BRAIN TRAUMA BLUEPRINT

STATE OF THE SCIENCE SUMMIT

SEPTEMBER 12-13, 2018

Diagnosis of Trauma-Related Disorders with a Focus on Post-Traumatic Stress Disorder (PTSD)

Inaugural Summit Proceedings

Cohen Veterans Bioscience

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Proceedings of the Inaugural Brain Trauma Blueprint State of the Science Summit: Diagnosis of Trauma-Related Disorders with a focus on Post-Traumatic Stress Disorder (PTSD)

Abstract Overview:
Cohen Veterans Bioscience (CVB), is leading the development, advocacy and implementation of a Brain Trauma Blueprint (BTB) collectively created from past and current research activities to help guide development efforts and accelerate the progression towards a new generation of precision diagnostics and targeted therapeutics for trauma related brain disorders. The development of the BTB is facilitated through a series of *State of the Science Summits* (SOSS) that will foster collaboration across a multidisciplinary stakeholder community to advance translational research.

Better aligning clinicians and researchers around diagnostic methodologies and assessment tools could increase diagnostic validity, facilitate biomarker discovery, and accelerate the rate of therapeutic development for a range of trauma-related disorders. This inaugural SoSS sought to gain consensus and make evident the state of the science in seven key areas relevant to diagnosis of post-traumatic stress disorder (PTSD) and the gaps in our knowledge and technology that, if filled, could advance the development of diagnostics and therapeutics for these disorders. The output of the first SoSS was a prioritized list of specific recommendations to fill the identified gaps and advance the field to advocate for expanded funding and adoption by diverse stakeholders, and to inform the next generation of translational research and precision medicine.

Method: For the inaugural SoSS, a group of diverse thought leaders from the field of Brain Trauma was selected to form a Scientific Planning Committee (SPC) to envision, plan, and execute the working meeting and the current state of the science. The initial steps involved synthesizing a literature review of the most essential research conducted to date in diagnosing trauma-related brain disorders. This synthesis provided a landscape and guided discussions for a productive working group meeting with more than 100 thought leaders in clinical research of trauma-related brain disorder diagnosis, genomics, proteomics, neural circuitry, psychophysiology, comorbidities, developmental factors, biomarker discovery and validation, and data analysis and modeling methodology. Stakeholders considered the purpose and value of diagnosing these disorders, evaluated current and proposed methodologies for diagnosis, and debated potentially adjusting the perspective on diagnosis by aligning diagnostic methodologies and assessment tools with the underlying mechanism of the conditions. Attendees represented a variety of prominent academic institutions; government agencies, including the Veterans Administration, Department of Defense, and the National Institutes of Health; advocacy groups; and other not-for-profit organizations. Attendees worked to build consensus around knowledge gaps and discuss strategies to leverage the combined intellectual resources of the scientific and clinical communities in order to create a translational research activity blueprint and explore research priorities to augment those activities and fill gaps. Working groups have formed for post-conference discussions to generate a formal statement of consensus on research priorities.

Conclusion: The SoSS strengthened the cohesion of the scientific, clinical, and patient communities of PTSD to enhance opportunities for future collaboration. Immediately, the summit

resulted in seven documents summarizing different disease models of PTSD with the goal of perpetual updates to these documents as the research advances. These documents are considered “living”, as they will be hosted on the BTB website and available for comments and additions by the broader community. Moreover, the summit resulted in working groups committed to addressing the areas identified as needing additional follow-up. These working groups will develop and vet a strategic list of next steps in their specific area that can then be used by the community to fund and conduct future research leading to improved precision medicine diagnostics for patients experiencing PTSD and brain trauma related disorders.

Background

Exposure to trauma is a common occurrence with a lifetime prevalence of over 80% (Kilpatrick et al., 2013). Approximately 6% of trauma survivors, including 10 to 20% of military personnel suffer devastating long-term neurobiological symptoms. These post-traumatic sequelae can result in a diagnosis of post-traumatic stress disorder (PTSD), depression, substance abuse, chronic pain, and other psychological and somatic concerns. Traumatic brain injury (TBI) occurs following a physical insult to the brain, and long-term sequelae include memory loss, headaches, and symptoms similar to the aforementioned mood disorders, as well as other medical conditions. The prevalence of exposure to trauma and its ensuing sequelae make the diagnosis and treatment of trauma-related disorders a public health issue of great magnitude.

In spite of the prevalence of trauma and trauma-related brain disorders and the toll they take on individuals and their families, few pharmacological treatments are available. For example, no new medications have been approved for PTSD in the last 17 years, and the only two that are approved target the same biological mechanism, have shown equivocal results in some populations, and have side effects that can limit compliance. Furthermore, patients suffering from PTSD are often prescribed multiple medications that have not been thoroughly investigated for the treatment of PTSD and in some instances may be contraindicated (Krystal et al., 2011). Clearly, new diagnostics and therapies to relieve the long-term effects of trauma need to be identified and developed.

PTSD and TBI patient populations are extremely heterogenous, representing a major hurdle to assessing therapeutic efficacy. The clinical presentation and etiology of these disorders are also heterogeneous, highly complex, and frequently comorbid with other disorders. For this reason, the research community has repeatedly identified a need to establish a mechanism-based taxonomy for these conditions – one that could advance biomarker discovery, precision diagnosis, and targeted therapeutic development. Clinical diagnostic methods such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) serve an important clinical function. However, these approaches are categorical and syndromic in orientation. An increased understanding of the underlying biology of neuropsychiatric disorders indicates that other dimensional or construct-based models of diagnosis might better reflect the underlying pathology and hasten the identification of biomarkers and therapies. This kind of shift requires a review of current scientific knowledge, adoption of new scientific models, and identification of research and knowledge gaps.

The Brain Trauma Blueprint (BTB) is an initiative that seeks to accelerate the path to precision medicine in trauma-related brain disorders by bringing transparency to translational research efforts, and the gaps therein, to all stakeholders, regardless of sector. The BTB is operationalized through SoSS's that each explore in depth major gaps in understanding as identified by key stakeholders. Cohen Veterans Bioscience (CVB), in consultation with the Veterans Administration (VA), Department of Defense (DoD), and the National Institutes of Health (NIH), selected the topic for the first State of the Science Summits (SoSS) to be the diagnosis of trauma-related brain disorders, related to PTSD. The goal of this inaugural SoSS was to explore and assist in the shift to a mechanistic taxonomy of trauma-related brain disorders, related to PTSD.

Methods

The first SoSS was launched in January 2018 with the establishment of a chartered Scientific Planning Committee (SPC) consisting of an interdisciplinary group with deep expertise

in PTSD from different perspectives and employing various types of research tools (e.g., genomics, imaging, big data analytics). The role of the SPC was to guide the development of the inaugural SoSS as an engaging and dynamic working meeting with defined deliverables that would help move the field forward. The SPC helped to develop the agenda, identify speakers, and invite a broad array of expert stakeholders to join in the meeting preparation and activities. The SPC aimed to leverage and engage the broader ecosystem. In particular, the agenda included limited focus on the justification of the meeting, and instead honed in on gaining consensus on the work being done and the areas not yet under investigation or being fully addressed.

