NATIONAL ACADEMIES Sciences Engineering Medicine

Forum on NEUROSCIENCE and NERVOUS SYSTEM DISORDERS

Multimodal Biomarkers for Central Nervous System Disorders: Development, Integration, and Clinical Utility

A Workshop

Keck Center (Room 100) | 500 Fifth Street, NW, Washington, DC 20001

March 13, 2023, 2:00 pm - 5:00 pm ET

March 14, 2023, 9:30am - 4:00 pm ET

WORKSHOP OBJECTIVES

This public workshop will bring together experts and key stakeholders from academia, industry, government, philanthropic foundations, and disease-focused non-profit organizations to examine the potential to develop multimodal biomarkers for central nervous system (CNS) disorders through integration of different biomarkers. The workshop will explore steps toward this goal, such as data collection for biomarker discovery, development, validation, and assessment of clinical utility; standardization; and regulatory considerations.

Invited presentations and discussions may:

- Review current state of knowledge regarding biomarkers for CNS disorders (e.g., blood-based, imaging, molecular, proteomic, genetic, digital, and speech) and ongoing efforts to generate multimodal biomarkers.
- Examine current practices for data collection, cohort development, and measurement standards for discovery of biomarkers that are representative of the CNS disease phenotype.
- Explore the process of replicating biomarker research findings and validating single and multimodal biomarkers.
- Discuss opportunities to standardize the methodologies, terminology, and metadata for biomarker discovery, validation and use in order to increase applicability across diverse populations/cohorts and enable accessible data sharing.
- Review the current regulatory guidance for decision making regarding multimodal biomarkers for CNS disorders, current barriers, and implications for clinical utility.
- Discuss innovative and new methodologies for biomarker integration in CNS disorders, including consideration of lessons learned from other therapeutic areas.

MONDAY, MARCH 13, 2023 (All times listed in ET)

2:00–2:05pm **Welcome**

FRANCES JENSEN, University of Pennsylvania; *Co-chair, Forum on Neuroscience and Nervous System Disorders*

JOHN KRYSTAL, Yale University; *Co-chair, Forum on Neuroscience and Nervous System Disorders*

2:05–2:15pm **Workshop Overview**
LINDA BRADY, National Institute of Mental Health; *Workshop Co-Chair*
VIKAS SHARMA, Boehringer Ingelheim; *Workshop Co-Chair*

2:15–2:25pm **Understanding the Importance of Multimodal Biomarkers for CNS Disorders: Perspectives from Individuals with Lived Experience**

Key Questions:
- What are meaningful measures from individuals with lived experience or caregivers' perspectives?
- What are the ethical implications of multimodal biomarker discovery, development and clinical utility that should be taken into consideration from the lived experience or caregiver perspective?
- How do robust individual/multimodal biomarkers impact the diagnosis, care, and prognosis of patients with CNS disorders?

JILLIAN PAPA, Emotions Matter
MARÍA DE LEÓN (*via Zoom*), The Michael J. Fox Foundation for Parkinson's Research

2:25-2:35pm **Moderated Discussion**

2:35–2:55pm **Keynote: Defining and Understanding the Role of Biomarkers**

Key Questions:
- What is the FDA's definition and terminology around biomarkers and their context-of-use?
- What is a multimodal biomarker? What are the advantages of combining biomarker types?

MARY THANH HAI, Food and Drug Administration

2:55–4:50pm **Session 1: State of Science of Multimodal Biomarkers for CNS Disorders**

Session Objective: Review current state of knowledge regarding biomarkers for CNS disorders (e.g., Alzheimer's, Parkinson's, etc.) and ongoing efforts to generate multimodal biomarkers.

Key Discussion Questions:
- Why are multimodal biomarkers needed for CNS disorders?
- What is the process for moving from individual biomarkers to combining biomarker types to generate multimodal biomarkers?
- What are some of the common challenges of multimodal biomarker development across CNS disease areas and how have these been successfully overcome?
- What are the advantages and disadvantages of integrative and multiplex biomarkers?

2:55–3:00pm **Session Overview**
SAMANTHA HUTTEN (*via Zoom*), The Michael J. Fox Foundation for Parkinson's Research; *Planning Committee Member; Session Co-Moderator*

3:00–3:15pm **Alzheimer's Disease**
CLIFFORD JACK, Mayo Clinic

3:15–3:30pm **Parkinson's Disease**
KIRSTEN TAYLOR (*via Zoom*), Roche

3:30–3:40pm **BREAK**

3:40–4:55pm **Huntington's Disease**
JANE PAULSEN, University of Wisconsin

3:55–4:50pm **Moderated Panel and Audience Q&A**

Moderator: ALESSANDRA ROVESCALLI, National Institute of Aging, *Planning Committee Member, Session Co-Moderator*

Discussant:
MARY THANH HAI, Food and Drug Administration
CHARISSE WINSTON, University of California, San Diego; *Planning Committee Member*

4:50–5:00pm **Day 1 Synthesis and Preview to Day 2 of the Workshop**
LINDA BRADY, National Institute of Mental Health; *Workshop Co-Chair*
VIKAS SHARMA, Boehringer Ingelheim; *Workshop Co-Chair*

TUESDAY, MARCH 14, 2023 (All times listed in ET)

9:30–9:35am **Welcome and Recap of Day 1 Themes**
LINDA BRADY, National Institute of Mental Health; *Workshop Co-Chair*
VIKAS SHARMA, Boehringer Ingelheim; *Workshop Co-Chair*

9:35–11:30am **Session 2: Precision Medicine Opportunities, Challenges, and Lessons Learned in Multimodal Biomarkers for CNS Disorders**

Session Objective: Discuss case studies of multimodal biomarker development in central nervous system disorders to examine current challenges and opportunities.

