symptoms of menopause, including sleep disturbance, mood changes, and cognitive complaints ("brain fog"), as well as for the primary prevention of dementia. Clinical guidelines from The Menopause Society and the International Menopause Society agree that MHT may improve sleep in women with VMS and that estrogen therapy can improve mood in perimenopausal women with depressive symptoms. However, MHT is not recommended to treat cognitive difficulties or prevent dementia.

These recommendations are supported by longitudinal studies demonstrating small declines in verbal memory during the menopausal transition and by evidence that abrupt estrogen loss following surgical menopause is associated with verbal memory decline that improves with MHT. In contrast, randomized clinical trials consistently show no improvement in memory or other cognitive outcomes with MHT in naturally postmenopausal women.

Two major evidence gaps remain: the absence of large-scale randomized trials evaluating cognitive outcomes in perimenopausal women and the lack of trials specifically examining cognition in women with bothersome VMS. Current evidence suggests that although MHT does not improve cognition in naturally postmenopausal women, treatment of VMS may yield secondary cognitive benefits by alleviating

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symptoms that impair attention, sleep, and daily functioning. Importantly, effective nonhormonal therapies for VMS may provide similar benefits.

Four recent large-scale epidemiological studies consistently report a modest (9–22%) but statistically significant increase in Alzheimer's disease risk among women using MHT, regardless of formulation, timing of initiation, or duration of use. By conventional standards, this absolute risk is considered rare to uncommon (<100 cases per 10,000 women). In contrast, women with premature menopause appear to benefit from MHT until the average age of natural menopause, with evidence supporting maintenance of cognitive function and possible reduction in Alzheimer's disease risk. Overall, current evidence supports prescribing MHT for established menopausal indications rather than for cognitive enhancement or dementia prevention.

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Menopause, MHT and Alzheimer's Biomarkers in Women

Author: *Rachel Buckley, PhD, Massachusetts General Brigham Hospital*

Of all patients living with Alzheimer disease (AD) dementia in the United States it is estimated that two-thirds are women, and yet the biological mechanisms underlying this sex-specific disparity remain incompletely understood. The menopausal transition represents a period of neuroendocrine change during which declining ovarian hormones may intersect with emerging AD pathophysiology. This plenary will examine relationships among menopause, menopausal hormone therapy (MHT), and AD biomarkers to provide an understanding of state of play of the literature.

Across cohorts of cognitively unimpaired adults, women and men generally show similar levels of amyloid-β burden, but women have been consistently found to exhibit greater tau deposition at a given level of amyloid. Recent longitudinal evidence suggests that this difference may emerge early in the disease process: at higher amyloid levels, women show greater plasma phosphorylated tau 217, followed by greater regional tau accumulation, and subsequently, faster rates of cognitive decline. Menopause-related factors may further modify these trajectories. Earlier age at menopause and later initiation of MHT have been associated with greater tau burden, particularly in the presence of elevated amyloid. Longitudinal findings also suggest that historical MHT use is associated with faster tau accumulation among women older than 70 years, whereas associations are minimal in younger women.

These observational findings do not establish causality for menopause on the manifestation of AD pathophysiology or that MHT should be used to prevent cognitive decline. Rather, they underscore reproductive-associated heterogeneity across women and the importance of age, treatment timing, formulation, underlying amyloid burden, and other health factors. Prospective studies beginning during perimenopause are needed to determine when sex differences in AD biology emerge, identify modifiable sources of vulnerability and resilience, and generate evidence capable of informing individualized clinical care.

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Menopause, MHT and Neurologic Disease

Author: *Eliza Miller, MD, MS, FAHA, University of Pittsburgh*

All women who survive to midlife undergo menopause. Managing the menopausal transition goes beyond the purview of gynecologists and requires a collaborative approach in neurological care. Menopause brings profound changes to female physiology as women transition from fertility to post-fertility, which can in turn affect underlying neurological disorders. Perimenopause leads to unpredictable fluctuations in hormone levels, which can influence the course and treatment of pre-existing conditions like migraine and epilepsy. Common symptoms of menopause such as sleep disturbances, "brain fog," bladder dysfunction, hot flashes, and mood changes may

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overlap with, mimic, or exacerbate symptoms from neurological disorders (e.g. multiple sclerosis, neurocognitive disorders). Neurological comorbidities such as migraine with aura and cerebrovascular disease must be considered in decision-making regarding menopausal hormone therapy. Post-menopausal women with epilepsy taking antiseizure medications, or women with impaired mobility due to neurological disorders, may be at higher risk for osteoporosis and fractures. In addition, following the menopausal transition, the trajectory of cerebrovascular risk and cognitive aging changes for many women, making both primary and secondary preventive measures critical. Timing of menopause influences both stroke and dementia risk. Using clinical case vignettes, we will illustrate how a collaborative, woman-centric preventive neurology approach can be used to help manage the menopausal transition in women with, or at risk for, neurological disease. Neurologists should be educated in the basics of menopausal physiology and symptom management to provide the best care for our female patients, and to help dispel the fear, shame, and stigma surrounding this milestone in a woman's life.

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