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The Traumatic Brain Injury Endpoints Development (TED) Initiative: Progress on a Public-Private Regulatory Collaboration To Accelerate Diagnosis and Treatment of Traumatic Brain Injury

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Abstract

The Traumatic Brain Injury Endpoints Development (TED) Initiative is a 5-year, Department of Defense–funded project that is working toward the ultimate goal of developing better designed clinical trials, leading to more precise diagnosis, and effective treatments for traumatic brain injury (TBI). TED is comprised of leading academic clinician-scientists, along with innovative industry leaders in biotechnology and imaging technology, patient advocacy organizations, and philanthropists, working collaboratively with regulatory authorities, specifically the U.S. Food and Drug Administration (FDA). The goals of the TED Initiative are to gain consensus and validation of TBI clinical outcome assessment measures and biomarkers for endorsement by global regulatory agencies for use in drug and device development processes. This article summarizes the Initiative's Stage I progress over the first 18 months, including intensive engagement with a number of FDA divisions responsible for review and validation of biomarkers and clinical outcome assessments, progression into the prequalification phase of the FDA's Medical Device Development Tool program for a candidate set of neuroimaging biomarkers, and receipt of the FDA's Recognition of Research Importance Letter and a Letter of Support regarding TBI. Other signal achievements relate to the creation of the TED Metadataset, harmonizing study measures across eight major TBI studies, and the leadership role played by TED investigators in the conversion of the NINDS TBI Common Data Elements to Clinical Data Interchange Standards Consortium standards. This article frames both the near-term expectations and the Initiative's long-term vision to accelerate approval of treatments for patients affected by TBI in urgent need of effective therapies.

Keywords: biomarkers; clinical outcome measures; CT; FDA; MRI; traumatic brain injury

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Introduction

Unmet needs and burden of traumatic brain injury

Traumatic brain injury (TBI) is a major public health issue that impacts populations at risk across the entire demographic spectrum of age, race, sex, and socioeconomic status. TBI affects at least 2.5 million individuals annually in the United States[1]; the lifetime incidence rate is estimated at 40%.[2,3] Even for the 75% of TBIs classified as ''mild'' or concussive events,[3] there may be long-term impairments in physical, cognitive, behavioral, and/or social functioning.[4] These long-term consequences have gained visibility with highly publicized attention on the impact of concussion and repetitive head impact exposure.[5–7] Worldwide, TBI is recognized as the leading cause of mortality and morbidity in children and young adults.[8] With the annual cost to Americans assessed at over $70 billion a year,[9] TBI also has far-reaching economic impact on society.

To date, no therapeutic drugs have been approved for treatment of acute TBI, despite the advancement of numerous therapeutic candidates through pre-clinical studies and the completion of nearly 30 large, randomized, controlled clinical trials over the past two decades. Importantly, despite the fact that the path to drug approval is through the portal of government regulatory agencies, few early-stage therapeutic TBI clinical trials have been launched with consideration to regulatory science. Global initiatives and public-private partnerships that focus on regulatory science have potential to accelerate paths to successful treatments. Regulatory initiatives in both the United States and Europe are already paving the way in many central nervous system (CNS) conditions of high unmet need.[10–13]

In 2013, the U.S. Department of Defense (DoD), through its Defense Medical Research and Development Program on Combat Casualty Care Research, published an announcement for a competitive award focused on TBI. The Traumatic Brain Injury Endpoints Development (TED) Initiative was aimed at supporting the development of collaborative, multidisciplinary research teams to advance validation of endpoints acceptable to the U.S. Food and Drug Administration (FDA), for use in trials involving novel diagnostics and therapies of TBI. Of primary importance to this effort was the explicit call for immediate and ongoing collaboration with the FDA. The announcement specifically required that infrastructure be developed to share data and disseminate results, as well as provide public access to any validation tools that might be developed. The DoD also required that data elements be reported and collected using National Institute for Neurological Disorder and Stroke (NINDS) TBI Common Data Elements (TBI-CDEs). Finally, the announcement also encouraged the recruitment of private partners from industry and patient advocacy groups to collaborate and provide resources to advance the validation efforts.

Our team proposed a collaboration to harmonize and curate clinical, proteomic, neuroimaging, and genomic datasets from large-scale civilian (NINDS-funded Transforming Research and Clinical Knowledge in Traumatic Brain Injury [TRACK-TBI]), military (DoD/VA-funded CENC [Chronic Effects of Neurotrauma Consortium]), and sport-related (Concussion Research Consortium [CRC]) TBI studies. The clinician-researchers of these studies then joined with regulatory consultants, data curation and analytics experts, and partners from the pharmaceutical and imaging industries to begin building consensus around the evidence-based approaches necessary to interrogate this massive dataset. The ultimate aim is to validate a range of more refined clinical outcome assessments (COAs) and a variety of sensitive biomarkers that the FDA could consider for use in stratification of patients for clinical trials.

We report here on the first 18 months (Stage I) of the TED Initiative's progress in creating the TED Metadataset, successful efforts to establish productive advisory channels across the FDA, and the launch of preliminary validation studies. Finally, we describe the framework of TED's continuing activities to advance research and clinical tools for TBI drug and device development.

Background

Development of successful treatments for TBI poses unique challenges, including the complex pathophysiological mechanisms (primary and secondary) of injury, the rapidly evolving time course of pathophysiological changes, and the heterogeneity of the injury itself. Progress toward definitive diagnosis and effective treatments

Table 1. List of Acronyms

ADNI	Alzheimer's Neuroimaging Initiative
CAMD	Coalition Against Major Diseases
CC1	Consensus Conference 1
CDER	FDA Center for Drug Evaluation and Research
CDEs	Common Data Elements
CDISC	Clinical Data Interchange Standard Consortium
CDRH	FDA Center for Devices and Radiological Health
CENC	Chronic Effects of Neurotrauma Consortium
COAs	Clinical outcome assessments
COU	Context of Use
COBRIT	The Citicoline Brain Injury Treatment Trial
C-Path	Critical Path Institute
CPIM	Critical Path for Innovation Meeting
CRC	Concussion Research Consortium
CSF	Cerebrospinal fluid
CT	Computerized tomography
DDTs	Drug Development Tools
DNP	FDA Division of Neurology Products
DoD	U.S. Department of Defense
EMA	European Medicines Agency
EWGs	Expert Working Groups
FDA	U.S. Food and Drug Administration
GCS	Glasgow Coma Scale
GFAP	Glial fibrillary acidic protein
GOS-E	Glasgow Outcome Scale-Extended
GRE	Gradient Recalled Echo
IND	Investigational new drug
LOI	Letter of Intent
MDDTs	Medical Device Development Tools
MRI	Magnetic resonance imaging
NCAA	National Collegiate Athletic Association
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NDA	Nondisclosure agreement
NRAP	National Research Action Plan
OTS	FDA Office of Translational Sciences
PDMA	Japan's Pharmaceuticals and Medical Devices Agency
ProTECT	Progesterone for the Treatment of Traumatic Brain Injury III
TBI	Traumatic brain injury
TED	Traumatic Brain Injury Endpoints Development Initiative
TRACK-TBI	Transforming Research and Clinical Knowledge in TBI study
UCHL1	Ubiquitin carboxyl-terminal hydrolase isozyme L1
VA	U.S. Department of Veterans Affairs