Key Discussion Questions:

- What lessons learned in data collection, cohort development, measurement standards, and biomarker replication can be applied across CNS therapeutic areas?
- What success metrics from Session 1 can help push other CNS disease areas closer to the finish line?
- How can we generate biomarkers that are applicable to a wide range of racial/ethnic groups? What have been some of the successes and challenges in developing generalizable biomarkers?
- What are the ethical considerations that need to be addressed when developing multimodal biomarkers?
- What are the pitfalls of machine learning?

9:35–9:40am **Session Overview**
HARTMUTH KOLB, The Janssen Pharmaceutical Companies of Johnson & Johnson, *Planning Committee Member, Session Co Moderator*
CAROL TAYLOR-BURDS, National Institute of Neurological Disorders and Stroke, *Planning Committee Member, Session Co-Moderator*

9:40–9:55am **Understanding the Need for Meaningful Measures Across Diverse Populations**
CARLOS LARRAURI (*via Zoom*), National Alliance on Mental Illness

9:55–10:10am **Precision Psychiatry**
LEANNE WILLIAMS (*via Zoom*), Stanford University

10:10–10:25am **Pediatric Neuroradiology**
ELLEN GRANT, Boston Children's Hospital

10:25–10:40am **Neurodevelopmental Disorders**
ADRIANA DI MARTINO, Child Mind Institute; *Planning Committee Member*

10:40-10:55am **Successes and Challenges of Developing Generalizable Biomarkers**
JP ONNELA, Harvard University

10:55–11:35am **Moderated Panel and Audience Q&A**
Discussant: DIEGO PIZZAGALLI, Harvard University

11:35–12:30pm **LUNCH**

12:30-2:00pm **Session 3: Standardization and Methodological Considerations**

Session Objective: Discuss opportunities to standardize the methodologies, terminology, and metadata for biomarker discovery, validation and use to increase applicability across diverse populations/cohorts and enable accessible data sharing.

Key Discussion Questions:

- How have data science approaches (e.g., unbiased machine language) been used for integration of biomarker data types in classification (subtypes) or to develop predictors of disease course/severity?
- What are some of the opportunities and challenges with incorporating real-time measurements (e.g., digital measures, speech, etc.)?
- What is the balance between accessible data sharing and protecting patient privacy?

12:30–12:35pm **Session Overview**
ALAN ANTICEVIC (*via Zoom*), Yale School of Medicine; *Planning Committee Member*

12:35–1:15pm **Speakers**
HAO ZHU, Food and Drug Administration
AMIT ETKIN, Alto Neuroscience; Stanford University
VISAR BERISHA, Arizona State University
EMILY DENNIS (*via Zoom*), University of Utah

1:15–2:00pm **Moderated Panel and Audience Q&A**
Moderator: STUART HOFFMAN, Department of Veterans Affairs; *Planning Committee Member*
Discussant: ADAM FERGUSON, University of California, San Francisco

2:00-2:10pm **BREAK**

2:10–3:10pm **Session 4: Regulatory Guidance and Decision Making for Multimodal Biomarkers**

Session Objective: Review the current regulatory guidance for decision making regarding multimodal biomarkers for CNS disorders, current barriers, and implications for clinical utility.

Key Discussion Questions:

- What are examples of context of use of multimodal biomarkers in CNS disorders?
- How can multimodal biomarkers be used in decision-making processes both from a drug development and clinical perspective?
- What are the challenges for implementation of multimodal biomarkers both from a regulatory and clinical perspective?
- What is the regulatory path of integrative versus multiplex biomarkers?

2:10–2:15pm **Session Overview**
VALENTINA MANTUA, Food and Drug Administration; *Planning Committee Member; Session Moderator*

2:15–2:55pm **Panel Discussion**
TERINA MARTINEZ, Critical Path Institute
LUCA PANI, University of Miami; University of Modena
MARTIEN KAS, University of Groningen
CHRIS LEPTAK, Greenleaf Health
BILL MARTIN (*via Zoom*), The Janssen Pharmaceutical Companies of Johnson & Johnson

2:55–3:10pm **Audience Q&A**

3:10–4:00pm **Session 5: Synthesis and Potential Next Steps**

Session Objective: Synthesize key themes from the workshop and discuss what is needed for innovative and new methodologies for biomarker integration in CNS disorders.

Key Discussion Questions:

- What actions are needed to address current challenges and maximize opportunities to develop multimodal biomarkers in CNS disorders?

3:10–3:15pm **Synthesis of Workshop's Key Themes**
LINDA BRADY, National Institute of Mental Health; *Workshop Co-Chair*
VIKAS SHARMA, Boehringer Ingelheim; *Workshop Co-Chair*

3:15–3:45pm **Next Steps and Opportunities**
REBECCA EDELMAYER, Alzheimer's Association
ELIAS SOTIRCHOS, Johns Hopkins University
ALESSIO TRAVAGLIA (*via Zoom*), Foundation for the National Institutes of Health; *Planning Committee Member*
MARC AAFJES, Deliberate.ai
ARTHUR SIMEN, Takeda

3:45–3:55pm **Audience Q&A**

3:55–4:00pm **Acknowledgements and Concluding Remarks**
LINDA BRADY, National Institute of Mental Health; *Workshop Co-Chair*
VIKAS SHARMA, Boehringer Ingelheim; *Workshop Co-Chair*

4:00pm **ADJOURN**