The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on NEUROSCIENCE and NERVOUS SYSTEM DISORDERS

From Molecular Insights to Patient Stratification for Neurological and Psychiatric Disorders: A Workshop

October 5-6, 2021 | Virtual

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 discuss new genetic and neuroscience technologies and explore how these discoveries can be used to elucidate disease mechanisms and to advance the development of biomarkers and targeted therapies for people with neurological and psychiatric disorders.

Invited presentations and discussions will be designed to:

- Explore the critical need for ancestral diversity and inclusion of individuals with severe or less common disorders—in genetics and the biological specimens needed to follow up on genetics—to advance both scientific analyses and global health equity/precision medicine.
    - Discuss the importance of improving existing biobanks and developing new biobanks in locations worldwide to reflect diverse populations.
    - Examine the need for special efforts to obtain samples from people at risk and those in early stages of disease to better understand disease onset and progression.
    - Consider oversampling of individuals at risk for experiencing severe neurologic and psychiatric disorders often absent from population-based cohorts.
- Examine the use of genetics and other technologies to facilitate identification of genetic variation, understand the effects of both common and rare variants on disease relevant function, and gain insights into disease mechanisms and molecular pathways in order to identify biomarkers that enable patient stratification to advance therapeutic development.
    - Consider how these steps will benefit from advanced computational approaches and "big data" produced by new technologies ranging from the molecular to neural systems-level, to human phenotyping.
    - Discuss the challenges associated with identification and interpretation of common variant function (e.g., identification of causal variation, directionality of effect, placement in disease-relevant pathways).
- Highlight lessons learned from recent advances in disorders associated with rare, penetrant genetic variants, and explore how resulting lessons can be applied to more common neuropsychiatric disorders.
- Explore challenges and promising approaches to nominating and validating stratification, disease progression, and treatment biomarkers.

- Explore challenges of designing innovative clinical trials that are based on deep mechanistic understanding of diseases and coupled with target engagement strategies in patients.
- Discuss a conceptual structure and opportunities to enable advanced technologies and computational approaches to be used more broadly, effectively, and rationally for new disorders, including considering data sharing and stakeholder engagement.

Workshop Planning Committee

Steven Hyman, MD, ***Co-chair,*** The Broad Institute of MIT and Harvard
Dimitri Krainc, MD, PhD, ***Co-chair,*** Northwestern University
Eline Appelmans, MD, MPH, Foundation for the National Institutes of Health
Paola Arlotta, PhD, Harvard University
Linda Brady, PhD, National Institute of Mental Health
Bradford Casey, PhD, Michael J. Fox Foundation for Parkinson's Research
Carole Ho, MD, Denali Therapeutics
Frances Jensen, MD, University of Pennsylvania Perelman School of Medicine
Bill Martin, PhD, Janssen Research & Development
John Ngai, PhD, National Institutes of Health BRAIN Initiative
Amir Tamiz, PhD, National Institute of Neurological Disorders and Stroke
Sarah Tishkoff, PhD, University of Pennsylvania
Stacie Weninger, PhD, FBRI
Alice Zhang, Verge Genomics

DAY 1: October 5, 2021

2:00pm ET **Welcome**
Frances Jensen, University of Pennsylvania; *Co-chair, Forum on Neuroscience and Nervous System Disorders*

2:05pm **Overview of Workshop: Exploring a New Trajectory for Research and Development in Neurological and Psychiatric Disorders**
Steven Hyman, The Broad Institute of MIT and Harvard, *Workshop Co-chair*
Dimitri Krainc, Northwestern University, *Workshop Co-chair*

2:15pm **Leveraging New Genetic and Neuroscience Technologies in Humans to Advance Therapeutic Development: What is it going to take?**
Bill Martin, Janssen Research and Development

Session 1: Increasing Ancestral Diversity in Emerging Precision Medicine for Neurological and Psychiatric Disorders

Session Objective: Explore the need for better inclusion of minority and underrepresented populations throughout the entire R&D trajectory to generate more robust, generalizable, and equitable findings.

Key Discussion Questions:

- What lessons have been learned from efforts aimed at enhancing ancestral diversity in genetic studies and biobanks, and what would move the field forward in a manner that is ethical and that advances strong partnerships when collaborating with disadvantaged populations and in low- and middle-income countries?
- What are some effective approaches to including participants at risk and those in early stages of disease?

2:25pm **Session Overview**
Sarah Tishkoff, University of Pennsylvania, *Session Moderator*

2:35pm **Speakers**
Alicia Martin, Massachusetts General Hospital; Harvard Medical School; Broad Institute of MIT and Harvard
Li-San Wang, University of Pennsylvania
Ekemini A. U. Riley, Aligning Science Across Parkinson's

3:05pm **Moderated Discussion with the Speakers and Q&A**

3:25pm **BREAK**

Session 2: Leveraging New Methodologies to Interpret Genetic Data in Neurological and Psychiatric Disorders

Session Objective: Explore how new technologies and methodologies for genetic variant interpretation among common and rare variants, as well as common variant studies, can be used to identify pathways and mechanistic insights that lead to nomination of biomarkers and therapeutic targets.