has been hampered by reliance on blunt outcome measures that are not sufficiently sensitive for assessing clinically meaningful changes or therapeutic response. To date, the only tools routinely recognized by the FDA for selection and stratification into a clinical trial intervention are the Glasgow Coma Scale (GCS)[14] and absence or presence of acute pathological findings on a computed tomography (CT) scan (please refer to Table 1). This is particularly challenging for mild TBI (mTBI) where clinical diagnosis primarily relies on clinical features (GCS, duration of unconsciousness, and duration of post-traumatic amnesia) and consensus about neuroimaging findings are inconsistent. Definitions promulgated by the Centers for Disease Control and Prevention do not include neuroimaging as a criterion, whereas the DoD defines mTBI as having normal imaging. However, the DoD does not stipulate the imaging modality (CT or magnetic resonance imaging [MRI]) or the time post-injury when neuroimaging studies are performed.[15,16] TBI patients are often divided into categories of GCS mild, moderate, or severe, when this overall measure of consciousness can be confounded by comorbid factors unrelated to the pathophysiology of TBI (e.g., alcohol intoxication or post-traumatic stress disorder [PTSD]).[17] Overall outcome post-TBI is often measured by the Glasgow Outcome Scale-Extended (GOS-E),[18] a global TBI outcome measure that has traditionally served as an FDA-accepted endpoint. The GOS-E is neither specific to TBI disability nor potentially sensitive enough to discern outcomes in specific cognitive or psychological health domains of deficit or recovery that might be targeted in a clinical diagnostic or treatment trial. Further, it may not differentiate pre-existing conditions such as psychiatric disorder and comorbidities (e.g., PTSD), which must be considered because they are confounders.

Clinical trials to date have included subjects with a broad range of severities and trial-specific parameters (inclusion/exclusion criteria, time for onset of treatment, dose, etc.). These have frequently not aligned with pre-clinical data that have supported specific therapeutic candidates. The existing tools utilized in TBI trials do not permit selection of patients with more uniform injury characteristics or pathophysiology that may preferentially respond to targeted therapies. Biomarkers are urgently needed that can: 1) accurately and objectively detect brain injury (diagnostic biomarkers); 2) identify subsets of patients at risk for persistent disability post-TBI to aid in both clinical management and for selection of patients for clinical trials (prognostic biomarkers); 3) categorize patients by their likelihood to respond to a targeted therapy (predictive biomarkers); and 4) demonstrate target engagement by showing that a biological response has occurred after a therapeutic intervention (pharmacodynamics biomarkers).

New initiatives have been launched to support the development of world-wide networks to collectively advance the field of TBI both in terms of basic scientific discoveries, epidemiology, and new therapeutics and technologies.[19] Examples of such initiatives include the International Initiative for TBI research (IntBIR)[20];

https://intbir.nih.gov/), One Mind (http://onemind.org/), the European project CENTER-TBI (https://www.center-tbi.eu/), and the U.S-based longitudinal cohort study TRACK-TBI (https://tracktbi.ucsf.edu/). Global alliances will enable efficiencies in conducting multi-site international clinical trials in the future.

The Traumatic Brain Injury Endpoints Development strategic objectives

Development of a unique collaborative approach to traumatic brain injury. The TED Initiative was built to leverage the expertise and experience of academia, philanthropies, patient advocacy organizations, and a committed cadre of pharmaceutical, imaging, and emerging technology industry members, with the contribution of financial and in-kind resources by all participants (Fig. 1). By design, TED is disrupting the traditional model of siloed TBI research with its creation of a collaborative model in the precompetitive space, governed by data sharing and intellectual property agreements that consider the concerns of all signatories. This is in contrast to historical efforts that have often been underpowered, hampered by lack of data standardization, and, until recently, undertaken with limited multi-disciplinary collaboration.

Multi-disciplinary expertise is evidenced by co-Investigators representing the fields of neurotrauma, neurological surgery, neuropsychology, neuroradiology, psychiatry, neurology, sports medicine, pediatrics, geriatrics, health economics, biostatistics, and informatics.

Guidance in the regulatory arena has been provided by the Critical Path Institute (C-Path), in data standardization by the Clinical Data Interchange Standard Consortium (CDISC), and by One Mind, a patient advocacy and philanthropic organization. Private partners are showing great interest in the TED model of an ''end-to-end'' research enterprise and have contributed time and regulatory expertise at face-to-face meetings and conference calls to help select and improve biomarker and clinical outcome assessment tools. They have also provided in-kind support to identify, test and/or validate new proteomic, neuroimaging, and genomic biomarkers, as well as to develop advanced analytic methodologies and novel platforms for their execution.

Together, TED collaborators come from 76 different institutions, agencies, and private sector industry and philanthropic partners. This type of cross-cutting collaboration is essential to overcome the myriad challenges of TBI research.

Why regulatory science? Regulatory pathways and incentivizing industry. Large pharmaceutical companies have been reluctant to invest in TBI drug development given the high risk and failure rate, similar to the case of therapeutics for acute stroke nearly a decade ago.[21] To incentivize investment by both small and large industry sponsors, a focus on regulatory science represents a path with unique and noteworthy advantages. Traditionally, regulators are approached by a single sponsor when the company's specific drug candidate or device is in the late stages of development and a sponsor is seeking approval. Historically, academic researchers do not interact with regulatory agencies. With the recognition by FDA leadership, through the Critical Path Initiative[22] launched in 2006, that the convention of advancing single treatments one at a time can be inefficient, costly, and time-consuming, the FDA has promulgated a series of mechanisms through which drug and/or device developers may enter formal processes for evaluation, validation, and qualification of drug development tools (DDTs) or medical device development tools (MDDTs), *independent of single sponsor research and one drug target*. DDTs include, but are not limited to, COAs, blood- or urine-based biomarkers, and imaging biomarkers.

