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Further understanding the connection between Alzheimer's disease and Down syndrome

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CONFLICTS OF INTEREST

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Abstract

Improved medical care of individuals with Down syndrome (DS) has led to an increase in life expectancy to over the age of 60 years. In conjunction, there has been an increase in age-related co-occurring conditions including Alzheimer's disease (AD). Understanding the factors that underlie symptom and age of clinical presentation of dementia in people with DS may provide insights into the mechanisms of sporadic and DS-associated AD (DS-AD). In March 2019, the Alzheimer's Association, Global Down Syndrome Foundation and the LuMind IDSC Foundation partnered to convene a workshop to explore the state of the research on the intersection of AD and DS research; to identify research gaps and unmet needs; and to consider how best to advance the field. This article provides a summary of discussions, including noting areas of emerging science and discovery, considerations for future studies, and identifying open gaps in our understanding for future focus.

Keywords

Alzheimer's disease; Down syndrome; trisomy; vascular contributions

1 | INTRODUCTION

Improved medical care of individuals with Down syndrome (DS) over the past several decades has led to a dramatic increase in life expectancy to over the age of 60 years. In conjunction with this new aging population of adults with DS, there has been an increase in age-related co-occurring conditions including Alzheimer's disease (AD). Nearly all individuals with DS develop AD neuropathology by the age of 40. AD neuropathology can also be seen in very early life,[1–3] yet not all individuals will develop clinical symptoms of AD and the age of onset of clinical symptoms varies substantially. The prevalence of clinical dementia in DS doubles approximately every 5 years, from about 9% among individuals in their 40s to about 80% in those over age 54 and over 95% in those who live to the age of 68.[4–6] Dementia, cardiovascular disease, and lung pneumonia infections make up the most common causes of death in people with DS over the age of 36 years.[7]

Understanding the factors that underlie the variation in symptom presentation and age of clinical presentation of dementia in people with DS may provide insights into the pathophysiological mechanisms of both sporadic and DS-associated AD (DS-AD), including the association among amyloid beta (Aβ), tau-containing neurofibrillary tangles, neurodegeneration, vascular changes, and dementia.[3,8] The high incidence of AD in the DS population, combined with the ability to readily identify individuals with DS, also suggests synergies between research for DS and AD, including the potential for AD-targeted therapeutic clinical trials in individuals with DS, including prior to the onset of dementia.[9] A similar rationale has been used to support clinical studies in people with autosomal dominant AD (ADAD).[10] The mean age of AD diagnosis in persons with DS is between 53 and 55,[5,11,12] which is somewhat earlier than the mean onset of symptoms in people with ADAD (although the mean age of onset may differ in ADAD based on the mutation present).[13] Today, there are as many as 6 million people worldwide living with DS compared to about 250,000 with ADAD dementia.[14]

In 2012, the Alzheimer's Association, the Linda Crnic Institute for Down Syndrome, and the Global Down Syndrome Foundation convened a workshop to explore the commonalities between DS and AD and to identify opportunities for interdisciplinary engagement within the research communities.[15] Since then, additional collaborations and increased funding from the National Institutes of Health (NIH), two joint funding initiatives of the Alzheimer's Association and the Global Down Syndrome Foundation, as well as interest from other research and advocacy organizations and pharmaceutical companies, have encouraged many AD researchers to expand their studies to incorporate investigation of AD in DS.

Recognizing the importance of the links between AD and DS, the NIH launched the INCLUDE (Investigation of Co-occurring Conditions across the Lifespan to Understand Down Syndrome) Project in 2018. This trans-NIH initiative will include studies of multiple conditions that occur more or less frequently among people with DS in comparison to the general population. People with DS have a higher risk of developing not only AD but also leukemia, certain congenital heart defects, diverse autoimmune disorders, autism, and other conditions. However, they are at lower risk of developing many types of solid tumor cancers, some forms of adult cardiovascular disease (such as hypertension and ischemic

heart disease), and lower levels of potentially contributing vascular risk factors. Thus, the INCLUDE Project will uniquely provide double benefits by increasing understanding of whether and how these co-occurring conditions are associated with AD in DS and will also advance understanding of each co-occurring condition and the potential shared biological underpinnings.

In March 2019, the Alzheimer's Association, Global Down Syndrome Foundation, and the LuMind IDSC Foundation partnered to convene a workshop to explore the state of the research on AD and DS pathophysiology, risk factors, biomarkers, and drug development; to identify research gaps and unmet needs; and to consider how best to advance the field. This article provides a summary of the discussions at this workshop, including noting areas of emerging science and discovery, considerations for future studies, and identifying open gaps in our understanding for future focus.