This SoSS was designed as a two-day retreat for over 100 stakeholders to come together to impact research and development for trauma-related disorders. The SPC designed the meeting such that it was not redundant with other efforts in the field, that all attendees started on the same page, and that everyone had a clear understanding of where we are in the field. To that end, the SPC identified key areas of research that inform either disease mechanisms of action, potential susceptibility or risk factors, and the tools with which to investigate these areas. In recognition of psychological health as a dynamic interaction between molecular, humoral, neurocircuitry, psychophysiology, social, behavioral, comorbidity, and environmental factors, the SPC divided the translational research work into these seven areas. With CVB team members and more than 20 experts in the field, the SPC synthesized the state of the science related to the diagnosis of trauma-related brain disorders for each of these topics. This approach supports the idea that diagnosis of trauma-related disorders warrants an expanded, multidimensional approach that must be validated using various investigative domains and methods. These summaries served as the launching point for the working sessions of the meeting and optimized productivity.

The inaugural SoSS was held September 12th and 13th, 2018 in Silver Spring, Maryland. At the meeting, stakeholders considered the purpose and value of diagnosing trauma-related disorders, discussed the current and proposed methodologies for diagnosis, and debated potentially adjusting the perspective on diagnosis by aligning diagnostic methodologies and assessment tools with the underlying mechanism of the conditions (see agenda below). Attendees represented a variety of prominent academic institutions and government agencies, including the VA, DoD, and NIH; advocacy groups; and other not-for-profit organizations. Diverse representation was essential for creating an effective translational research activity blueprint and exploring research priorities to augment those (see list of organizations represented in Appendix 1).

In addition to lectures and debates, the meeting included two working sessions. For the working session of the first day, participants were divided into breakout groups based on expertise and topic of interest and asked to discuss one of the seven areas that impact the diagnosis of PTSD. For the working session of the second day, cross-team discussion was encouraged as participants were randomly assigned to one of four groups and asked to consider forward-looking questions including (1) discuss how identified gaps in one area might be addressed by information in another area, (2) consider how tools from one area could be used to evaluate research questions in another area, and (3) prioritize gaps and identify short-term opportunities for improvements. During the final session of the meeting, attendees voted upon joining future working groups to further discussions around gaps that were identified building toward the future BTB development.

Proceedings of the Inaugural SoSS

Opening Session

Session Goal: To demonstrate the need for a new taxonomy while orienting attendees to the use of the interactive event app.

In an interactive opening, Keith Robinson, CVB Director of Operations and Theresa Frangiosa, CVB Board Secretary, presented the results of a focused market research effort interviewing emergency room (ER) physicians, psychiatrists, and clinical psychologists with the goal of understanding how and why we currently diagnose trauma-related disorders and whether new tools leading to more precise diagnostics would be accepted by the clinical community. The take-home messages from these physicians were:

(1) ER physicians do not attempt to diagnosis PTSD, partly because of the amount of time the current diagnostic tools require and partly due to a lack of training in the area. However, they would consider using a rapid objective diagnostic tool, if available.
(2) Clinicians primarily use clinical history over scales such as the Clinician-Administered PTSD Scale (CAPS) or the PTSD checklist (PCL) as their primary diagnostic tool.
(3) Most clinicians report treating patient symptoms irrespective of diagnosis, particularly in acute stages of disease.

This last point is in contrast to the tools that researchers and diagnostic and therapeutic developers use in their clinical development programs. Indeed, in an audience-participation poll during the presentation more than 85% of clinicians reported treating patients based on symptoms, compared to the 15% who treated based on a diagnosis.

The audience then voted on a list of clinical priorities to move the field of diagnosis forward:

(1) Identifying candidate biomarkers for diagnosis and treatment;
(2) Determining whether there are biological differences between combat-related and non-combat-related (civilian) PTSD;
(3) Understanding the mechanisms underlying trauma-related symptoms; and
(4) Identifying moderators that could impact the development and presentation of PTSD and the neuropsychiatric sequelae of TBI.

Key Take-Away: These major priorities focused the rest of the SoSS activities.

Welcome and Call To Action

Session Goal: To preview the goals and processes of the meeting, consider the overall mission, and deliver the call to action.

The next session included orientation and welcoming addresses by CVB, the VA, and the George W. Bush Institute. Dr. Allyson Gage, CVB's Chief Medical Officer, presented the overall meeting goals and highlighted the value of public-private partnerships in such efforts. Dr. Gage gave examples of precision diagnostic approaches applied successfully in other fields. One example was cardiovascular disease where extensive research has shown the value of objective tests in the diagnostic process, including histology, blood pressure, heart rate, blood tests, electroencephalogram, and imaging. The diagnostic landscape of each individual patient allows targeted treatments to be developed for their specific pathology.

Kacie Kelly, Deputy Director of the George W. Bush Presidential Center's Military Service Initiative, indicated that her organization is uniquely positioned to bring together thought leaders and diverse expertise to solve problems on a national and international level. The Center's Warrior Wellness Alliance connects high-quality care providers and veteran peer networks to

help support treatment for the invisible wounds of war, including PTSD. The Alliance has convened 13 organizations across the public-private sectors, including veteran peer networks and research or clinical groups who are working collaboratively to address the invisible wounds of war. Ms. Kelly stressed the importance of our "customers" being integrated into the solution building and urged participants to come together to develop a strategy to develop better treatments for trauma-based mental health disorders.

Rachel Ramoni, DVM, Chief Research and Development Officer at the VA, indicated the VA's view of the BTB as an organizing force to understand the shape of diagnosis, treatment, and prevention of these conditions. Dr. Ramoni highlighted the substantive resources available through the VA, including access to over 20 years of health records and 24 million people with a predisposition to service. For example, the Million Veteran Program (MVP) has enrolled around 700,000 veterans to build one of the largest and most comprehensive medical databases. The MVP links the genetic information, military exposure, lifestyle, and health information of veteran volunteers, making them available for medical research. Dr. Ramoni indicated that the VA is eager to collaborate under the BTB and could make available several resources that might be useful for classifying disease taxonomy and improving the diagnosis of PTSD and chronic TBI. For example, the VA could analyze health records to find sub-phenotypes that cluster together. Due to the VA's ongoing collaboration with the Department of Energy, data scientists and the most powerful computers could be available to do advanced analytics on these data. Dr. Ramoni closed the session with a powerful call to action: stating that if the SoSS working groups provide prioritized, specific, and actionable research goals, her office would consider these in future strategic planning. This would make the work done at the SoSS immediately impactful in the field and accelerate the realization of precision medicine in trauma-related brain disorders.

WHY A DISEASE TAXONOMY?

Session Goal: The goal of this session was to explore the concept of nosology and how the taxonomy we use directly impacts our ability to leverage scientific and technological advances to find targeted therapeutics.

Dr. Magali Haas, M.D., Ph.D., CVB's Chief Executive Officer and President, started the session by describing the historical development of diagnostics originating from Babylon around 1000 B.C.E. with a systematized diagnosis syndromic classification approach that survives in the current medical handbooks of mental health, including the ICD-11 and the DSM-5. Dr. Haas emphasized that phenomenological nosology does not map well onto biomarker-driven constructs, pathways, and circuits that underlie disease pathology. Further, theoretical frameworks that consider neuropsychiatric disorders such as PTSD as homogeneous conditions undermine progress in therapeutic target identification and development of precision approaches that might target a patient subset.