Formal qualification has widespread implications for candidate therapies; it may confer broad applicability across multiple drug candidates, independent of the mechanism of action of the drug or of the contributing sponsor as well as across multiple clinical disorders, drugs, or drug classes.[23,24] In addition, qualified DDTs or MDDTs become public open guidance for the scientific community. The FDA has qualified a total of 14 biomarkers to date.[25] Specific examples of past regulatory qualifications include cardiac troponins for assessment of drug-induced cardiotoxicity in non-clinical species, fibrinogen for enrichment of chronic obstructive pulmonary disease (COPD) patients into clinical trials, and total

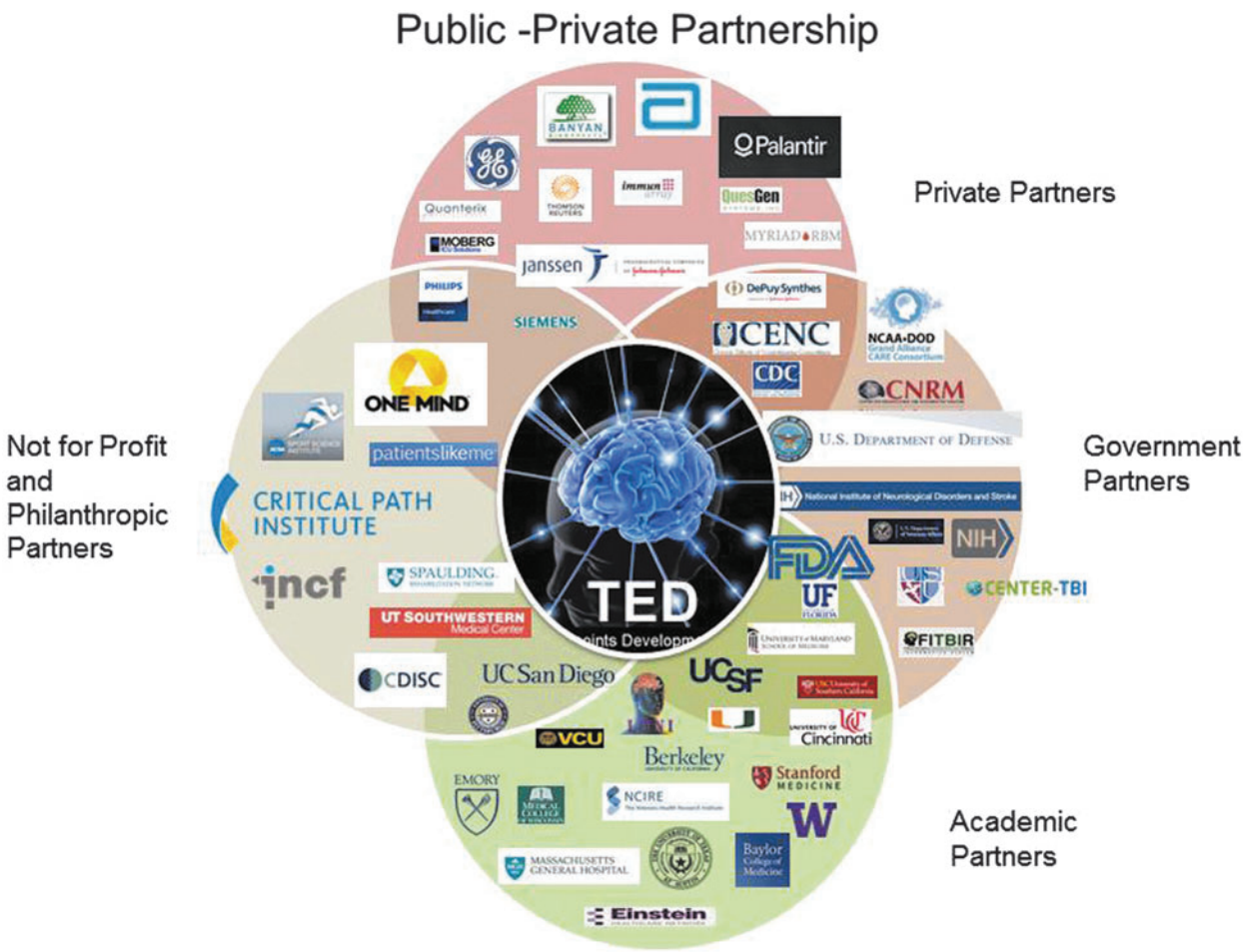

FIG. 1. The TBI Endpoints Development Initiative Public-Private Partnership. Color image is available online at www.liebertpub.com/neu

kidney volume as an imaging biomarker for enrichment in clinical trials of polycystic kidney disease. To date, there have been no regulatory endorsed biomarkers validated or qualified for TBI, a critical need for the advancement of brain injury clinical trials and development of new therapeutic drug targets.

Since the inception of the FDA's qualification program, worldwide regulatory agencies have adopted similar mechanisms (Japan's Pharmaceuticals and Medical Devices Agency [PDMA] and European Medicines Agency [EMA]). Qualified opinions from the EMA include biomarkers, particularly several in the area of predementia Alzheimer's disease (AD), as well as clinical outcome assessments.

Detailed, publicly accessible guidance documents and Manual of Policies and Procedures outline the steps for all pathways of the FDA, including DDT qualification.[26–28] Similar DDT guidance documentation resources are also available in Europe.[29]

The FDA has recently instituted several new mechanisms to augment engagement with the Agency. These include Critical Path Innovation Meetings (CPIM), letters of support for promising biomarker candidates, and public workshops aimed at communicating evidentiary standards and expectations for regulatory qualification. With these, the FDA is portraying a clear dedication to increased transparency and focus on the patient.

Recent successes in regulatory-endorsed drug development tools, including for brain disease,[30] provide support for the creation of consortia and initiatives such as TED. These take advantage of data pooling across individual studies and create standardized, validated assays and imaging technology parameters for reliable biomarker measurement, as well as pave the way toward regulatory acceptance of outcome assessments. The EMA has likewise instituted the letter of support mechanism for biomarkers (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp#section15). There are examples of biomarkers for CNS conditions such as Parkinson's disease, with letters from both agencies.

Traumatic Brain Injury Endpoints Development First Consensus Conference, February 2015. Among its first objectives, TED organized a TBI Consensus Conference (CC1), held on February 2–3, 2015 at the National Institutes of Health (NIH). The conference drew over 120 attendees from academic research, several divisions of the FDA, device and drug developers, as well as patient advocacy and philanthropic communities, to share expertise toward the common goal of developing more precise TBI diagnostic tools, clinical endpoints, and effective therapies.

FDA representation included participants from its Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH). Dr. Douglas Throckmorton, Deputy Center Director for Regulatory Programs at CDER, opened with a presentation describing ''FDA Regulatory Pathways,'' followed by a panel discussion consisting of five FDA representatives from the Division of Neurology Products (DNP), CDRH, Clinical Outcome Assessment staff, and the Office of Translational Sciences.