2 | INTERSECTION OF AD AND DS: COMMONALITIES AND DIFFERENCES

The link between AD and DS is thought to be related to the triplication of the amyloid precursor gene (*APP*), which is encoded on chromosome 21. A small percentage of individuals with DS have partial trisomy of chromosome 21 without an extra copy of the *APP* gene (ie, they are disomic for *APP).* These individuals do not have the same elevated risk to develop AD but instead have a risk more consistent with that of the general population.[16,17] Furthermore, there are rare families exhibiting autosomal dominantly inherited AD caused by three copies of the *APP* gene due to a small locus of duplication on one chromosome 21.[18,19] Taken together these findings support the conclusion that three copies (ie, an extra dose) of the *APP* gene are sufficient to cause AD.[16,17]

Moreover, trisomy of chromosome 21 results in increased gene dosage for all genes on this chromosome, including several genes in addition to *APP* that may also be involved in related mechanisms. These include *SOD1*, which is involved in redox metabolism; *ABCG1*, which is involved in cholesterol metabolism; *CSTB, BACE2*, and *SYNJ1* involved in Aβ processing and clearance; *DYRK1A*, which is involved in tau phosphorylation; *RCAN*, which is involved in mitochondrial dysfunction; *S100B* involved in inflammatory responses; and others involved in neuronal development.[20] Chromosome 21 also encodes interferon receptor genes (IFNRs). Increased *IFNR* gene dosage results in IFN hyperactivation, IDO1 induction, kynurenine (KYN) dysregulation, and the production of quinolinic acid (QA), a neurotoxin that induces excitatory toxicity.[21,22] QA is associated with cognitive decline in older adults with AD and is a potent convulsant involved in epilepsy and seizures.[23] Thus, the clear importance of *APP* in AD in both the general and DS populations can be modulated by other genes.

2.1 | Biological underpinnings of DS and AD

Neuropathological studies of DS brains demonstrate that by age 40, there are changes fully consistent with the neuropathological diagnosis of AD. Interestingly, comparisons of DS brains from individuals with and without dementia have demonstrated the same differences in Aβ burden in the frontal cortex and striatum, but greater tau pathology and atrophy in the brains of individuals with dementia.[24] Some work suggests that there may be a greater role

of tau lesions in the onset of dementia.[18] Single gene expression profiling of tau containing cortical projection neurons revealed a differential downregulation of several gene classes in the brains of individuals with DS and dementia compared to individuals with DS but no dementia, including genes related to Aβ and tau biology, neuro-transmission, and cell death, suggesting potential novel drug discovery targets.[24]

Dendritic spines are integral to synaptic plasticity and memory storage. Spine pathology has been reported not only in traumatic brain injury and neurodegenerative diseases including AD, but has also been reported in DS.[25] Spine density declines significantly and early in brain regions affected by AD pathology.[26] Reduced spine number and altered spine morphology also characterize the DS brain. Molecular pathways underlying spine defects in DS include those involving *DSCR1*, which helps regulate spine morphogenesis, and *DYRK1A*, which regulates spine formation and actin dynamics.[27]

Trisomic astrocytes also play a role in spine pathology and reduced spine density.[28] Co-culture of human DS astrocytes with rat hippocampal neurons showed deficient secretion of thrombospondin 1 (TSP-1), a protein that modulates spine density and morphology in DS astrocytes.[29] Increased interferon (IFN) signaling also inhibits TSP-1 secretion in DS astrocytes.[30] These overlapping mechanisms suggest the potential for therapeutic approaches that target TSP-1, IFN, and amyloid in the DS brain.

Cerebrovascular pathology seen in people with DS-AD differs from those with sporadic AD. Cerebral amyloid angiopathy (CAA) occurs more frequently and is more severe in individuals with DS-AD compared to those with sporadic AD, probably as a result of *APP* overexpression.[31,32] AD-specific neuropathology is also associated with CAA small vessel disease, which can contribute to the development of dementia. Further, CAA accumulation may reflect an imbalance between Aβ production and clearance and exacerbate Aβ plaque deposition,[33] although this has not been explored systematically in people with DS. Further, the presence of CAA may lower the threshold for the development of cognitive impairments.[34] However, other vascular pathologies such as hypertension, atherosclerosis, and arteriosclerosis are rarely seen in DS, and in comparison with individuals with duplication of *APP* (thus a similar overdose of amyloid protein), which would suggest that individuals with DS appear to have some degree of protection against severe CAA.[35] However, given that CAA is higher in DS, it is likely that APP overexpression overrides these systemic protective factors. The consequences of increased CAA in the DS and sporadic AD brain include an increased frequency of microhemorrhages, which increase exponentially with age and can contribute to earlier onset of dementia.[31,36] CAA magnetic resonance imaging (MRI)-related abnormalities including micro-and macrohemorrhages and white matter malformations are found more frequently in DS (and in ADAD) than in sporadic AD or healthy controls, however; this is likely due to a multitude of factors and may be independent of one another.[37] If mechanisms contributing to AD pathology are different in DS-AD compared to sporadic AD, this may have implications regarding therapeutic development for DS-AD.