The complex, multifactorial and dynamic nature of most neuropsychiatric disorders means that focusing on individual 'omics (genomics, transciptomics, etc.) in isolation, are insufficient for developing mechanistic models of disease. Emerging evidence suggests that approaches involving systems' modeling to identify biotypes, and analyses of datasets on multiple dimensions, might result in better outcomes. As an example of where this novel approach is yielding promising results, Dr. Haas presented data provided by Dr. Carol Tamminga from the Bipolar-Schizophrenia Network for Intermediate Phenotypes. Patients with psychoses and their first-order relatives were parsed using cognitive and neurophysiological measures as well as

traditional classification. The study showed that data-driven biotypes were better predictors of the gray matter density than symptom-based classification and could accurately identify healthy controls and different affected populations (Ivleva et al., Biol Psych, 2017). Using another novel approach, Dr. Steve McCarroll's group combined analyses of 65,000 individual genomes, 700 postmortem brains, and mouse genetic engineering to identify genetic factors associated with schizophrenia. The results were surprising: overexpression of complement component 4, a synaptic pruning protein never before hypothesized to be involved in psychiatric disorders, was associated with greater risk of schizophrenia (Sekar et al., 2016). Research approaches such as these highlight the importance and viability of developing a mechanism-based taxonomy of disease, as it could lead to objective outcomes. Dr. Haas highlighted the mission and approach of the Aetionomy project, led by Dr. Martin Hofman-Apitius in Europe, to develop a mechanistic-based taxonomy for Alzheimer's disease (AD) and Parkinson's disease (PD). Their big data approach leverages existing data to extract causal relationships, organize data in novel ways, examine how findings relate to each other, and optimize causal models for AD and PD. This approach has identified new pathways and mechanisms that were not previously associated with AD and has established taxonomies based on data rather than the phenomenology of disease.

Dr. Haas concluded her keynote address by supporting the use of similar approaches for trauma related brain disorders and the integration of multiple methods, including nanotechnology, neuroimaging, biosensors, patient-powered networks, and multimodal biomarker identification. Research suggests that biomarker identification in this population might also need to include areas such as the microbiome, the envirome, psychobiotics, and the social interactome. Dr. Haas charged the SoSS participants to help develop a blueprint to bridge this translational gap and map the future of brain health.

Key Take-Away: To move the field forward, we must identify biomarkers of susceptibility or risk, prognosis, disease severity, and treatment response for clinically relevant constructs of trauma-related disorders, yielding screening tools, a novel taxonomy and, ultimately new therapeutics for trauma-related disorders.

DECONSTRUCTING THE PRAZOSIN STUDY: LESSONS LEARNED

Session goal: To explore a recent PTSD clinical trial for lessons learned and discuss how biomarker collection might have impacted outcomes or informed next steps.

Prazosin is prescribed to 17% of veterans diagnosed with PTSD. This antihypertensive drug targets central nervous system alpha-1-adrenergic receptors that increase arousal and alertness. These receptors are activated in response to novel or threatening stimuli in prior small-to-moderate-sized randomized controlled trials (RCTs) of prazosin for PTSD and had positive but mixed results leading to a larger and longer-duration multi-center study of veterans with PTSD. The hypothesis was that reducing alpha 1-adrenergic receptor activity would reduce trauma nightmares, sleep disruption, and daytime hyperarousal. In this session, the study chair of the prazosin study, Murray Raskind, M.D., Director, VA Northwest Network MIRECC, and Professor, University of Washington, discussed some of the implications of the study's results with CVB's Dr. Allyson Gage.

Dr. Raskind described the design and results of the 304-patient, six-month RCT of prazosin in veterans diagnosed with PTSD. Dr. Raskind suggested that some aspects of the

study design may have contributed to a lack of separation between the prazosin and placebo groups in the primary (CAPS-4) and secondary outcomes, including the CAPS-4 distressing dreams item and the Pittsburgh Sleep Quality Index. Among these were:

(1) **Inclusion and exclusion criteria.** Excluding more severely distressed and unstable patients due to concerns about suicide and other safety-related reasons may have excluded those who would benefit most from the treatment. For example, people with psychosocial instability or alcohol dependence were excluded. Dr. Raskind suggested that future trials should consider how to include less stable patients with more severe presentations. It was noted that this may be a broader concern as several VA Cooperative Studies have unexpectedly had negative results of treatments for United States (US) combat veterans, including naltrexone for alcohol use disorder (2001), trauma-focused psychotherapy for PTSD (2003), sertraline for PTSD (2007), depot antipsychotics for schizophrenia (2011), and risperidone for PTSD (2011).

(2) **Six-month placebo control**. In cases in which patients met inclusion criteria but still had significant symptoms to treat, physicians were hesitant to refer them to a study with a 50% possibility of being put on the placebo for six months. Dr. Raskind proposed an alternative design of a double-blind discontinuation study in which all patients are put on active treatment and responders to that treatment are randomized to either continued active treatment or to placebo with availability of a rescue treatment. Aggregated N-of-1 trial designs, which can reflect clinical practice, were also suggested.

(3) **Objective assessments and biomarkers.** The study did not include any measures of hyperarousal as inclusion criteria, despite the fact that prazosin had been hypothesized to decrease PTSD symptoms by decreasing hyperarousal. In fact, pre-treatment blood pressure levels provided indirect evidence that the study population may not have had adrenergic hyperarousal. The study's mean baseline blood pressure of 130/80 was atypically low for a predominantly Vietnam Veteran PTSD sample. Dr. Raskind noted that one of the prior smaller studies of active duty soldiers with PTSD demonstrated that a higher-standing blood pressure at baseline predicted a positive response to prazosin. Future studies should consider the following inclusion criteria: higher baseline blood pressure, autonomic arousal (sweating, tachycardia) accompanying nightmares and sleep disruption, and large muscle movements during dream-stage sleep (REM sleep without atonia).

Key Take-Away: Future trials of prazosin or other anti-adrenergic drugs should include the most affected patients, use objective clinical and biomarker assessments to better select participants most likely to respond to the mechanism of the treatment, and incorporate alternative designs to capture the most distressed patients safely.

RESEARCH AND DEVELOPMENT LANDSCAPE

Session goal: To examine funding and research trends of trauma-related brain disorders from different stakeholder perspectives.

Sonja Batten, Ph.D., Senior Associate with Booz Allen Hamilton (BAH), discussed the utility of looking at complex issues such as trauma-related brain disorders using a mega-community approach. A mega-community examines the overlapping interests of members from civil society, the private sector, and the public sector, aiming to generate innovative ways of approaching the issue and engaging all stakeholders with a commitment to mutual action. Dan Logsdon, M.S., Biomedical Scientist with BAH, discussed an engagement conducted earlier in the year in support of this SoSS effort. BAH conducted a *pro bono* project consisting of expert interviews of stakeholders from 19 organizations to understand the research challenges in the field. These interviews revealed that industry research and development (R&D) programs in trauma-related diagnostics and therapeutics have been hampered by:

1. the lack of objective diagnostic measures that reflect an underlying pathophysiology and have high signal-to-noise ratios even in the presence of comorbid disorders;
2. evolving diagnostic criteria that make regulatory endpoints a moving target;
3. funding limitations, as investors seem to consider the development of diagnostics and therapeutics for PTSD riskier than many other therapeutic areas;
4. the high degree of heterogeneity and animal models that do not predict response in humans;
5. insufficient or non-scalable technology; and
6. the need for data sharing mechanisms, especially private-public relationships and consortium efforts.

Viewpoint of a Father
Frank Larkin, Former Navy SEAL

Essential to understanding brain trauma research, is the ability to understand the importance of this research and future treatments to patients and their families. Frank Larkin described his experience as a parent whose son took his own life after struggling with an undetected brain injury as a result of blast explosions. Mr. Larkin noted that many people are doing wonderful things but none of that talent is being shared. We need to embrace a cultural change, a new sense of collaboration and sharing. We need to reach veterans who are suffering.