Representatives from the CDRH outlined the parameters for success in neurodiagnostics and device development, including the recent formation of the MDDT program.[31,32]

Qualification of DDTs through the formal qualification path was described.[33] The FDA reports that as of June 2016, there were 28 active biomarker projects and 49 COAs in the formal qualification program, with increased attention to the process being communicated by various stakeholders.[34,35] As detailed above, the FDA explained that the benefit of the qualification pathway was to make DDTs publicly available for a specific Context of Use (COU) to expedite drug development and review of regulatory applications. However, the FDA officers stressed that qualification is *not* required nor is it a prerequisite for a novel biomarker or COA to be used in a clinical trial, and, conversely, acceptable clinical trial endpoint measures do not have to be qualified DDTs. FDA would consider and confirm the suitability of the biomarker or COA within the context of the specific confidential Investigational New Drug (IND) or New Drug Application. New COAs and biomarkers can also be proposed and advanced to the FDA through the traditional IND pathway with the appropriate review division.

TED Investigator-led Expert Working Groups (EWGs) were formally convened with participation from regulatory consultants and industry partners. During multiple breakout sessions, the EWGs reviewed and refined landscape analyses of existing and pipelined TBI COAs, as well as genomic, proteomic, and imaging biomarkers, and emerging technology devices. EWGs also developed work plans for the advancement of TBI endpoint validation research (described below).

FDA participants attended the EWG sessions, contributing their perspectives on regulatory science and standardization, and suggesting areas of regulatory needs and requirements for EWG focus. Consultation and discussions between TED and the FDA on strategies for moving forward on a path to measurement evaluation and validation have continued throughout the year. The communications with the FDA are fostered by having two colleagues from the FDA's CDRH as members of the TED Government Steering Committee and an alliance with the Critical Path Institute, the nonprofit organization that was founded to deliver on the FDA's Critical Path Initiative.

TED's Alliance with C-Path has been essential to the team's progress. C-Path is an independent, non-profit organization dedicated to bringing scientists from the FDA, industry, and academia together to share data and collaborate to improve the drug development and regulatory processes for medical product development. C-Path has helped TED to foster alignment and collaborations with FDA and other organizations, facilitating the integration of novel regulatory science initiatives and applying knowledge from C-Path's Coalition Against Major Diseases (CAMD) to target drug development in patients with neurodegenerative disease.[47, 48]

Traumatic Brain Injury Endpoints Development Stage I Accomplishments and Progress

Collaboration with the U.S. Food and Drud Administration

Submission of two responses to the U.S. Food and Drud Administration's request for information on biomarkers. Following TED's Consensus Conference, the Initiative engaged with regulators on a variety of fronts. In February 2015, the FDA released a Federal Register notice docket (FDA-2014-N-2187) requesting comments on *Identifying Potential Biomarkers for Qualification and Describing Contexts of Use to Address Areas Important to Drug Development*. TED investigators from the Blood-based Biomarker EWG submitted a response proposing that TBI protein biomarkers could be useful in assisting drug development as predictive, pharmacodynamic, or surrogate biomarkers. This response focused on glial fibrillary acidic protein (GFAP) because it fulfills a majority of the attributes of a biomarker for TBI drug development.[36]

The Neuroimaging EWG likewise submitted a response addressing the critical need for more definitive diagnostic and prognostic markers of mild TBI to permit better patient stratification into therapeutic and rehabilitative interventions.[37] The group posited that pathoanatomic lesions on brain structural MRI will provide greater diagnostic sensitivity than CT, the only currently approved modality.

Response to the U.S. Food and Drud Administration Clinical Outcome Assessment Compendium. In February 2016, the FDA announced the establishment of a docket to receive suggestions, recommendations, and comments from interested parties on their pilot ''Clinical Outcome Assessment Compendium'' (COA Compendium). Comments received on the pilot COA Compendium are intended to help FDA determine its utility and may assist the FDA in developing future iterations of the COA Compendium and identifying best methods for conveying COA Compendium information on the FDA's website. The TED COA EWG submitted a response to the compendium, which is now of public record.[38]

Critical Path Innovation Meeting. Working with regulatory experts from C-Path, TED initiated an FDA Critical Path Innovation Meeting on March 22, 2016. Using this formal mechanism, the FDA's CDER can engage investigators from industry, academia, patient advocacy groups, and government to improve efficiency and success in drug development. The objectives of the meeting were 3-fold: 1) obtain advice on regulatory pathways the FDA believes are most appropriate for advancing the proposed types of biomarkers for use in TBI clinical trials; 2) discuss evidentiary considerations for biomarker standardization in support of reliability and reproducibility of candidate biomarkers; and 3) obtain FDA input on the ongoing and prospective observational clinical cohort studies of neuroimaging and/or biofluid biomarkers for use as diagnostic, prognostic, and predictive biomarkers in TBI trials.

The meeting specifically explored the TED team's proposal for the imaging biomarker T2*-weighted gradient recalled echo (GRE) MRI, and GFAP as a biofluid biomarker as tools for pathoanatomic stratification of patients with TBI and enrichment of cohorts for clinical trials. The CPIM was convened by CDER and was attended by leadership from CDRH, DNP, and other divisions, along with biostatisticians and other FDA personnel. The robust discussion regarding the evidence base for these two biomarkers resulted in the FDA's recommendation that we explore the Letter of Support pathway as a public first step toward the FDA's acceptance of these modalities as enrichment biomarkers with diagnostic properties for use in future clinical trials, and, depending upon future analysis of the evidence, as prognostic or predictive biomarkers, following validation studies. A Letter of Support was issued on March 31, 2017, to further explore neuroimaging prognostic biomarkers that may be used to enrich TBI clinical trials with patients who display particular pathoanatomic features that have been associated with poor short-to-medium outcome following mild TBI. This letter, signed by Dr. Janet Woodcock, Director, FDA Center for Drug Evaluation and Research, represents a significant step forward for the field and an important accomplishment for the TED initiative. In addition, TED also received a FDA Recognition Letter of Research Importance regarding TBI. It is signal

recognition of the importance and value FDA places on TED's collaborative work with the NINDS-funded TRACK-TBI investigators and our public and private partners.

U.S. Food and Drud Administration Public Workshop: Advancing the Development of Biomarkers in Traumatic Brain Injury. Although not an undertaking of the TED Initiative, the FDA convened a public workshop in March 2016 on *Advancing the Development of Biomarkers in TBI* under the aegis of an FDA working group including an appointed FDA Commissioner's Fellow specifically tasked with coordinating FDA's collaborations with the TED enterprise, and the Agency's efforts to engage in regulatory science with research and industry communities in the field of TBI. A number of TED investigators served as speakers and panelists in this day-long meeting that discussed challenges and solutions related to biomarker development methodologies, and strategies for data standardization, sharing, and analysis of big datasets for TBI.