Even non-DS forms of AD may result, in part, from the occur-rence of chromosome 21 trisomy in other cells—a phenomenon known as mosaic aneuploidy caused by

nondisjunction during mitosis.[38] Trisomy 21 mosaicism has been observed in cells from people with sporadic AD, familial AD, and autosomal dominant presenilin mutations.[39] The number of hyperploid neurons increases in relation to AD-related pathophysiological changes in the brain but decreases at later stages of disease progression because hyperploid neurons are more prone to cell death.[40] Increased aneuploidy and apoptosis have also been observed in other neurodegenerative diseases such as frontotemporal lobar degeneration (FTLD)[41] and Huntington's disease (HD)[42] and in developmental disorders such as autism.[43] These findings suggest that genomic instability may represent a common mechanism across neurodegenerative and neurodevelopmental diseases and could be a therapeutic target. They further suggest that DS-AD and other co-occurring conditions may arise in people with DS through both developmental and aging-related cell cycle defects leading to variable mosaic aneuploidy in addition to trisomy 21. This could explain the high level of variability.[44]

2.2 | Regional pathology

In DS, amyloid pathology begins in the late teens with deposits of diffuse plaques initially within the temporal lobe consistent with Thal phase 1,[45] then spreading to neocortical regions and the hippocampus (Thal phase 2), reaching subcortical regions (Thal phases 3 and 4) and the cerebellum (Thal phase 5) by the late 40s. After 50 years of age, every region of the brain, including the cerebellum, is littered with amyloid plaques (Thal phase 5).[45] Over the lifespan, amyloid pathology begins as early as age 13 years with a pattern typical of AD typically reached by 55 years of age.[46] CAA begins at ≈40 years of age, ≈25 years after initial deposition of Aβ as plaques.[31]

The earliest sites of tau pathology include the entorhinal and transentorhinal cortex, spreading to the hippocampus, then temporal cortex and eventually to other regions of cerebral cortex, finally reaching the visual association cortex and primary visual cortex.[46] Tau pathology begins at ≈35 years of age within the hippocampus and spreads to neocortical regions after 45 years of age.

2.3 | Co-occurring conditions in DS-AD

Hypothyroidism, epilepsy, anemia, and weight loss are more common in people with DS and dementia compared to those without dementia.[47] Early-onset epilepsy and multi-morbidity may be associated with earlier onset of dementia;[48] however, the contribution of other co-occurring conditions (such as hypothyroidism) to both age of onset and survival of individuals with DS-AD appears relatively modest.[11] Diagnostic issues may explain some of the variability in age of onset. Individuals with more severe intellectual disability and sensory impairment may be more difficult to diagnose. In addition, studies suggest that individuals living at home rather than in care facilities are diagnosed earlier, possibly because families are more sensitive to subtle changes in cognition and function.[11]

In individuals with DS, dementia is also associated with a five-fold increase in mortality rate compared to individuals without dementia; age is also a confounder that should be considered.[48] In individuals with DS, it is unclear if apolipoprotein E (ApoE) ε4 impacts AD and mortality risk as in the general population; some studies suggest the risk is similar

and some studies have suggested otherwise.[49–51] Seizures are also linked to dementia in DS, with new-onset epilepsy often appearing in the early stages of dementia.[52] Seizures may eventually occur in >70% of individuals with DS-AD,[6] which are associated with accelerated cognitive decline[53] and increased mortality.[48]

2.4 | Risk factors in DS-AD

In the general population, studies have shown an association between risk of developing AD and lifestyle factors such as diet, physical activity, and social and cognitively stimulating leisure activities.[54–56] Adults with DS often have maladaptive lifestyles (eg, low physical activity and few social or leisure activities); thus, researchers have begun to investigate the association between lifestyle factors and biomarkers of early AD neuropathology and cognitive decline in DS. In a recent study, adults with DS without dementia who engaged in higher levels of cognitively stimulating and social leisure activity experienced less decline across three years in episodic memory. Moreover, leisure activity at baseline mitigated the association between an increase in Aβ assessed via positron emission tomography (PET) imaging and decline in episodic memory across three years, suggesting that these behaviors could play a role in benefiting cognition in the early stages of AD in DS.[57]

In the general non-DS population, high blood pressure, hypertension, and other vascular risk factors appear to increase the risk of developing dementia as well as cerebrovascular and AD pathology, presumably by putting white matter at risk of injury.[58] Although hypertension is low in DS, high rates of cerebrovascular disease (CVD) including microbleeds are seen, suggesting vascular contributions to the DS-AD phenotype need to be better understood.[37] It is possible that lifestyle factors that reduce risk of vascular disease could potentially also be an important target for intervention of dementia.