Mr. Larkin concluded by mentioning the history of PTSD and TBI through Lord Charles Moran, Winston Churchill's physician, who wrote about trauma-related brain disorders extensively during World War I.

Cara Altimus, Ph.D., Associate Director, Milken Institute, Center for Strategic Philanthropy, built on the topic of landscaping with a case study of the *Tau Funding Database*. This database includes 1,995 unique grants totaling over $1.8 billion to fund over 1,000 researchers. Dr. Altimus leveraged the database to explore the R&D landscape. She found that the pathogenesis of disease, especially for AD, was the top-funded topic. Additionally, the US government was the predominant funder with 85% of the funding coming from the NIH and only 6% coming from private pools. Specific to TBI and chronic traumatic encephalopathy, the database included 69 grants, 43 principal investigators, and $94 million. For biomarkers, imaging, surrogate, and tissue-based studies are equally well funded for TBI. The change in the funding landscape is leading to increased publications and new investigators entering the Tau/TBI field each year, although the type of proposed research changes based on where funding tends to go.

Key Take-Aways: Collaborative opportunities within the mega-community of trauma-related brain disorders could help focus research on the hurdles facing those developing treatments and

thus propel the field forward. Additionally, these collaborations would inform funders of the areas most in need of support.

RATIONALE FOR AND IMPACT OF A NEW TAXONOMY

Session goal: To explore current and developing taxonomies, their pros and cons, and their use-cases.

Current diagnostic systems of mental disorders present challenges: they are dichotomous, symptoms are given equal weight, boundaries between disorders are blurred, and the stability of definitions is poor. This session, led by Richard Bryant, Ph.D., University of New South Wales, provided an overview of the current diagnostic systems for PTSD and TBI, including the ICD-11 and DSM-5, as well as Research Domain Criteria (RDoC), Hierarchical Taxonomy Of Psychopathology (HiTOP), and clinical guidelines.

The soon-to-be-released ICD-11 is maintained by the World Health Organization and aims to help psychiatrists categorize patients for treatment and reimbursement. It is the preferred diagnostic tool outside of the US but is not intended for research purposes. The ICD-11 diagnosis of PTSD focuses on three clusters: re-experiencing, avoidance, and heightened sense of threat. Potential advantages of this approach are that it (1) is in accordance with current extinction-based treatment models of PTSD, (2) recognizes complex PTSD, defined as PTSD plus impairment in emotional regulation, relations, and self-identity, and (3) results in a more homogenous population with fewer comorbidities than the DSM-5. These same features, however, limit the ICD-11 because they ignore non-fear circuitry presentations and, therefore, limit the ICD-11's ability to advance our understanding of the biological underpinnings of PTSD.

The DSM-5 model, described in this session by Brian Marx, Ph.D., National Center for PTSD at VA Boston Healthcare System and Boston University School of Medicine, is the most popular classification system in the US. The DSM is considered a descriptive classification system and classifies disorders as distinct entities with defined boundaries. The advantages of this approach are that it (1) serves a common language for clinicians, billing and reimbursement, and decision-making, (2) facilitates assessment and inter-rater reliability, and (3) is a dynamic model that is continuously revised with new research findings. Limitations of the DSM include the fact that it (1) is a medical model that relies on assumptions when clustering symptoms, (2) focuses on the symptoms rather than the cause, (3) may over-pathologize normal reactions, (4) and adds and removes disorders as it integrates new research and evolves. To this last point, changes with each version of the DSM make it difficult to generalize prior findings and do not necessarily improve diagnostic accuracy, utility, and communication.

To increase our mechanistic understanding of behavioral disorders, the NIH advanced the research domain criteria (RDoC) framework in 2010. Joshua Gordon, M.D., Ph.D., National Institute of Mental Health (NIMH), described the intentions of RDoC: to connect behavioral presentations of disorders with biological mechanisms so that we can better focus development of therapeutics and better predict treatment outcomes. Although RDoC was developed from a research perspective, on a large scale this approach could help us understand and classify illness in a way that yields clinical guidance. In this system, behavioral dimensions underlying psychiatric disease ("constructs") are measured by changes in molecules, circuits, or proteins. These constructs are then rolled up into overarching behavioral systems called domains (e.g., cognition, social interactions, emotions), which map to the various syndromic criteria required to meet a diagnosis. Therefore, the RDoC model moves away from categorical diagnosis and

instead examines different symptom clusters that may overlap among disorders, representing an important pivot in the search for a more mechanistic nosology. For example, anxiety disorders could be categorized by RDoC-derived dimensions, such as startle responses, to yield different symptom profiles, or constructs, and reveal different biotypes that could be treated with unique approaches appropriate to the domain. For PTSD, there is a continuum of causes that raise the probability of getting the disorder; at different levels, these causes may actually evoke different kinds of PTSD. In 2018, most NIMH studies are still using the DSM approach, though about 50% will incorporate an RDoC component. These studies vary in size but, importantly, are able to include prodromal cases when using continuous scales. The RDoC ontology also facilitates the use of multimodal approaches, which would allow data-oriented clinicians more than one measure per construct or domain to guide decision-making.

Roman Kotov, Ph.D., Stony Brook University, described the history of Hierarchical Taxonomy of Psychopathology (HiTOP) and the current work using this approach. The HiTOP model of classifying psychopathological disorders was developed to deal with the challenges of comorbidity, heterogeneity, and subthreshold cases, aiming for a better nosology for both research and clinical practice that is driven by data. This dimensional approach offers another organized framework for studying mechanism and can be applied to trauma-related brain disorders. A potential benefit of this method is getting more information from each patient in shorter windows of time. One limitation of the current dimensional model is that you do not get symptom presentation over time, which is important for diagnosis. To address this, Dr. Kotov suggested that studies could plot longitudinal assessments and trajectories, asking patients to fill out evaluations over time.

The next presentations of the panel explored how the diagnostic systems are employed in the clinic practically. Michelle J. Bovin, Ph.D., National Center for PTSD at VA Boston Healthcare System and Boston University School of Medicine, described how the DSM is operationalized at the NC-PTSD for a PTSD diagnosis. The CAPS, a clinician-administered structured interview, is the gold standard. It provides a severity score and, while structured, it does allow the clinician to go off script. Interview-based assessments are only as good as the reporter and some biases can occur, including cultural and communication differences. Alternatively, some patients are given a questionnaire-based assessment known as the PCL to complete themselves. This test can measure distress and dysfunction levels. Limitations in interpretations and communication differences still occur and an additional challenge for self-report assessments is a lack of clinical guidance. Currently, training for diagnostic tools is not included in graduate or medical school, increasing training variability and decreasing reliability. Furthermore, Criterion A (exposure to a traumatic experience) can be difficult to assess and varies from person to person.