Expert Working Group objectives

The Neuroimaging EWG set an overarching goal to identify the requirements and expectations necessary for validation of an imaging method for utilization as a diagnostic, prognostic, or predictive modality for TBI. A secondary objective was to review current imaging methods as they pertain to TBI and make recommendations regarding what, if any, further validation is required and/or if new imaging modalities are needed.

Following discussions with the FDA's CDRH, in May 2016, the Neuroimaging EWG submitted TED's proposal to the MDDT qualification program, nominating two imaging common data elements, contusions and hemorrhagic axonal injury assessed according to a panel of MRI sequences, as prognostic neuroimaging biomarkers. These prognostic biomarkers are to serve as enrichment tools for the recruitment of participants into TBI clinical trials. This proposal was the first to be accepted by the CDRH into the Incubator Phase of the MDDT Pilot Program and, following iterative feedback and submission of analytic plans, has moved to the qualification stage. The tool is designed to facilitate the inter-rater reliability of imaging studies by linking each Neuroimaging CDE descriptive item with the pathoanatomic abnormality it describes, delineated directly on the images. As an MDDT tool, this will permit investigators and clinicians to systematically apply the CDEs to evaluate brain MRI scans for the presence of lesions in patients with suspected TBI.

The Blood-based Biomarker EWG set goals aimed at coordinating biosample collection and data collection among TED-linked major clinical TBI studies and advancing one or more blood-based biomarker(s) to regulatory acceptance, potentially through the FDA Biomarker Qualification Program. A preliminary step under consideration is a Letter of Support for the candidacy of GFAP and ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL-1) as prognostic biomarkers. Finally, a number of the scientific experts of this group are also contributors to the IntBIR biomarker working group. Scientific discovery and development of novel biomarkers with focus on standards and validation processes are being coordinated across both TED and IntBIR in order to maximize knowledge sharing and global impact.

The COA EWG set as its ultimate goal the development of a complex, multi-dimensional modeling of TBI outcome measurement that moves us closer to a neurobiopsychosocial understanding of TBI effects and recovery. The neurobiopsychosocial model suggests that the understanding and prediction of outcome post-mTBI relies on a broad matrix of predictor domains that incorporates pre-injury function (e.g., cognitive, behavioral, and psychosocial function, genotype), injury specifics and context (e.g., severity, frequency, mechanism, and pathology), immediate post-injury events (e.g., acute characteristics, diagnosis, and treatment), and intervening life events (e.g., life stressors). A multi-dimensional approach to outcome measurement (e.g., neurobiological, cognition, psychological health, quality of life, and vocational/life function) is critical to capture the full-spectrum outcome. The EWG has created an initial roadmap for development of a proposed model intended to measure outcomes across functional domains commonly affected by TBI in a hierarchical framework that allows characterization of acquired impairment at the global, phenotypic, or specific skill level.

Curating and harmonizing multiple studies to create the Traumatic Brain Injury Endpoints Development Metadataset

Development of a curation and harmonization methodology. By leveraging legacy datasets from studies led by TED Co-Investigators, the wider international TBI community, and the ongoing TRACK-TBI study, the TED Metadataset has been created. The TED Metadataset contains granular data on nearly 5000 mild, moderate, and severe TBI study participants across eight studies. The constituent studies include TRACK-TBI Pilot, TRACK-TBI, COBRIT, TBICare, Concussion Research Consortium, ProTECT III, and Mission Connect, and a NINDS-funded mTBI imaging study. These datasets combine to form a wealth of TBI clinical research studies addressing the spectrum of injury severity, and include a wide range of COAs, neuroimaging data, and biospecimens.

Extensive and ongoing work by TED teams has resulted in a methodology that permits harmonization of data collected from the myriad outcome assessments used in the different studies that comprise the Metadataset.[39] Individual tables map the baseline characteristics and clinical variables that have been collected across Metadataset studies (Supplementary Appendix) (see online supplementary material at http://www.liebertpub.com) and a table of contents is accessible through the TED website (https://tbiendpoints.ucsf.edu/). This essential step will now permit TED investigators and potential collaborators to have both a high-level overview of the Metadataset, as well as harmonized demographic and clinical data when planning potential research projects.

Data Use and Human Materials Transfer Agreements, a Publication and Authorship Policy Guideline, and a Research Collaboration Policy for the TED Initiative, were drafted and posted to the TED website to serve as the backbone intellectual property agreements for collaborations utilizing the TED Metadataset.

Consensus data standards for traumatic brain injury. TED's early focus on data standardization has included our investigators' productive partnership with NINDS, the CDISC, One Mind, and C-Path to translate the TBI CDEs into TBI CDISC therapeutic data standards.[40] The TBI-CDEs were the first consensus-based approach to establish data standards for TBI research. They include demographics, clinical care, genetic and proteomic biomarkers, neuroimaging, and outcome measures[41–45] and have expanded recently into preclinical CDEs.[46]

This standardization represents another essential go-forward mechanism to enable efficient analyses and integration of future prospective TBI studies that integrate novel blood-based and neuroimaging biomarkers, as well as COA measures, into

observational and randomized, controlled, clinical trials. The overall benefit is reduced costs and a shortened timeline for providing patients with safe, effective new treatments.

The FDA's Data Standards Strategy calls for comprehensive data standards to facilitate the review of regulatory submissions, and will soon be required in most FDA submissions. In addition, to improve efficiency in regulatory review, these standards will reduce variability of data mapping, and enable reviewers to combine data from multiple sources in a consistent format for analysis.

Validation studies: The TED Seed Projects. The program announcement for the TED Initiative called for the allocation of TED funds for four Seed Projects—competitively selected foundational work to be completed in 1 year and designed to advance regulatory validation studies of COAs and biomarkers. The focus was on reproducibility, reliability, and regulatory science, with proposals utilizing the TED Metadataset preferred.

The Seed Projects call for proposals was developed by the TED Executive Committee and its announcement was publicized to the global scientific community in mid-2015. Forty-one Letters of Intent were received in response to the Request for Application. Following review by the TED Executive Committee, 11 were invited to submit full applications, of which 10 were received. Internationally known experts across all relevant domains of TBI investigation, including COAs, proteomic biomarkers, neuroimaging, and biostatistics, served as reviewers. In addition, each full application was reviewed by C-Path to assess its state of FDA regulatory science readiness.

Four, 1-year Seed Project awards have been selected by the Government Steering Committee and were launched in early 2016: Two are COA-focused and in keeping with the overarching TED aim of identifying COA's that are valid for use in TBI clinical trials, with particular consideration of different Contexts of Use (COUs). One proposes a methodology to assess and compare COAs; the other proposes development of a novel composite cognitive outcome measure. One proposal in neuroimaging seeks to validate as a prognostic imaging biomarker the NIH imaging CDEs for mild-to-moderate TBI (and is the basis of the proposed MDDT tool, described above), and one proposal in biofluid protein blood biomarkers will systematically and rapidly fill in knowledge gaps concerning standardization of assay formats for key biomarkers and improve their overall regulatory readiness.