Sleep is another factor that may play a bi-directional role in the development of AD.[59] Sleep disorders are not only more prevalent in AD but also may predict future development of AD.[60] Sleep is thought to increase the clearance of toxins such as amyloid.[61] Adults with DS frequently experience sleep disruption, which could have multiple causes, and also have a high prevalence of obstructive sleep apnea (OSA),[62] which is a risk factor for AD.[63] OSA has been hypothesized to be associated with cognitive decline in DS.[64] In large population studies of elderly individuals without DS, OSA is associated with increased amyloid burden as individuals age.[65] The high prevalence of sleep disruption in DS suggests that this population may provide a window into understanding the links among sleep, amyloid, and dementia.[62]

Cognitive reserve is the idea that individuals who engage in more cognitively stimulating lifestyles, often measured by level of formal education or complexity of employment and mentally engaging activities (eg, crossword puzzles), better tolerate early AD pathology.[66] Specifically, such lifestyles are posited to promote the recruitment of alternative neural networks and/or foster more efficient use of existing networks to cope with early AD pathophysiologic insult (Stern, 2012).[67] In aging non-DS populations, cognitively stimulating lifestyles have been found to be associated with reduced Aβ accumulation[68] and a longer preclinical AD stage, in which early AD neurodegeneration is present but cognitive functioning remains intact (eg, Kemppainen et al.[69]). Historically, adults with DS have

experienced lifestyles with low cognitive stimulation as a result of limited adult disability services, low community involvement, and a lack of employment opportunities.[70,71] However, more recent shifts in the disability and employment system have provided a pathway for more cognitively stimulating lifestyles. The extent to which these shifts, and/or variability in level of cognitive stimulation, delay the onset of AD in the DS population needs more research attention.

3 | AD BIOMARKERS IN DS

Diagnosing AD in people with DS is complicated in part because of the need for tools to distinguish intellectual disability from cognitive decline.[72] Biomarkers can help mitigate this challenge but require studying AD biomarkers in DS populations because the diagnostic and prognostic performance may be different from that seen in non-DS AD. Biomarker (measures of biological activity, function, and/or change) studies in DS populations could also elucidate differences in AD pathophysiology in DS, as compared to AD in the general population and ADAD, and may be able to predict onset of dementia as well as potential success of preventive treatments aimed at lowering AD pathology. Some biomarkers have been validated in DS populations and would be helpful for participant selection and for monitoring treatment efficacy in clinical trials for all types of AD.

The National Institute on Aging (NIA) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) launched the 5-year Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS) initiative in 2015, funding two research teams—the Neurodegeneration in Aging Down Syndrome (NiAD) research group and the Alzheimer's Disease in Down Syndrome (ADDS) research group. In Europe, the Horizon 21 consortium, which includes several groups such as the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) and the LonDownS study in the United Kingdom are working together to establish a trial-ready cohort to study AD biomarkers in DS.[14] Such efforts aim to recapitulate in the DS population the work of the Alzheimer's Disease Neuroimaging Initiative (ADNI), which has illuminated the pathogenesis of sporadic AD. In combination, there are significant collaborative efforts internationally to establish biomarker studies and clinical trial ready cohorts.

3.1 | Imaging biomarkers

Neuroimaging provides insight into the pathogenesis and progression of AD, enables diagnosis, and provides biomarkers for drug discovery and clinical trials.[73] When Jack et al. published the landmark hypothetical model of dynamic biomarkers of the AD pathological cascade in 2010, the major imaging modalities included PET to assess fibrillar Aβ plaque deposition (Aβ PET) and two measures of neurodegeneration: fluorodeoxyglucose PET (FDG-PET), a measure of brain metabolism, and structural MRI to assess brain atrophy.[74] It is worth noting that while these tools have advanced biomarker development, they may not yet detect the earliest protein deposits, containing diffuse, non-fibrillar plaques. Over the years, many other imaging modalities have been applied to the study of AD and related dementias; examples of these modalities include additional PET ligands to image tau and other pathologies, functional MRI (fMRI) to examine the functional

activity of brain networks, diffusion weighted MRI (DW-MRI) to assess microstructure, electroencephalography, and retinal imaging.[75]

Cross-sectional studies of individuals with DS without dementia evaluated with Pittsburgh compound B (PiB-PET) demonstrated that when compared to individuals without DS, there was a similar prevalence of elevated amyloid in the absence of cognitive symptoms. In addition, it appears that the deposition of Aβ follows a similar time course, becoming evident about 20 years before the median age of symptom onset, however, at an earlier age of onset.[76–79] There is a wide variability in the age of PiB-PET positivity onset.[57] Individuals with DS show a pattern of Aβ accumulation—initiating in the striatum—similar to patterns seen in people with ADAD but different from what is seen in sporadic AD in which Aβ deposition predominates in the neocortex.[45,80] Longitudinal studies suggested that AD pathogenesis shifts from Aβ-negative to Aβ-positive earlier in DS compared to the general population but does not progress at a faster rate.[81]

Assessment of tau burden by PET scanning in people with DS shows similarities to the binding pattern and progression observed in non-DS AD.[82] Specifically, tau accumulation is associated with amyloid positivity and age, as well as with progressive neurodegeneration measurable using FDG and MRI. Accumulation of tau correlates with cognitive decline, as do AD-specific hypometabolism and atrophy.[82] Studies are ongoing to assess longitudinally the relationship of tau burden to cognitive and behavioral measures in DS.