Kristen Dams-O'Connor, Ph.D., of Icahn School of Medicine at Mount Sinai, described the diagnosis of chronic sequelae of TBI. The first step is characterizing a TBI event, ideally using multiple methods. For instance, relying only on medical records (e.g., the ICD-9/10, chart abstraction, and claims data) can miss exposures that were unreported or overshadowed by other injuries. To highlight this point, it is estimated that of the 1.5 million Americans who sustain a TBI each year, only 1.1 million visit an ER and 235,000 are hospitalized (CDC). In research settings, self-report is also used; while structured interviews (e.g., BISQ, OSU-TBI-ID, and BAT-L) add a time burden, they are better than single-item screeners. Most patients suffering from a mild TBI recover completely within days or months. However, chronic TBI induces behavioral and neuropsychiatric changes that can span months or years. TBI is heterogeneous in its etiology and can manifest in many ways. Over five years, 30% of people get worse, 22% die, and 26% improve – even when controlled for age. An additional complication in diagnosing the

chronic sequelae of TBI is the potential presence of post-traumatic dementia, of which the etiology involves both an injury and underlying preexisting conditions and biological factors. Biologically, post-traumatic dementia involves many phenotypes, including Lewy bodies, tau tangles, and amyloid beta plaques. Future work should address how post-traumatic dementia compares to other neurodegenerative diseases and whether this progression tracks with decline during life.

After the presentations, a lively discussion commenced among the panelists and the audience. Portions of that discussion are highlighted below.

- When diseases are variable and symptoms are diverse, it can be difficult to define a control group with which to develop diagnostic frameworks, diagnostics, and therapeutics. Certain clustering analyses help by reducing the number of permutations that would garner a diagnosis.

- Translating etiologic information to clinicians, researchers, and patients is challenging; audience members posed questions as to whether mental illness classification systems should integrate biological etiologies.

- Overall, construct validation is needed in any framework. Most studies have relied on the symptoms and symptoms clusters of the operating system, creating a self-limiting process. This was presented as a key gap in the advancement of the field.

Key Take-Away: While diagnostic methods need to match the setting, the development and validation in research settings of objective assessments, whether biological measures or an easily accessible panel of patient characteristics, would enable more precise measurement and more informed and effective treatment decisions in the clinic.

Breakout Working Session

The prior sessions established the rationale for a mechanism-based taxonomy. Subsequently, all attendees participated in one of seven working group breakout sessions, each led by an SPC member or a facilitator. Each breakout session centered around a domain, external factors, or a model of illness of trauma-related brain disorders. Prior to the meeting, strawman summaries of the state of the science were drafted for each of the seven areas as a tool to facilitate the working group discussions. The goal of the working sessions was to review, revise, and augment these summaries and identify any open questions. The breakout groups were asked to synthesize the key concepts within the domain, the key tools used to explore that domain, and identify the main gaps in our knowledge from the point of view of that domain, including the tools that might be needed to achieve this knowledge.

Discussions are summarized below and will be incorporated into the more extensive SoSS summaries which will be available for open comment to guide a comprehensive Brain Trauma Blueprint. As new relevant information becomes available, these summaries will be updated.

Molecular group: Led by SPC member John H. Krystal, M.D., Yale University School of Medicine, and facilitated by Magali Haas, CVB, and Laramie Duncan, Ph.D., Stanford University, the Molecular Breakout group discussed how genetic, transcriptomic, and epigenetic factors might alter susceptibility, course, and severity of trauma-related brain disorders. Participants

discussed that priorities for the field should include: (1) establishing a large biorepository for well-defined PTSD samples that academic, industry, and government researchers could access; (2) performing genome-wide association studies and other big-data screens with larger sample sizes; (3) conducting follow-up pathway analyses, CRISPR screens, induced pluripotent stem cell studies, longitudinal analyses, and STARmap analyses to produce deep datasets that could yield biomarker insights; (4) reanalyzing existing data; and (5) developing and validating better animal models.

Humoral Factors group: Led by Ann Rasmusson, M.D., Boston University School of Medicine, and facilitated by Retsina Meyer, Ph.D., CVB, and Nikolas Daskalakis, Ph.D., the Humoral Breakout group discussed the influence of humoral factors, such as hormones, proteins, peptides, neurotransmitters, and other circulating factors on PTSD risk, severity, chronicity, and comorbidity. The group indicated a need for standardization in the field, including determining the ideal core assessments, methods for sample collection, and "best-in-class" criteria for selecting existing datasets for analysis, and ensuring all analysis plans are pre-specified prior to initiating new studies or new analyses of old datasets. In addition, the group noted that not every study needs to include every assay, and ultimately, there should be a push to make things practical to both ensure that they can be completed and better reflect what might be done in the clinic. Participants felt that priorities for the field include: (1) collecting each data type in a standard way; (2) including measures at both resting/baseline and during a challenge such as a loud tone test or during fear conditioning; and (3) carefully accounting for the subject's state at the time of the measure including assessing smoking, drinking, exercise, and diet.

Circuit Dysregulation group: Led by SPC member Amit Etkin, M.D., Ph.D., Stanford University, and facilitated by Mohammed Milad, Ph.D., University of Illinois at Chicago, and Israel Liberzon, M.D., Department Head of Psychiatry, Texas A&M College of Medicine, the Circuit Dysregulation Breakout group discussed the ability to identify key individual differences in circuit function that might explain underlying disease mechanisms, have prognostic or diagnostic potential, be used to develop treatments, or be useful biomarkers. Overall, the group noted that there is a lot of skepticism within the field about the state of current research, including how to define a circuit, but agreed on the likely relevance to trauma-related brain disorder constructs and ways to move forward. Participants felt that priorities for the field include: (1) assessing causal significance of circuit changes in individuals measured before and after trauma; (2) assessing the effects of interventions on these circuit changes; (3) performing individual-level analyses as well as collecting longitudinal assessments to understand the circuit and behavioral profile within an individual; and (4) addressing study design challenges facing the field, such as sample biases introduced by funding sources and by availability of patients.

Psychophysiology group: Led by SPC member Tanja Jovanovic, Ph.D., Emory University School of Medicine, facilitated by Lisa McTeague, Ph.D., Medical University of South Carolina, and Seth Norrholm, Ph.D., Emory University, the Psychophysiology Breakout group discussed psychophysiology measures of PTSD and whether they can be used to predict susceptibility and disease trajectory, as well as define potential patient subtypes. The group noted that while the field is starting to gather large amounts of data, analyzing it is challenging; group members suggested that researchers need to collaborate with data scientists to derive meaningful results. Participants felt that priorities for the field include: (1) developing and validating wearables and other tools that capture the physiological data; (2) establishing baselines for validation studies; and (3) developing apps with questionnaires to determine that individual's state when the

physiological data is being collected as well as built-in incentives for compliance (e.g., gamification).

Behavioral group: Led by SPC member Sheila A. M. Rauch, Ph.D., Emory University School of Medicine, and facilitated by Brian Marx, Ph.D., VA National Center for PTSD, Justin T. Baker, Ph.D., McLean Hospital and Harvard Medical School, and Jessica Wolfe, Ph.D., CVB, the Behavioral Breakout group discussed clinical presentations of PTSD and whether the individual behaviors and/or symptom clusters can be used to predict vulnerability, trace disease trajectories, and define potential patient subtypes. Participants felt that priorities for the field include: (1) refining the symptoms scoped for diagnostics to those important for treatment and functionality; (2) combining sources of behavioral information such as patient reports and provider reports with other biological information to establish multi-modal diagnostic capabilities; (3) facilitating training and implementation of best practices in behavioral assessment by creating fellowships for practitioners that provide in-depth training and understanding of the varieties of use cases such as in research, in the clinic, or in clinical trials; (4) establishing construct validity of existing and potential symptom clusters; and (5) improving the measurement of exposure and trajectory.