Alignment with the National Research Action Plan. In 2012, President Obama issued an Executive Order directing the Department of Defense, Veteran Affairs, Health and Human Services and Education to develop a National Research Action Plan (NRAP) on TBI, post-traumatic stress disorder, and other mental conditions ''to improve the coordination of agency research into these conditions and reduce the number of affected men and women through better prevention, diagnosis, and treatment.'' The TED initiative is responsive to several of the key, cross-cutting research priorities identified in the NRAP.[49] By maximizing the impact of existing research through the NIH/NINDS-funded TRACK-TBI, DoD/VA-funded CENC, and DoD/NCAA Concussion Assessment, Research and Education Consortium, and utilizing existing and emerging information technology to facilitate access and analysis of the TBI Metadataset, the TED Public-Private Partnership is improving our understanding and care for individuals with TBI.

Future Directions

Near-term goals

TED will continue its collaborative work with the FDA toward validation of novel COAs and validation methodology for blood-based and neuroimaging biomarkers, and support dissemination of results to the communities of interest through publications, scientific workshops/conferences, and FDA public meetings.

Long-term goals

TED's forward objectives will lead to a streamlined path for FDA endorsement of a library of novel biomarkers and improved outcome measures. The cross-cutting nature of TBI sequelae (cognitive, psychological, and neurobehavioral) with other neurological diseases suggests that progress in TBI biomarker and COA measure development has implications for improvements in these conditions and other diseases as well. The timing of TED activities aligns well with the FDA's growing attention to change and transparency and are in accord with the FDA's recommendations to embrace common clinical data standards and biospecimen databases for novel candidate biomarkers.[50,51]

Current government, policy, and regulatory attention to precision medicine[52,53] clearly align with TED's vision to improve stratification of heterogeneous patient subgroups within the traditional TBI population.

Conclusion

The current landscape of health care is a crowded space where public private partnerships and pre-competitive collaborations are commonplace.[54] In fact, industry colleagues have expressed concern about the possibility of ''consortia fatigue,'' particularly in disease areas such as AD for which there are many ongoing pre-competitive initiatives.[55] Initiatives such as the Alzheimer's Neuroimaging Initiative (ADNI) clearly paved the way for open data sharing, consensus data standards, and collaboration.[56] The TBI equivalent of the ADNI, TRACK-TBI, shares many attributes with the ADNI and is already making significant progress in advancing the unmet needs for TBI.[44,57–61]

The TBI landscape is distinct, however, given the paucity of therapies under active development compared to other neurological diseases. In TBI, the necessity for pre-competitive collaboration in order to share the cost and risk is critically evident in an area where: 1) currently no treatments exist; 2) the failure rate in clinical trials of potential treatments is very high; and 3) there is a lack of sensitive, well-validated biomarkers and clinical endpoints.

TED's ''all-encompassing'' strategy of regulatory science and engagement has the potential to be transformational and reduces the risk of focusing on a single pathway, drug, or device for success. As commercial entities, such as device companies and the pharmaceutical industry, engage with TED, the balance between the focus on expanding pre-competitive space while simultaneously supporting individual candidate diagnostic and drugs for approval will be an issue to address.

In summary, TED's regulatory science focus exceeds that of most all diseases. Even in some diseases that have been engaged in regulatory qualification for years,[48] progress has been slow. It is anticipated that with TED's proactive strategy to aggressively tackle bottlenecks and barriers that have proved to be challenging in other consortia (e.g., lack of sharing/consent for use of biospecimen repositories and absence ofconsensus data standards) will

facilitate progress, with an impact that will be substantial, measurable, and significant.