The ABC-DS Project includes a study examining the correlation among Aβ burden, hypometabolism, and gray matter volume reductions in people with DS. FDG-PET can be used to assess brain metabolism; it is thought to provide a measure of glucose uptake and may mirror synaptic activity. In this same study, regional brain volume is assessed by MRI. In sporadic AD, changes in glucose uptake are seen prior to AD clinical symptom development and follow a characteristic pattern. In ADAD, one study suggests that glucose metabolism declines about 5 to 8 years before symptom onset and in another 14 years before expected onset.[83,84] In DS-AD as in sporadic AD, glucose hypometabolism and AD-related gray matter volume reductions occur only in older subjects with higher Aβ burden.[85] Interestingly, early work using FDG-PET in nondemented adults with DS suggests hypermetabolism in the entorhinal cortex prior to the development of dementia, suggesting a possible compensatory effect.[86] These studies confirm that glucose hypometabolism and brain atrophy both represent biomarkers of neurodegeneration in DS.

With lower rates of hypertension compared to the general population, people with DS provide a window into the role of CVD in dementia without the confound of systemic vascular disease.[87] CVD does not appear to be associated with elevated levels of Aβ (as measured by PET), suggesting that these features are not driven by Aβ pathophysiological changes. CVD seen in individuals with DS may be related to specific AD pathophysiological changes or may be independent; this is an area of further research needed to better understand the roles these factors may play related to clinical progression. In DS, markers of CVD visualized with MRI—white matter hyperintensities (WMH), micro-bleeds, infarcts, and enlarged perivascular spaces—increase in a dose-response manner across dementia-related diagnostic groups.

Changes in structural connectivity in white matter, which are detectable using DW-MRI, are also under investigation as potential biomarkers of AD progression in studies of individuals with DS-AD. As young as 35 years of age, people with DS show frontal white matter integrity losses that correlate with cognitive function.[88] In sporadic AD, regional structural changes in white matter across the continuum of disease begin in the preclinical stage, with decreased connectivity associated with increased Aβ burden.[89] Functional connectivity deficits of the default mode network assessed using fMRI[90] also show changes correlating with amyloid deposition in people with DS.

3.2 | Non-imaging biomarkers

Low levels of cerebrospinal fluid (CSF) Aβ42 (soluble) and elevated levels of total tau (t-tau) and phosphorylated tau (p-tau) are detectable in people with mild cognitive impairment (MCI) or AD. There have been a limited number of CSF studies in individuals with DS. These studies show that elevated levels of Aβ42 and other amyloid species are apparent in early childhood, although CSF tau levels remain low. As these individuals age, however, CSF Aβ42 levels decline and CSF tau levels increase.[91] To understand Aβ and tau dynamics in individuals with DS, further CSF studies are needed, as well as studies of other blood-based biomarkers that would not require individuals to undergo lumbar puncture (LP).

The DABNI study demonstrated good diagnostic performance of CSF AD-associated biomarkers and plasma neurofilament light (NfL, a component of the axonal cytoskeleton, is a marker of neuronal damage and degeneration[92]) in adults with DS;[93] and that LP is a safe procedure in this population.[94]

While not specific to AD,[95] CSF NfL concentrations increase during disease progression.[96] In the context of DS, in which the differential diagnosis often involves non-degenerative conditions (comorbidities) that do not elevate NfL levels, it is also specific for measures related to neurodegeneration. Similarly, plasma NfL concentrations increase as cognition declines in the non-DS population, and importantly, NfL is the only biomarker for which there is good correlation between plasma and CSF levels.[97] In the ADAD population, serum NfL predicted both cortical thinning and cognitive change in the presymptomatic stage of disease.[98] In people with DS, plasma NfL levels appear to increase with age, can distinguish between DS and DS-AD, and are associated with decreased adaptive behavior scores, supporting its role as a predictive biomarker of dementia in DS.[93,99–101] Plasma NfL levels correlate with standard biomarkers of AD pathology such as amyloid PET along with markers of neurodegeneration (regional cerebral glucose metabolism as assessed with FDG-PET and hippocampal atrophy) as well as cognitive and functional decline.[102]

Endophenotype strategies are also being used to identify biomarker profiles for diagnosing or predicting risk of AD in different populations, including DS.[103] This approach groups individuals by endophenotypes established using cognitive, biochemical, genetic, neuroimaging, and behavioral markers to identify subgroups who may respond to different therapeutic approaches. For example, a proinflammatory endophenotype may be able to predict who would respond to anti-inflammatory therapy. Metabolic and depressive endophenotypes may also prove relevant to better understanding and developing treatments for DS-AD.