Developmental group: Facilitated by Joan Kaufman, Ph.D., Johns Hopkins School of Medicine, Ryan J. Herringa, M.D., Ph.D., University of Wisconsin School of Medicine, and Cecile Ladoucer, Ph.D., University of Pittsburgh, the Developmental Breakout group discussed how early-life trauma affects resilience and vulnerability to trauma-related disorders. The group agreed that there is little understanding in the field about the normal baseline of brain development. Participants felt that priorities for the field include: (1) performing longitudinal assessments in validated animal models and in humans to establish normal development within all identified domains; (2) understanding normal and abnormal developmental of sleep, cognition, and emotional regulation; (3) augmenting the ABCD study, which is longitudinally following children for ten years, by including exposure trauma as one of its measures; (4) finding avenues to accurately assess trauma exposure in children to augment current parent and child reporting practices; (5) developing more behavioral outputs and dynamic assessments for child development that tap into different domains; (6) understanding how abnormal sleep impacts brain function and understanding the role of memory consolidation during sleep on trauma outcome; and (7) incorporating validated wearables (for both children and their caretakers) in studies of development.

Comorbidity and Complex Phenotypes group: Led by SPC member Richard Bryant, Ph.D., University of New South Wales, and facilitated by Dallas Hack, M.D., CVB, Thomas Mellman, M.D., Howard University, and Allyson Gage, Ph.D., CVB, the Comorbidity Breakout group discussed the implications of comorbid PTSD and chronic sequelae of TBI, as well as other comorbidities for understanding the biological mechanisms underlying these disorders and developing treatment and prevention strategies. The group found that the difficulty in precisely defining PTSD itself makes coming to consensus on how to define and understand how another disorder, subthreshold disorder, or overlapping symptoms impact PTSD a challenge. Participants felt that priorities for the field include: (1) recording trajectories of trauma-related symptoms and comorbidities; (2) understanding the relationship(s) between PTSD and chronic sequelae of TBI, including whether co-morbid presentation can aggravate one or both of the disorders, whether PTSD can arise from a TBI, or if symptoms that appear to meet criteria for PTSD are just overlapping symptoms of chronic TBI; (3) investigating the validity of subtypes of

PTSD (e.g., dysphoria, dissociative, complex); (4) identifying post-trauma biomarkers, for example in an ER setting, that are predictive of the disorders or symptoms/symptom clusters that an individual might experience or be diagnosed with; and (5) developing algorithms that indicate level of pre-trauma psychiatric risk of developing PTSD or chronic sequelae of TBI.

Synthesis of Working Groups

Group leaders convened after the breakout sessions to synthesize the identified gaps and priorities at a high level. The goal was to determine if there were any similar themes across the groups or areas that stood out as priorities for review with all attendees. Seven major themes emerged:

I. **Cataloging and leveraging existing work and datasets**
II. **Collaborating and collecting well-designed prospective datasets**
III. **Improving training and establishing best practices**
IV. **Filling a variety of technological gaps**
V. **Developing new incentive models and innovative funding opportunities to support team science and risky projects**
VI. **Establishing national platforms and biorepositories to support the field as a whole**
VII. **Integrating the use of bioinformatics and systems modeling to better understand the data**

These themes were reviewed and revised with all participants the next morning.

BRAIN COMMONS

Session Goal: To discuss the launch of a next-generation cloud-based brain health digital ecosystem for translational research enabling computational discovery by all levels of stakeholders in the brain health community.

Lee Lancashire, Ph.D., Chief Information Officer, CVB, presented the BRAIN Commons, a scalable, cloud-hosted, big data repository and computing platform. This next-generation digital ecosystem provides core services for data-driven brain health, such as data curation, harmonization, and upload as well as a wide-range of computational tools to foster translational discovery. The BRAIN Commons ecosystem allows scientists to share data within and between brain disease areas, explore the full potential of data, utilize machine learning and analytics, and allow for data transformation, harmonization, and integration. The system rests on three pillars: data, community, and tools. *Data* are the building blocks of the BRAIN Commons. The structure of the BRAIN Commons allows for multi-modal datasets with all types of data to be able to be integrated at all spatial scales using a unified data model. Access to datasets are restricted according to the zone to which they are assigned; data can be shared with the public, with authenticated researchers (protected under strict user agreements) or shared only with specific partners (private) while still allowing for creative collaboration. *Community* involves a social media cognitive network fostering new collaborations among researchers with shared interests even if they are in different fields; each researcher can tailor their suggested connections by the interests they list. *Tools* that couple advanced computational modeling with intuitive visualization are available for users at all levels: casual users, biologists, bioinformaticians, data scientists, and machine learning engineers.

Key Take-Away: The BRAIN Commons platform is a next-generation solution available to the entire brain health community that meets the challenges inherent in big data collection and complex analytics in neuroscience, facilitates data sharing, and breaks down research silos through collaboration.

APPLICATION OF BIG DATA ANALYTICS AND MODELING IN TRAUMA-RELATED BRAIN DISORDERS

Session goal: The overarching goal for the field is precision medicine or tailoring treatment to individual patients and their biology. This session explored the data challenges to that vision and the computational tools needed to overcome those challenges.

Lee Lancashire, Ph.D., of CVB, introduced the session by discussing the challenges of big data analytics, including the unprecedented rate at which data is being generated, the multi-causal nature of trauma-related brain disorders, and the frequent inability to build on results of past research due to underpowered and incompatible study designs. He described two types of machine learning in current use: (1) **supervised learning (e.g., classification)**, used to predict an output from a given collection of input data following a model training process; and (2) **unsupervised learning (e.g., cluster analysis),** used to discover the underlying structure of the data in the absence of any sample labeling. He explored an example of machine learning applied to PTSD, specifically the use of latent growth mixture modeling to identify PTSD symptom trajectories. These models suggested certain causal relationships via a variety of classification and feature selection parameters. The next two talks presented examples of the power and potential of these techniques in neuroscience.

Stephen Glatt, Ph.D., Associate Professor, SUNY Upstate Medical University, described work by the Psychiatric Genetic Epidemiology and Neurobiology Laboratory. Due to their static nature, genetic polymorphisms do not make good biomarkers. Circulating factors (or peripheral biomarkers), on the other hand, are more dynamic making them more pertinent to disease trajectory monitoring. For example, in the Marine Resiliency Study blood samples were collected before and after deployment. It was found that immune/inflammatory markers at baseline were higher in individuals who later developed PTSD, indicating these factors could potentially mark an increased susceptibility to develop PTSD. Questions remain as to how these are moved forward from candidates to biomarker since some models will fail to predict patient clusters outside of the dataset they are trained on. One approach to overcome this lack of generalization is to use ensembles of machine learning techniques to build a variety of classifiers that embrace the heterogeneity of the population and can integrate poly-omic datasets. These can be improved through stratification by, for example, gender or age, identifying subgroups by cluster analysis, or by transcriptome types. Dr. Glatt argued these types of analyses are progressing the field, and even results with imperfect accuracy may provide important information about a subset of individuals. During discussions with the audience, a question was asked about how well the field can rely on peripheral biomarkers when the locus for the disorder is the brain. Dr. Glatt made the point that blood-based biomarkers need not be a cause of the phenotype or even resemble the pathogenesis at its site as long as they reliably work for patient classification. He emphasized that this is what these methodologies strive for: reproducible classifiers with better-than-chance accuracy. If discoveries within this domain shed light on mechanisms, that is a secondary success but not a requirement for a biomarker.