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References

1. Coronado, V.G., McGuire, L.C., Sarmiento, K., Bell, J., Lionbarger, M.R., Jones, C.D., Geller, A.I., Khoury, N., and Xu, L. (2012). Trends in traumatic brain injury in the U.S. and the public health response: 1995–2009. J. Safety Res. 43, 299–307.
2. Centers for Disease Control and Prevention. (2011). Nonfatal traumatic brain injuries related to sports and recreation activities among persons aged </=19 years—United States, 2001–2009. MMWR Morb. Mortal. Wkly. Rep. 60, 1337–1342.
3. Centers for Disease Control and Prevention (CDC), National Center for Injury Prevention and Control. (2003). Report to Congress on mild traumatic brain injury in the United States: steps to prevent a serious public health problem. Centers for Disease Control and Prevention: Atlanta, GA.
4. Faul, M., Xu, L., Wald, M.M., Coronado, V., and Dellinger, A.M. (2010). Traumatic brain injury in the United States: national estimates of prevalence and incidence, 2002–2006. Inj. Prev. 16, A268–A268.
5. Plassman, B.L., Havlik, R.J., Steffens, D.C., Helms, M.J., Newman, T.N., Drosdick, D., Phillips, C., Gau, B.A., Welsh-Bohmer, K.A., Burke, J.R., Guralnik, J.M., and Breitner, J.C. (2000). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 55, 1158–1166.
6. Omalu, B., Hammers, J.L., Bailes, J., Hamilton, R.L., Kamboh, M.I., Webster, G., and Fitzsimmons, R.P. (2011). Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. Neurosurg. Focus 31, E3.
7. DeKosky, S.T., Blennow, K., Ikonomovic, M.D., and Gandy, S. (2013). Acute and chronic traumatic encephalopathies: pathogenesis and biomarkers. Nat. Rev. Neurol. 9, 192–200.
8. Thurman, D.J., Alverson, C., Dunn, K.A., Guerrero, J., and Sniezek, J.E. (1999). Traumatic brain injury in the United States: a public health perspective. J. Head Trauma Rehabil. 14, 602–615.
9. Research!America. (2013). Investment in research saves lives and money. [Fact sheet]. Arlington, VA. http://www.researchamerica.org/sites/default/files/TBI_%202016.pdf (last accessed June 20, 2017).
10. Haas, M., Mantua, V., Haberkamp, M., Pani, L., Isaac, M., Butlen-Ducuing, F., Vamvakas, S., and Broich, K. (2015). The European Medicines Agency's strategies to meet the challenges of Alzheimer disease. Nat. Rev. Drug Discov. 14, 221–222.
11. Kozauer, N., and Katz, R. (2013). Regulatory innovation and drug development for early-stage Alzheimer's disease. N. Engl. J. Med. 368, 1169–1171.
12. Butlen-Ducuing, F., Petavy, F., Guizzaro, L., Zienowicz, M., Haas, M., Alteri, E., Salmonson, T., and Corruble, E. (2016). Regulatory watch: challenges in drug development for central nervous system disorders: a European Medicines Agency perspective. Nat. Rev. Drug Discov. 15, 813–814.
13. FDA. (2015). Targeted drug development: why are many diseases lagging behind? FDA: Silver Spring, MD.
14. Teasdale, G., and Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. Lancet 2, 81–84.
15. Ruff, R.M., Iverson, G.L., Barth, J.T., Bush, S.S., and Broshek, D.K.; NAN Policy and Planning Committee. (2009). Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper. Arch. Clin. Neuropsychol. 24, 3–10.
16. Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury. (2010). Department of Defense Coding Guidance for Traumatic Brain Injury Fact Sheet [Fact Sheet]. Silver Spring, MD. http://dcoe.mil/files/Fact-Sheet-Summarizing-VA-DoD-Evidence-Based-Clinical-Practice-Guidelines-for-Management-of-Concussion-Mild-Traumatic-Brain-Injury.pdf (last accessed June 20, 2017).
17. Furger, R.E., Nelson, L.D., Brooke Lerner, E., and McCrea, M.A. (2016). Frequency of Factors that Complicate the Identification of Mild Traumatic Brain Injury in Level I Trauma Center Patients. Concussion 1, Future Medicine, Ltd. on behalf of the Drake Foundation, London, United Kingdom.
18. Wilson, J.T., Pettigrew, L.E., and Teasdale, G.M. (1998). Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J. Neurotrauma 15, 573–585.
19. Rubiano, A.M., Carney, N., Chesnut, R., and Puyana, J.C. (2015). Global neurotrauma research challenges and opportunities. Nature 527, S193–S197.
20. Tosetti, P., Hicks, R.R., Theriault, E., Phillips, A., Koroshetz, W., and Draghia-Akli, R. (2013). Toward an international initiative for traumatic brain injury research. J. Neurotrauma 30, 1211–1222.
21. Garber, K. (2007). Stroke treatment—light at the end of the tunnel? Nat. Biotechnol. 25, 838–840.
22. FDA. (2015). Critical Path Initiave. FDA: Silver Spring, MD.
23. Woodcock, J., Buckman, S., Goodsaid, F., Walton, M.K., and Zineh, I. (2011). Qualifying biomarkers for use in drug development: a US Food and Drug Administration overview. Expert Opin. Med. Diagn. 5, 369–374.
24. Woodcock, J., Griffin, J.P., and Behrman, R.E. (2011). Development of novel combination therapies. N. Engl. J. Med. 364, 985–987.
25. FDA. (2016). Biomarker Qualification Program. FDA: Silver Spring, MD.
26. CDER. (2014). Qualification Process for Drug Development Tools. FDA Center for Drug Evaluation and Research: Silver Spring, MD.
27. EMA. (2009). Qualification of novel methdologies for drug development: guidance to applicants. European Medicines Agency: London.
28. FDA. (2015). Manual of policies & procedures. FDA: Silver Spring, MD.
29. Isaac, M., and Gispen-de Wied, C. (2015). CNS biomarkers: potential from a regulatory perspective: case study—focus in low hippocampus volume as a biomarker measured by MRI. Eur. Neuropsychopharmacol. 25, 1003–1009.
30. Hill, D.L., Schwarz, A.J., Isaac, M., Pani, L., Vamvakas, S., Hemmings, R., Carrillo, M.C., Yu, P., Sun, J., Beckett, L., Boccardi, M., Brewer, J., Brumfield, M., Cantillon, M., Cole, P.E., Fox, N., Frisoni, G.B., Jack, C., Kelleher, T., Luo, F., Novak, G., Maguire, P., Meibach, R., Patterson, P., Bain, L., Sampaio, C., Raunig, D., Soares, H., Suhy, J., Wang, H., Wolz, R., and Stephenson, D. (2014). Coalition Against Major Diseases/European Medicines Agency biomarker qualification of hippocampal volume for enrichment of clinical trials in predementia stages of Alzheimer's disease. Alzheimers Dement. 10, 421–429.e3.
31. McMurry-Heath, M., and Hamburg, M.A. (2012). Creating a space for innovative device development. Sci. Transl. Med. 4, 163fs143.
32. O'Callaghan, K. (2013). Medical Device Development Tools, Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff. FDA: Silver Spring, MD.
33. FDA. (2015). Drug Development Tools (DDT) Qualification Programs. FDA: Silver Spring, MD.
34. Lavezzari, G., and Womack, A.W. (2016). Industry perspectives on biomarker qualification. Clin. Pharmacol. Ther. 99, 208–213.