Exosomes are small, endosomal-derived vesicles released into the bloodstream from all cells, including neurons, that contain proteins, lipids, messenger RNA, long non-coding RNA, and microRNA, as well as cell-identifying surface markers. Exosomes may have potential to provide more accurate disease biomarkers, because their cargo contains specific cellular content from the cell of origin, that is, brain tissue.[104] Exosomes facilitate cell signaling and transfer of cellular pathogens among cells and help in the removal of waste products.[105] In AD, exosomes are thought to play a role in Aβ clearance and possibly in the cell-to-cell spread of tau and Aβ peptides.[97] It has been shown that AD biomarkers including Aβ and p-tau are present in the cargo of neuron-as well as astrocyte-derived exosomes many years before any onset of dementia symptoms in the general population.[106,126] A study of neuron-derived exosomes purified from the blood of individuals with DS suggested that levels of exosomal Aβ peptides and p-tau are significantly elevated in early life compared to individuals without DS,[105] decades prior to the onset of dementia. The findings in that study demonstrated no association between age and exosomal Aβ42 levels, but a continuous increase in levels of p-S396-tau with the diagnosis of dementia in DS-AD. Levels of these exosomal biomarkers also correlate with cognitive measures and with some CSF biomarkers in the DABNI study. Further studies in additional cohorts will be needed to validate these findings but initial data suggest that exosomal cargo biomarkers may provide a more targeted biomarker method without having to perform repeated LPs in those with DS, because we can isolate exosomes originating only from neurons and glia from a single blood sample.[127]

The blood-brain barrier and choroid plexus are likely to play a role in determining pathology by controlling which biochemical factors, sub-cellular fractions, or cell subtypes traverse into and out of the brain parenchyma; some of which may be putative biomarkers with roles such as neuroprotection distributed in various fluid compartments being measured.[107,108]

4 | FUTURE CLINICAL TRIALS: AD DRUG DEVELOPMENT IN PEOPLE WITH DS

Advancing drug discovery in DS-AD will require a better understanding of underlying pathophysiological and genetic mechanisms, which requires suitable animal and/or cellular models that reflect gene dosage effects and alteration of regulatory sequences in chromosome 21. Many mouse models have been generated that duplicate various human chromosome 21 (Hsa21) genes. These models have yielded a better understanding of genotype-phenotype relationships and enabled the identification and exploration of potential therapeutic targets and assessment of new therapeutic approaches.[109–112] However, the lack of a DS animal model that reproduces the pathological lesions found in DS and AD remains a major focus for the DS and AD research communities.

Human models using induced pluripotent stem cells (iPSCs) and directly induced neurons (iNs) have also emerged and are proving useful for the study of neurological diseases associated with aging including AD and DS-AD. iPSCs provide a pure genetic model but are limited in their ability to model age-related changes, at least those linked to changes in the epigenome while iNs can maintain age-associated features of aging neurons.[113]

4.1 | Pipeline of clinical interventions

At the time of the workshop, only a few clinical trials were focused on DS-AD, yet there are many potential pharmacological and non-pharmacological approaches that may be able to benefit people with DS-AD. Moreover, successful trials in DS may translate readily to AD in the non-DS population.[3] There is a strong rationale for testing anti-Aβ therapies in the DS population and such approaches may be even more efficacious in this population due to less age-related co-occurring conditions and fewer non-amyloid vascular risk factors.

The anti-Aβ vaccine ACI-24 is being evaluated in an NIH-funded phase Ib study in adults with DS (NCT02738450). It is a multi-center, double-blind, randomized, placebo-controlled, dose-escalation study of the safety, tolerability, and immunogenicity of ACI-24 in adults with DS. The study is fully enrolled with 16 adults with DS, aged 25–45 years. Primary endpoints include measures of safety, tolerability, and immunogenicity. Secondary endpoints include effects on biomarkers of AD pathology as well as cognitive and clinical function. Another study in DS involved scyllo-inositol, which is an endogenous myo-inositol isomer that has shown amyloid anti-aggregation effects.[114,115] It has also shown amyloid-lowering effects in CSF and brain and demonstrated beneficial trends on cognition in mild AD.[116] A phase II randomized, double-blind, placebo-controlled study of oral scyllo-inositol, which included pharmacokinetic studies, has been successfully completed in 24 adults with DS.[117]

Normalization of *APP* gene dose represents a potential therapeutic strategy to further explore. In a mouse model of DS, deleting one copy of *APP* eliminated endosomal pathology.[118] Reducing *APP* gene dose could potentially be accomplished by targeting APP mRNA levels with antisense oligonucleotides (ASOs), *APP* mRNA translation, *APP* processing with γ-secretase modulators, removal of Aβ with immunotherapy, or reducing a key regulator of intracellular trafficking, Ras related protein a4 (Rab5), activation with ASOs.