Sean Hill, Ph.D., Director, Krembil Centre for Neuroinformatics, CAMH, introduced the Brainhealth Databank, which aims to integrate research with evidence-based care. This model organizes data into a graph structure that allows users to search through heterogeneous data and houses several projects including the Blue Brain Project. The Blue Brain Project uses integrative multiscale modeling of cortical excitability across neurodisorders to simulate a microcircuit and test hypotheses *in silico*. One hypothesis tested on the Blue Brain Project examined cortical excitability by modeling the electrical diversity of neurons, dendritic/somatic features, synaptic transmission, and short-term plasticity. The project allows researchers to characterize the response to inputs in an *in vivo*- versus *in vitro*-like state, pointing to potential variables responsible for the differences seen in plasticity that could then be tested and validated *in vitro.* For example, the Blue Brain Project explored sleep disruption, common across brain disorders, by including the circadian modulation of cortical excitability in the system. These simulations predicted the ability of parts of the brain to be "asleep" during wakefulness. The study found that theta waves in sleep-deprived animals changed with cortical firing changes and greater sleep deprivation was correlated with less neuronal plasticity, highlighting theta waves as a potential biomarker for sleep disorders. This highlights the potential of using multi- and micro-scale modeling to help identify biomarkers. In the future, these systems could even be augmented to perform "virtual patient modeling": whole brain network modeling using information from brain imaging to build personalized models, integrate longitudinal data, and create personal brain health profiles across dimensions.

Key Take-Away: Advanced machine learning and data modeling techniques, with careful attention to the methods, datasets used for training, and interpretation of results, are likely to be powerful tools to identify robust and reproducible biomarkers for trauma-related brain disorders.

REAL-WORLD EVIDENCE: INTEGRATION OF RESEARCH INTO PRACTICE

Session goal: To consider how to use real-world data (RWD) and real-world evidence (RWE) to accelerate research and improve care for individuals with trauma-related brain disorders.

Rebecca Miksad, M.D., Senior Medical Director, Flatiron Health, described work by Flatiron Health to generate RWE in oncology. RWD, which includes data captured in electronic health records (EHRs), insurance claims, billing activities, product and disease registries, and other sources such as mobile devices, are data captured during a patient's routine care rather than in clinical trials. With this data, one can monitor the use of a drug in real patients in real contexts and in real time. The challenges in using RWD for regulatory and discovery efforts are many, including how to combine structured and unstructured data and how to combine data of the same type but collected in different formats. These challenges require a significant amount of human engagement and manual effort. However, the approach is promising as it can (1) identify changes in treatment paradigms as they happen, (2) measure the use of biomarker testing, and (3) investigate the effect of treatments on the full spectrum of patients not just those in clinical trials. For example, RWD demonstrated the impact of Food and Drug Administration (FDA) approval of immunotherapies for lung cancer: a concomitant increase of immunotherapy adoption and biomarker use from 0 to 50% of patients in just four years. These same data demonstrated that the average age of the populations using these drugs is considerably higher

than the patients who participated in the clinical trial for approval. The next frontier is for these data to provide RWE to support approval of new treatments with regulatory bodies, inform treatment guidelines for practitioners, and further enhance clinical decision-making.

Anthony Hassan, Ed.D., Chief Executive Officer and President, Cohen Veterans Network (CVN), then provided an example of how RWD can be collected in a systematic manner that enhances its use for improving patient care. CVN is a clinically integrated network delivering mental health services to post-9/11 veterans and their family members via standard replicable protocols by clinicians trained in a robust training program. CVN is growing its network in a deliberate manner that ensures that is a learning mental health system: collecting, analyzing, and utilizing data in a continuous learning and improvement cycle. A proprietary EHR is customized for the CVN data warehouse, where the data are de-identified and can be used in machine learning analytics, reports, insights, and dashboards. CVN is working with advanced analytic strategies, like natural language processing, to synthesize the data it is collecting more efficiently and use this information to improve care. These real-time RWD serve as a real-world database, with a goal that as the network matures CVN will create opportunities to share de-identified data with outside researchers to improve our collective understanding of mental health and mental health treatment. In the future, CVN hopes to expand their data capture in specific populations and partner with organizations like CVB to advance the field through clinical trials and innovation. CVN is also developing a telehealth, mobile, and wearable data source strategy.

Key Take-Aways: Analysis of RWD and RWE for trauma-related brain disorders to support regulatory and clinical decision-making could help drive the field forward. Flatiron, CVN, and other companies are learning how to take non-regulatory quality data and perform quality assurance that would satisfy the FDA as evidence toward approvals. As the capture and structure of this data become standard, the cost and timelines to utility will decrease.

WORKING LUNCH BREAKOUTS

Following the sessions discussing the value and challenges in bringing together and analyzing multiple data types from multiple sources, attendees broke into four groups that each included members from all of the Day 1 breakouts to reevaluate the state of the science in cross-functional manner. Goals of this session were to take what each person learned from their deep-dive sessions on Day 1 and (1) discuss how identified gaps in one area might be addressed by information in another area, (2) consider how tools from one area could be used to evaluate research questions in another area, and (3) prioritize gaps and identify short-term opportunities for improvements. Attendees were also asked to consider the impact of aging, sleep/circadian rhythms, and gender during their discussion. If time permitted, two challenges were posed to the groups. The first two groups were asked to design a study to develop an ER risk prediction tool that predicts later development of a trauma-related disorder. The second two groups were challenged to identify tools that they could combine to determine meaningful patient population stratifications for future treatment trial protocols.

Conclusions of the breakouts:

The breakout groups highlighted the limitations of animal models and the need for models that target facets of the disorder that are actually useful and translatable to the human population.

The groups also pointed out that now that we have tools to investigate trauma responses in humans, these studies should be prioritized as they could be a more direct path the clinic. The groups also discussed how most studies have used males, and sex differences should be considered in future studies. Aging, medication use, and the menstrual cycle can also affect symptoms, and should be considered during study design. Due to the heterogeneity of trauma-related disorders, studies should model variability and stratify patients when differential responses are expected. Finally, the groups commented on the limited access of current data and the need for collaborations to overcome data availability issues and propel the field forward through team science.

SYNTHESIS

Throughout the literature review and summit discussions, several priorities emerged for the field of brain trauma-related research, including (1) developing data collection standards and analytic methods; (2) collecting and developing databases of prospective data/samples; (3) improving availability of existing work and datasets (such as FDA data); (4) bringing all stakeholders together to address technological gaps; (5) developing new funding models that support group research; (6) developing national platforms (such as blood and tissue repositories) as another opportunity to bring all stakeholders together; and (7) funding and developing programs for training and best practices.

Attendees also tackled the following questions as additional areas for future research:

1. Can you design a study to enable the development of a risk prediction tool for ER physicians for long-term trauma? Both groups assigned to the first question agreed that data must be collected longitudinally over time with repeated measures. Physiological measures, as well as responses to challenges, should be included in the study design. Some discussion focused on what the appropriate study population should be: patients in an ER setting after trauma or service members who could be examined before and after trauma.

2. What tools would you combine to determine what patient population stratifications there are for future treatment trial protocols? Those discussing the second question considered that stratification depends on the intervention, outcome, and predictors used in the study. For some study designs, for instance, stratifying by low-mild and moderate-severe CAPS scores could be useful. Group members discussed the use of existing data sets, as well as a range of potential measures and markers, to determine what tools would be most informative. The group discussed many possible measures, including computed tomography scans, hair samples, verbal memory, telomeres, imaging, positron emission tomography, magnetic resonance imaging, saliva, inflammatory, menstrual cycle, and baseline challenge tests. After determining what measures could work, and what data we already have, the next step will be to think about a prospective study design.