Key Discussion Questions:

- How can these new technologies be used to "separate the wheat from the chaff" in GWAS results to gain a better understanding of phenotypes?
- What are the relative advantages of disease-agnostic and disease-specific approaches for target identification, and how could these approaches be used in a complementary way?
- How can multimodal data be harnessed to yield more robust hypotheses?
- How would greater ancestral diversity in genetic studies yield higher quality hypotheses and inform variant interpretation?

3:35pm **Session Overview**
John Ngai, National Institutes of Health, *Session Moderator*

3:45pm **Speakers**
Hilary Finucane, Massachusetts General Hospital; Harvard Medical School; Broad Institute of MIT and Harvard

Jens Hjerling-Leffler, Karolinska Institute
Lea Starita, University of Washington
Danielle Posthuma, VU Amsterdam
Daniel Geschwind, University of California, Los Angeles

4:35pm **Moderated Discussion with the Speakers and Q&A**

4:55pm **Day 1 Synthesis**

Steven Hyman, The Broad Institute of MIT and Harvard, *Workshop Co-chair*
Dimitri Krainc, Northwestern University, *Workshop Co-chair*

5:00pm **ADJOURN**

DAY 2: October 6, 2021

10:00am ET **Welcome and Recap of Day 1**

Steven Hyman, The Broad Institute of MIT and Harvard, *Workshop Co-chair*
Dimitri Krainc, Northwestern University, *Workshop Co-chair*

Session 3: Identifying and Validating Molecular Pathways Using New Technologies for Human Biology

Session Objective: Explore novel technologies for validating molecular targets, pathways, and circuits in humans (e.g., iPSC derived neurons, astrocytes, microglia, oligos, vascularized organoids, pooled iPSC).

Key Discussion Questions:

- What is the role of different animal and human model systems for discovery and validation?
- How can these approaches be used to gain a better understanding of different variants' impact on the disease state (e.g., variant to function), including phenotypic expression and differential vulnerability.
- How can greater ancestral diversity and the incorporation of environmental influences in genetic studies provide better insight into the phenotypic expression of neuropsychiatric disease states, and what are the implications for target validation?
- What scientific findings and lessons learned from rare variants and monogenetic diseases can be applied to more genetically complex common disorders?
- What criteria do different decision makers use when deciding how to validate biomarkers and select which targets to invest in and advance to clinic?

10:05am **Session Overview**

Dimitri Krainc, Northwestern University, *Workshop Co-chair, Session Moderator*

10:15am **Speakers**

Helen Willsey, University of California, San Francisco
Fenna Krienen, Harvard Medical School
Paola Arlotta, Harvard University
Martin Kampmann, University of California, San Francisco
Daphne Koller, Insitro
Alice Zhang, Verge Genomics

11:15am **Moderated Discussion with the Speakers and Q&A**

12:15pm **LUNCH**

Session 4: Developing and Advancing Phenotyping and Biomarker Discovery to Enable Patient Stratification

Session Objective: Discuss opportunities to improve patient stratification by leveraging multimodal data to identify, validate, and use robust biomarkers, including early markers of disease.

Key Discussion Questions:

- How are novel biofluid-based biomarkers (e.g., genomics, proteomics, and biological pathways) being used for patient stratification in neurodegenerative disorders?
- What lessons learned and similarities can be applied to neuropsychiatric disorders, and when are different approaches required?
- How can well-correlated biomarkers in clinical data be used to identify patient subsets by leveraging natural history studies and opportunities for deep phenotyping with appropriate representation of ancestral diversity?
- Can polygenic scores be integrated with fluid and PET biomarkers to improve stratification?

1:00pm **Session Overview**

Linda Brady, National Institute of Mental Health, *Session Moderator*

1:10pm **Speakers**

Charlotte Teunissen, Amsterdam UMC
Danielle Graham, Biogen
Pamela Horn, Food and Drug Administration
Ernest Fraenkel, Massachusetts Institute of Technology
Nikos Koutsouleris, Ludwig Maximilian University of Munich; King's College London

2:00pm **Moderated Discussion with the Speakers and Q&A**

3:15pm **BREAK**

Session 5: Synthesis and Next Steps

Session Objective: Synthesize key themes from the workshop and discuss what is needed to shift the trajectory for R&D and enable these technologies and precision medicine approaches to be used more broadly, effectively, and rationally for new disorders.

Key Discussion Question:

- What is needed to move the field forward (e.g., data, ongoing efforts related to ancestral diversity, new infrastructure, opportunities for collaboration, and stakeholder engagement)?

3:25pm **Synthesis of Workshop's Key Themes**

Steven Hyman, The Broad Institute of MIT and Harvard, *Workshop Co-chair*
Dimitri Krainc, Northwestern University, *Workshop Co-chair*

3:35pm **Next Steps and Opportunities**

Panelists:

Eline Appelmans, Foundation for the National Institutes of Health
Bradford Casey, Michael J. Fox Foundation for Parkinson's Research
Kafui Dzirasa, Duke University
Carole Ho, Denali
Henne Holstege, Amsterdam UMC
John Ngai, National Institutes of Health
Amir Tamiz, National Institute of Neurological Disorders and Stroke
Stacie Weninger, FBRI

4:25pm **Audience Q&A**

4:55pm **Acknowledgements and Concluding Remarks**

Steven Hyman, The Broad Institute of MIT and Harvard, *Workshop Co-chair*
Dimitri Krainc, Northwestern University, *Workshop Co-chair*

5:00pm **ADJOURN WORKSHOP**