

**Driving Progress in Posttraumatic Stress Disorder Biomarkers**

Posttraumatic stress disorder (PTSD) is a common, debilitating disorder that affects ~8% of the U.S. population, with even higher estimates of ~20%, in U.S. veterans of Afghanistan and Iraq (1). Although psychotherapeutic and pharmacological interventions can significantly reduce PTSD symptoms, there remains considerable room for improvement (2,3). Only two pharmacological therapeutics, sertraline and paroxetine, have been approved by the U.S. Food and Drug Administration (FDA) for PTSD (2). Response to these selective serotonin reuptake inhibitors rarely exceeds 60%, and only 20% to 30% of patients achieve complete remission of symptoms (3). Thus, harnessing a better understanding of the biological underpinnings of this heterogeneous disorder and identifying biomarkers of PTSD and trauma-related brain disorders that can stratify the patient population and predict treatment response are overdue for enabling the development of novel therapeutics and precision medicine approaches (4–6).

In May 2017, Cohen Veterans Bioscience, in partnership with the U.S. Army Medical Materiel Development Activity, National Institute of Alcohol Abuse and Alcoholism, and the FDA, hosted a consensus conference in Washington, DC. This meeting brought together key thought leaders to evaluate challenges in developing novel diagnostics and interventions for trauma-related brain disorders. The consensus reached at the conference noted that biomarkers are essential components of drug discovery and development and are needed to advance molecular taxonomies of brain disorders; however, inadequately powered studies and a lack of replicated findings in putative biological pathways have delayed progress in this space. Moreover, the regulatory process for qualifying and validating biomarkers is lengthy and complex.

Participants at the PTSD consensus conference recognized an opportunity for large-scale, industrialized analysis of biofluid samples together with clinical, genetic, physiological, and imaging data in pursuit of biomarker discovery and replication. Substantial data in these domains are available from many large cohorts, which can enable the creation of large, systems biology-oriented datasets using banked samples. Implementing a strategic roadmap—developed around the following key pillars—will facilitate the discovery, replication, validation, qualification, and clinical deployment of PTSD biomarkers:

First, incentives for large-scale collaboration and public-private partnerships are needed to bring together key stakeholders from academia, government, industry, nonprofits, and patient advocacy groups in national and international pre-competitive efforts to develop critically needed infrastructure for biomarker discovery and replication.

Second, the path to regulatory approval necessitates the refinement of specific clinical contexts of use/intended use, i.e., a clear description of the way the biomarker will be used and the general purpose for the “test”/medical device along with risk-benefit assessments (7).

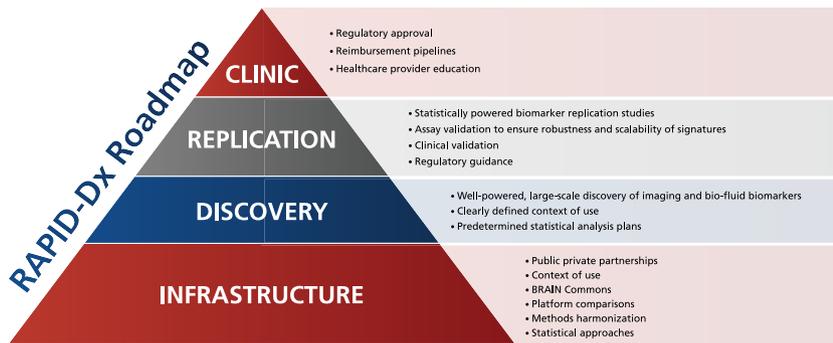
Third, removing barriers to big data science is necessary. The field must create “big” biomarker datasets to reproduce biomarker discoveries, incorporating appropriate power calculations into the statistical analysis plan.

Fourth, best-in-class infrastructure for data collection, harmonization, analysis, and sharing must be developed and utilized to pursue large-scale discovery of biomarkers to support drug development. Statistical analyses should be anchored to consistent neurobehavioral and multisystem biological constructs. As the volume of data increases, leveraging the latest advancements in machine learning (e.g., causal modeling, deep learning) is expected to increase the chance of successful replication and prospective validation.

Cohen Veterans Bioscience, in collaboration with different multi-institutional stakeholders, has formed the Research Alliance for PTSD/TBI Innovation and Development Diagnostics (RAPID-Dx) built on these pillars to accelerate the development, qualification, and adoption of biomarkers for PTSD and trauma-related brain disorders (Figure 1). Launched in February 2018, RAPID-Dx aims to be a platform for connecting researchers across public and private institutions to work together precompetitively with the necessary resources and joint goals to accomplish these goals.

In summary, the discovery and replication of biomarkers in PTSD and other trauma-related brain disorders represent critical steps for addressing the enormous biological heterogeneity of PTSD, which has challenged previous therapeutic development programs. Many biomarkers published in the literature have not been independently replicated, while many other studies are underpowered, often owing to a lack of resources or other factors. Given that biomarker development is a time-consuming and resource-intensive process, RAPID-Dx is actively working to create the critical infrastructure needed to support public-private partnerships in the PTSD space. Moving into 2019, RAPID-Dx has convened Working Groups to prioritize contexts of use to pursue, evaluating bioassay platforms for biomarker discovery, implementing best practices in sample collection and handling, and harmonizing data across cohorts in the state-of-the-art BRAIN Commons ([www.braincommons.org](http://www.braincommons.org))—all of which will ultimately support biomarker discovery and replication. By working together, key stakeholders from academia, government, industry, nonprofits, and patient advocacy groups can more effectively achieve a common goal of developing biomarkers for trauma-related brain disorders in years rather than in decades and, in turn, accelerate the development of diagnostic tests and therapeutic interventions for PTSD.

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**Figure 1.** The Research Alliance for PTSD/TBI Innovation and Development Diagnostics (RAPID-Dx) Roadmap is divided into four stages: infrastructure development, biomarker discovery, biomarker replication, and clinical implementation. First, infrastructure development involves the formation of public-private partnerships to share data across cohorts and provide funding for each step, consideration of specific clinical contexts of use to pursue, evaluation of bioassays to select best in class, industrialized platforms for biomarker discovery, implementation of best practices in samples collection, handling, and analytical approaches, consolidation of data into a single data commons (such as BRAIN Commons <http://braincommons.org>)

for deployment of large-scale analytics across harmonized datasets. Second, biomarker discovery will rely on the infrastructure developed in the first step, utilizing robust assays from platform evaluations, specific and targeted contexts of use, and accompanying statistical analyses plans to ensure statistical power, robustness, and replicability. Third, biomarker replication will build on discovery studies to validate assays and clinical contexts of use, complemented by the guidance of regulatory partners. Last, robust, replicated biomarkers will be developed further for clinical implementation through pursuit of regulatory approval, attainment of widespread reimbursement, and adoption into clinical practice.

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