Non-Aβ treatment approaches such as those that target tau, microglial function, interferon-related signal transduction, oxidative stress, or inflammatory events could also be beneficial in DS-AD. For example, granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine produced by the innate immune system, has been shown to reduce Aβ deposition in vivo and reverse memory deficits in aged DS and normal mice. However, GM-CSF, as a therapeutic, may have side effects that should be considered for therapeutic development.[119]

4.2 | Practical considerations for clinical trials

The conduct of clinical trials in the DS population raises many methodological challenges. Given the wide variability in baseline intellectual capabilities, the demands on memory, attention, and language ability must be taken into account for successful and accurate cognitive assessment and interpretation of results. Indeed, in the clinic, there can be a tremendous challenge in arriving at a firm diagnosis of AD dementia. The main defining feature of dementia in the typical population is a decline from the baseline level of function and performance of daily skills. Consensus guidelines for the evaluation and management in DS have been proposed.[71] In the absence of a personal historian who can accurately attest to an individual's baseline level of functioning, the assessment of a reported change may be

exponentially more complicated in DS. Moreover, the earliest signs of dementia in adults with DS may be subtle and will often require an astute observer to identify such changes. The history is the cornerstone of a dementia diagnosis. Currently, a thorough history must be obtained to build evidence consistent with declining cognition while probing for other features that might suggest other contributing factors. These contributing factors include concomitant medications, recent medical illnesses (including laboratory testing such as TSH and Vitamin B12), changes in health status (vision or hearing), or recent life events that can impact psychosocial functioning. Although some valid measures exist,[120,121] there is currently no standard clinical instrument for the assessment of dementia in adults with DS. Assessment of decline should therefore always be individualized and patient specific, with judgments made on the basis of deterioration from the patient's own individual baseline level of functioning.

Moreover, thoughtfully designed cognitive testing sessions using validated instruments that reflect clinical meaningfulness will be critical. In addition, developing inclusion and exclusion criteria for clinical trials in DS-AD can be challenging for several reasons including the high rate of sensory impairments and other health concerns, which may limit the generalizability of the sample.[122] Identifying prodromal symptoms or MCI in people with DS may also be difficult because of pre-existing impairments. Assessment tools must be able to demonstrate change in participants, which may require verbal abilities not present in all potential trial participants; however, it is also important to include people representative of the larger DS population, and not limit participation to those who are more cognitively advanced or motivated. In addition, trial design should take into consideration factors such as where the participant lives—in the home verses an assisted living facility—and how this may contribute to overall study engagement. This coincides with the role the care provider may play in trial participation, such as transport and identification of behavioral changes.

There is currently no generally accepted validated test battery to monitor medication effects in DS, and the variability in cognition and behavior among people with DS makes it difficult to assess treatment outcomes. A working group assembled by NICHD has identified measures that may be modifiable for use in people with DS to assess multiple cognitive and behavioral domains; however, additional work is needed to evaluate and validate these measures.[123] Recently, there has been progress in demonstrating the sequence of decline events and onset of symptoms during the prodromal stages of AD in DS. These studies are using standardized informant ratings of symptoms with tools such as the CAMDEX-DS questionnaire[124] to explore changes in behaviors related to frontal lobe dysfunction, and comprehensive cognitive test batteries such as the LonDownS battery to demonstrate early decline in memory and attention.

While neuroimaging biomarkers have demonstrated their value in AD clinical trials, DS-AD participants may have increased challenges because of the difficulty they may have in keeping still during the scan session and/or the length of the scan; these challenges increase as the disease progresses. As such, use of neuroimaging biomarkers may become more problematic as individuals with DS progress in AD. This complication should be considered as these biomarkers are developed and validated for potential use in clinical trials.

Finally, selection of appropriate interventions to evaluate in the DS-AD population should consider factors such as the increased CAA and inflammation in these individuals for both evaluation of interventions and cross-target complexities.

5 | CONCLUSIONS, GAPS, AND NEXT STEPS

Imaging studies suggest a similar pattern of pathology between DS-AD and sporadic AD but beginning at an earlier age in DS-AD. However, the basis of these studies is on current knowledge about AD. Genetics, metabolomics, lipidomics, and other -omics data in DS-AD may suggest other mechanistic lines of investigation resulting in the development of other biomarkers. DS-AD, unlike sporadic AD, is a genetically driven form of dementia. Moreover, the higher expression of APP and other chromosome 21 genes may interact with AD pathology in ways specific to DS-AD; for example, by inducing chronic oxidative stress.