OVERALL CONCLUSIONS

The inaugural SoSS brought together scientific, clinical, and patient communities to focus on key areas relevant to the diagnosis of PTSD. By bridging gaps between research and clinical assessment, the attendees identified key areas that can be prioritized to propel the field forward. To make immediate impact, working groups were formed at the summit to commit to addressing these areas of need. These working groups will develop and vet a strategic list of next steps in

their specific area that will be coordinated into an overall Brain Trauma Blueprint to be broadly shared with public and private funders, researchers and the brain health community. Cohen Veterans Bioscience and community stakeholders plan to lead the charge in addressing these priorities and gaps to guide future translational research.

Appendix 1. Attending Organizations

- Addex Pharmaceuticals
- Alkahest
- Alzheimer's Association
- Alzheimer's Org.
- American Foundation for Suicide Prevention
- American Life Science Pharmaceuticals, Inc.
- American Psychological Foundation
- Analgesic Solutions
- Aptinyx
- Aquinnah Pharmaceuticals
- Armgo Pharma Inc.
- Astrocyte Pharmaceuticals
- Avanir Pharmaceuticals
- Azevan Pharmaceuticals
- Banyan Biomarkers Inc.
- Baylor College of Medicine
- Biogen
- Bionomics
- Biosensics LLC
- BioXcel
- Bob Woodruff Foundation
- Booz Allen Hamilton
- Boston University
- Brain Scope
- Brigham And Women's Hospital
- Broad Institute
- Bush Institute for Brain Health
- C Light Technologies Inc.
- C2N Diagnostics
- Cadent Therapeutics
- Cardiff University School of Medicine
- Case Western Reserve University
- Center for Drug Evaluation and Research/Food and Drug Administration
- Center for Military Medicine Research
- Cephalogics
- Children's Hospital Boston
- Children's Hospital of Philadelphia
- Chronos Therapeutics
- Clínicum (Barcelona)
- Cogito Health Inc.
- Cohen Veterans Bioscience
- Cohen Veterans Network
- Colorado Clinical and Translational Science Institute
- Columbia University
- DARPA
- DART Neuroscience
- Dartmouth University
- Defense and Veterans Brain Injury Center
- DemeRx
- Disarm Therapeutics
- Donder's Institute
- Duke University
- ElMindA
- Emory University
- Exciva
- Exosome Sciences
- Flatiron
- Food and Drug Administration
- Gaia Medical Institute LLC
- General Electric Global Research Center
- Global Post Traumatic Stress Injury Foundation
- Guided Therapeutics
- GW Pharmaceuticals
- Harvard University T.H. Chan School of Public Health
- Headstrong
- HHMI
- Hospital for Special Surgery
- Howard University
- Icahn School of Medicine at Mount Sinai
- In Silico Biosciences
- INmune Bio
- Insight NeuroSystems
- Insys Therapeutics
- JED Foundation
- Johns Hopkins School of Medicine
- Johnson & Johnson
- Kavli Foundation
- KDAC Therapeutics
- Kennedy Krieger Institute
- Kent State University
- King's College London
- Kings Gulf Ware Illness
- Laureate Institute for Brain Research
- Lauren Sciences
- Leiden University Medical Center
- Lieber Institute of Brain Development
- Longevity Biotech
- Louisiana State University Health New Orleans

- Lundbeck
- Maastricht University
- MAPS
- Marcus Foundation
- Marcus Institute for Brain Health
- McGill University
- McLean Hospital
- Medical College of Wisconsin
- Medical University of South Carolina
- Michigan State University,
- Milford Regional Medical Center
- Milken Institute
- Mindstrong
- Minneapolis VA Medical Center
- MIT Lincoln Lab
- Mitre
- MTEC
- MVK Pharmaceuticals
- National Alliance on Mental Illness
- National Alliance on Mental Illness Montana
- National Institute of Health
- National Institute of Mental Health
- National Institute on Alcohol Abuse and Alcoholism
- National Institutes of Health
- National PTSD Alliance
- National Suicide Consortium
- Naval Medical Research Center
- Navy Seal Foundation
- Neural Analytics
- NeuraSense
- Neuro-Electronics Research Flanders
- NeuroGen
- Neurovation
- New University of Lisbon
- New York University Langone Medical Center
- Noveome
- Oculogica
- Oexia Biopharmaceuticals
- Office of Naval Research
- Opiant
- OTSG
- Otsuka Pharmaceuticals
- Oxeia BioPharma
- Panarea Partners
- Partner's Healthcare
- Paul Allen Family Foundation
- Peakmind
- Pherin Pharmaceuticals
- Pink Concussions
- PRAGMA Therapeutics
- Protagenic Therapeutics, Inc.
- Providence VA Medical Center
- Psychiatry New York University Langone Medical Center
- Queensland Institute of Medical Research Berghofer Medical Research Institute
- Rainwater Foundation/Tau Consortium
- Ralph H. Johnson VA Medical Center | MUSC
- RAND
- Resolute Biopharmaceuticals
- Rockefeller University
- Rodin Therapeutics
- Roskamp Institute, Inc.
- Rush University Medical Center
- Sanofi
- Scripps Research Institute
- Semper Fi Fund
- SpringWorks
- Stanford University
- Stony Brook University
- Student Veterans of America
- Sunovion Pharmaceuticals
- Systems Biology Institute
- Takeda Pharmaceuticals
- Team Red, White, Blue
- Team Rubicon
- Texas A&M University
- The Hospital for Sick Children, University of Toronto
- Third Rock Ventures
- Tonix Pharmaceuticals
- Tower Foundation
- Town Hall Ventures
- TriMaran Pharmaceuticals
- TruGenomix
- Tufts University
- U.S. Army Medical Materiel Development Activity
- Uniformed Services University of the Health Sciences
- United States Army Center for Environmental Health Research

United States Army Medical Research and Materiel Command
University of Colorado, Denver
University College London
University Hospital Würzburg
University Hospitals of Cleveland
University Medical Center Göttingen
University Medical Center Utrecht
University of Arizona
University of Buffalo
University of California Los Angeles Medical School
University of California, San Diego
University of California, San Francisco
University of California, Santa Barbara
University of Chicago
University of Cincinnati
University of Illinois
University of Illinois Urbana-Champaign
University of Miami School of Medicine
University of Minnesota
University of Nebraska Medical Center
University of Nevada Las Vegas
University of New South Wales
University of North Carolina Chapel Hill
University of Notre Dame
University of Oxford, Medical Sciences Division
University of Pennsylvania
University of Pittsburgh
University of Pittsburgh Medical Center
University of Rochester
University of South Florida
University of Southern California
University of Texas HCS
University of Virginia
University of Washington
University of Wisconsin-Madison
University of Wisconsin-Milwaukee
UPMC
Upstate Medical University
UT Southwestern Center for Depression
VA Boston Healthcare System
VA Veterans Administration Hospital
Vanderbilt University
Veteran's Affairs
Veteran's Affairs, Mental Illness Research Education Clinical, Centers of Excellence,
Veterans Against Alzheimer's
Veterans Health Administration - Veterans Affairs, NC-PTSD
Virginia Commonwealth University Medical Center
Walk for Hope
Washington University in St. Louis
Wounded Warrior Project
Yale University