35. Fehnel, S., DeMuro, C., McLeod, L., Coon, C., and Gnanasakthy, A. (2013). US FDA patient-reported outcome guidance: great expectations and unintended consequences. Expert Rev. Pharmacoecon. Outcomes Res. 13, 441–446.
36. Wang, K.K., Stephenson, D., Robbins, A., Markowitz, A., Diaz-Arrastia, R., Jeromin, A., and Manley, G. (2015). TRACK-TBI and TED team response to FDA biomarker RFI. https://www.regulations.gov/document?D=FDA-2014-N-2187-0015 (last accessed June 20, 2017).
37. Muhkerjee, P., Mac Donald, C., Stephenson, D., Robbins, A., Markowitz, A. and Manley, G. (2015). TRACK-TBI and TED team response to FDA biomarker RFI. https://www.regulations.gov/document?D=FDA-2014-N-2187-0022 (last accessed June 20, 2017).
38. Manley, G.T. and the TED Investigators. (2016). Clinical Outcome Assessment Compendium Request for Comments. https://www.regulations.gov/document?D=FDA-2015-N-5106-0010 (last accessed June 20, 2017).
39. TRACK_TBI_Investigators. (2015). TED Metadataset. Traumatic Brain Injury Endpoints (TED) Initiative: San Francisco, CA.
40. Clinical Data Interchange Standards Consortium (CDISC). (2016). Traumatic Brain Injury Therapeutic Area Data Standard User Guide v1, Austin, TX.
41. Saatman, K.E., Duhaime, A.C., Bullock, R., Maas, A.I., Valadka, A., and Manley, G.T.; ; Workshop Scientific Team and Advisory Panel Members. (2008). Classification of traumatic brain injury for targeted therapies. J. Neurotrauma 25, 719–738.
42. Duhaime, A.C., Gean, A.D., Haacke, E.M., Hicks, R., Wintermark, M., Mukherjee, P., Brody, D., Latour, L., and Riedy, G.; Common Data Elements Neuroimaging Working Group Members, Pediatric Working Group Members. (2010). Common data elements in radiologic imaging of traumatic brain injury. Arch. Phys. Med. Rehabil. 91, 1661–1666.
43. Wilde, E.A., and Levin, H.S. (2010). Introduction to the special issue on the use of advanced structural neuroimaging techniques in understanding brain-behavior relationships. Dev. Neuropsychol. 35, 231–232.
44. Yue, J.K., Vassar, M.J., Lingsma, H.F., Cooper, S.R., Okonkwo, D.O., Valadka, A.B., Gordon, W.A., Maas, A.I., Mukherjee, P., Yuh, E.L., Puccio, A.M., Schnyer, D.M., and Manley, G.T.; ; TRACK-TBI Investigators. (2013). Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury. J. Neurotrauma 30, 1831–1844.
45. Manley, G.T., Diaz-Arrastia, R., Brophy, M., Engel, D., Goodman, C., Gwinn, K., Veenstra, T.D., Ling, G., Ottens, A.K., Tortella, F., and Hayes, R.L. (2010). Common data elements for traumatic brain injury: recommendations from the biospecimens and biomarkers working group. Arch. Phys. Med. Rehabil. 91, 1667–1672.
46. Smith, D.H., Hicks, R.R., Johnson, V.E., Bergstrom, D.A., Cummings, D.M., Noble, L.J., Hovda, D., Whalen, M., Ahlers, S.T., LaPlaca, M., Tortella, F.C., Duhaime, A.C., and Dixon, C.E. (2015). Pre-clinical traumatic brain injury common data elements: toward a common language across laboratories. J. Neurotrauma 32, 1725–1735.
47. Romero, K., Ito, K., Rogers, J.A., Polhamus, D., Qiu, R., Stephenson, D., Mohs, R., Lalonde, R., Sinha, V., Wang, Y., Brown, D., Isaac, M., Vamvakas, S., Hemmings, R., Pani, L., Bain, L.J., and Corrigan, B.; ; Alzheimer's Disease Neuroimaging Initiative; Coalition Against Major Diseases. (2015). The future is now: model-based clinical trial design for Alzheimer's disease. Clin. Pharmacol. Ther. 97, 210–214.
48. Stephenson, D., Hu, M.T., Romero, K., Breen, K., Burn, D., Ben-Shlomo, Y., Bhattaram, A., Isaac, M., Venuto, C., Kubota, K., Little, M.A., Friend, S., Lovestone, S., Morris, H.R., Grosset, D., Sutherland, M., Gallacher, J., Williams-Gray, C., Bain, L.J., Aviles, E., Marek, K., Toga, A.W., Stark, Y., Forrest Gordon, M., and Ford, S. (2015). Precompetitive data sharing as a catalyst to address unmet needs in Parkinson's disease. J. Parkinsons Dis. 5, 581–594.
49. Department of Defense, Department of Veterans Affairs, Department of Health and Human Services, Department of Education. (2013). National Research Action Plan, Responding to the Executive Order Improving Access to Mental Health Services for Veterans, Service Members, and Military Families, Washington, DC.
50. Amur, S., LaVange, L., Zineh, I., Buckman-Garner, S., and Woodcock, J. (2015). Biomarker qualification: toward a multiple stakeholder framework for biomarker development, regulatory acceptance, and utilization. Clin. Pharmacol. Ther. 98, 34–46.
51. Amur, S.G., Sanyal, S., Chakravarty, A.G., Noone, M.H., Kaiser, J., McCune, S., and Buckman-Garner, S.Y. (2015). Building a roadmap to biomarker qualification: challenges and opportunities. Biomark. Med. 9, 1095–1105.
52. FDA. (2015). PrecisionFDA. FDA: Silver Spring, MD.
53. Bahcall, O. (2015). Precision medicine. Nature 526, 335–370.
54. Faster_Cures. (2015). Consortia-pedia. Millken Institute, Santa Monica, CA.
55. Snyder, H.M., Carrillo, M.C., Grodstein, F., Henriksen, K., Jeromin, A., Lovestone, S., Mielke, M.M., O'Bryant, S., Sarasa, M., Sjogren, M., Soares, H., Teeling, J., Trushina, E., Ward, M., West, T., Bain, L.J., Shineman, D.W., Weiner, M., and Fillit, H.M. (2014). Developing novel blood-based biomarkers for Alzheimer's disease. Alzheimers Dement. 10, 109–114.
56. Weiner, M.W., Veitch, D.P., Aisen, P.S., Beckett, L.A., Cairns, N.J., Cedarbaum, J., Donohue, M.C., Green, R.C., Harvey, D., Jack, C.R., Jr., Jagust, W., Morris, J.C., Petersen, R.C., Saykin, A.J., Shaw, L., Thompson, P.M., Toga, A.W., and Trojanowski, J.Q.; Alzheimer's Disease Neuroimaging Initiative. (2015). Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014. Alzheimers Dement. 11, 865–884.
57. Yuh, E.L., Mukherjee, P., Lingsma, H.F., Yue, J.K., Ferguson, A.R., Gordon, W.A., Valadka, A.B., Schnyer, D.M., Okonkwo, D.O., Maas, A.I., and Manley, G.T.; TRACK-TBI Investigators. (2013). Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. Ann. Neurol. 73, 224–235.
58. Lingsma, H.F., Yue, J.K., Maas, A.I., Steyerberg, E.W., and Manley, G.T.; TRACK-TBI Investigators. (2015). Outcome prediction after mild and complicated mild traumatic brain injury: external validation of existing models and identification of new predictors using the TRACK-TBI pilot study. J. Neurotrauma 32, 83–94.
59. McMahon, P., Hricik, A., Yue, J.K., Puccio, A.M., Inoue, T., Lingsma, H.F., Beers, S.R., Gordon, W.A., Valadka, A.B., Manley, G.T., and Okonkwo, D.O.; TRACK-TBI Investigators. (2014). Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. J. Neurotrauma 31, 26–33.
60. Ratcliff, J.J., Adeoye, O., Lindsell, C.J., Hart, K.W., Pancioli, A., McMullan, J.T., Yue, J.K., Nishijima, D.K., Gordon, W.A., Valadka, A.B., Okonkwo, D.O., Lingsma, H.F., Maas, A.I., and Manley, G.T.; TRACK-TBI Investigators. (2014). ED disposition of the Glasgow Coma Scale 13 to 15 traumatic brain injury patient: analysis of the Transforming Research and Clinical Knowledge in TBI study. Am. J. Emerg. Med. 32, 844–850.
61. Yuh, E.L., Cooper, S.R., Mukherjee, P., Yue, J.K., Lingsma, H.F., Gordon, W.A., Valadka, A.B., Okonkwo, D.O., Schnyer, D.M., Vassar, M.J., Maas, A.I., and Manley, G.T.; TRACK-TBI Investigators. (2014). Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study. J. Neurotrauma 31, 1457–1477.

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Appendix

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