Workshop participants identified a number of gaps in understanding the biological underpinnings and the role of risk factors, including novel vascular risk factors associated with DS-AD. Gaps also exist regarding what are the best biomarkers for DS-AD across the continuum of disease, including vascular markers, inflammatory markers, oxidative stress, excitation, calcification, and CVD markers.

Many international research consortia and collaborations are underway to advance the understanding of DS-AD. These include the Horizon 21 Genetics Consortium (funded by J-L Institute), AD Biological correlates in DS (NIH, PI Granholm), Inflammation and NGF Dysfunction in the Evolution of AD Pathology in DS (multicenter), Improving AD care in adults with DS (submitted to GBHI and Alzheimer's Association Pilot Award), Horizon 21 Cognitive Project, HEROES consortium funded by the JPND in Europe,[125] the NIH Alzheimer's Biomarker Consortium for Down syndrome (ABC-DS), and the Crnic Institute's Human Trisome Project (NCT02864108). Other projects are also underway studying exosomes, metabolomics, TREM2, Dyrk1A, neurotransmitters, NfL, novel biomarkers in DS, and modifiable risk factors including sleep.

The ABC-DS, LonDownS Consortium, Down Syndrome Biomarker Initiative (DSBI), and DABNI have collected critical data on the natural history of AD in DS to enable clinical trials. They have demonstrated that biomarker-enabled studies of AD in DS are indeed feasible and a small number of clinical trials have demonstrated the interest and willingness of adults with DS to successfully participate in placebo-controlled clinical trials for AD in DS.[117,126]

There is a need for increasing the number of postmortem brain tissues from well-characterized people with DS and AD available for study by the international research community. An initial network consisting of 10 participating universities in the United States and Europe, the Down Syndrome Biobank Consortium (DSBC), will develop standardized protocols for DS brain procurement, harmonized collection of brain tissues at the different sites, and harmonized tissue procurement and sharing within the research community.

Workshop participants suggested establishing a consensus research framework for DS-AD, including development of a data-driven consensus core assessment battery. To

advance clinical research and clinical trials, identify recruitment priorities, and power trials appropriately, more research is needed to better understand the risk factors for dementia in DS. Longitudinal measures are needed to better understand progression and phenoconversion. There was also discussion about the importance of establishing coordinated research and medical care centers of excellence within the framework of existing DS centers and/or AD centers to accelerate understanding and effective treatments.

Developing clinical trial networks and the infrastructure for multi-center collaborations using harmonized protocols is another important priority with several efforts currently underway, including the LuMIND IDSC Foundation Down Syndrome Clinical Trials Network (DS-CTN) and the NIH-funded Alzheimer's Clinical Trial Consortium-Down Syndrome (ACTC-DS). A multi-center observational study, the Longitudinal Investigation for Enhancing Down Syndrome Research (LIFE-DSR) study, is also underway. Studies aimed at prevention of dementia in the DS population should also be further explored, both pharmacological and non-pharmacological. Expanded utilization of brain banking, expanded data sharing and evaluation of data across studies, and expanded pharmacological and non-pharmacological intervention studies as well as combination therapy approaches are also urgently needed.

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RESEARCH IN CONTEXT

1. **Systematic Review:** Understanding the factors that underlie the variation in symptom presentation and age of clinical presentation of dementia in people with Down syndrome (DS) may provide insights into the pathophysiological mechanisms of both sporadic and DSassociated Alzheimer's disease (DS-AD), including the association among amyloid beta (Aβ), tau-containing neurofibrillary tangles, neurodegeneration, vascular changes, and dementia. The high incidence of AD in the DS population, combined with the ability to readily identify individuals with DS, also suggests synergies between research for DS and AD, including the potential for AD-targeted therapeutic clinical trials in individuals with DS, including prior to the onset of dementia. Building off past workshops, the Alzheimer's Association, Global Down Syndrome Foundation, and the LuMind IDSC Foundation partnered in March 2019 to convene a workshop to explore the state of the research on AD and DS pathophysiology, risk factors, biomarkers, and drug development; to identify research gaps and unmet needs; and to consider how best to advance the field.

2. **Interpretation:** This article provides a summary of the discussions at this workshop, including noting areas of emerging science and discovery, considerations for future studies, and identifying open gaps in our understanding for future focus.

3. **Future Directions:** The AD/DS Workshop participants identified a number of gaps in understanding the biological underpinnings, the role of risk factors, including novel vascular risk factors associated with DS-AD. Gaps also exist regarding what are the best biomarkers for DSAD across the continuum of disease, including vascular markers, inflammatory markers, oxidative stress, excitation, calcification, and cerebrovascular disease markers.