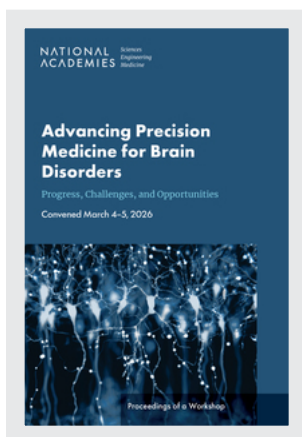


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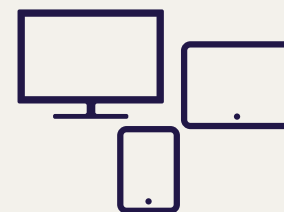
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Advancing Precision Medicine for Brain Disorders

Progress, Challenges, and Opportunities

Convened March 4–5, 2026

Janell Payano Sosa and
Sheena M. Posey Norris, *Rapporteurs*

Forum on Neuroscience and
Nervous System Disorders

Forum on Drug Discovery,
Development, and Translation

Roundtable on Genomics and
Precision Health

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**PRECISION MEDICINE IN NEUROSCIENCE:
TOOLS, TRANSLATION, AND IMPLEMENTATION
PLANNING COMMITTEE¹**

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This Proceedings of a Workshop was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We thank the following individuals for their review of this proceedings:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **AMY WAGNER**, University of Pittsburgh Medical Center. She was responsible for making certain that an independent examination of this proceedings was carried out in accordance with

standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

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Acronyms and Abbreviations

Aβ	amyloid beta
ACNP	American College of Neuropsychopharmacology
AI	artificial intelligence
ALS	amyotrophic lateral sclerosis
AMP	Accelerating Medicines Partnership
APA	American Psychiatric Association
APOE	apolipoprotein E
ARIA	amyloidrelated imaging abnormalities
ARPAH	Advanced Research Projects Agency for Health
BAARD	Biotype-assigned Augmentation Approach in Resistant late-life Depression
CAMH	Centre for Addiction and Mental Health
CHR	clinical high risk
CMS	Centers for Medicare and Medicaid Services
C-Path	Critical Path Institute
CSF	cerebrospinal fluid
CYP2C19	cytochrome P450 2C19
CYP2D6	cytochrome P450 2D6
DARPA	Defense Advanced Research Projects Agency
DAT	dopamine transporter
DRG	diagnosisrelated group

DSM	Diagnostic and Statistical Manual of Mental Disorders
ECNP	European College of Neuropsychopharmacology
EEG	electroencephalography
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EHR	electronic health record
eMERGE	Electronic Medical Records and Genomics Consortium
EVIDENT	Evidence-Based Validation & Innovation for Rapid Therapeutics in Behavioral Health
FDA	U.S. Food and Drug Administration
fMRI	functional magnetic resonance imaging
FNIH	Foundation for the National Institutes of Health
GPS	global positioning system
GWAS	genome-wide association studies
HIV	human immunodeficiency virus
IHI	Innovative Health Initiative
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSA	multiple system atrophy
NAMI	National Alliance on Mental Illness
nFl	neurofilament light chain
NIH	National Institutes of Health
PD	Parkinson's disease
PET	positron emission tomography
PPMI	Parkinson's Progression Markers Initiative
pQTL	protein quantitative trait locus
PRISM	Psychiatric Ratings using Intermediate Stratified Markers
PSP	progressive supranuclear palsy
QMS	quality management system
R&D	research and development
REM	rapid eye movement
SOD1	superoxide dismutase 1

ACRONYMS AND ABBREVIATIONS

xix

SSRI	selective serotonin reuptake inhibitor
UAB	University of Alabama, Birmingham
UCLA	University of California, Los Angeles

1

Introduction and Background¹

Neurological and psychiatric disorders are major contributors to morbidity, mortality, disability, and health care utilization worldwide, affecting individuals across the lifespan and placing substantial demands on patients, families, and health systems (Feigin et al., 2020; Steinmetz et al., 2024). Despite advances in understanding disease biology, many available treatments remain symptomatic or are effective only for subsets of patients, and clinical outcomes often vary considerably because of the biological and clinical heterogeneity that exists within current diagnostic categories. As neuroscience seeks to develop more individualized approaches to the prevention, diagnosis, and treatment of neurological and psychiatric disorders that better account for the underlying mechanisms of disease and sources of variability in treatment response, precision medicine has emerged as a promising framework for integrating biological, environmental, and behavioral information into health care decision making (Collins and Varmus, 2015). Interest in applying precision medicine to brain disorders has grown as researchers increasingly recognize that individuals with the same clinical diagnosis may differ substantially in disease mechanisms, progression, and treatment response (Insel and Cuthbert, 2015; Hampel et al.,

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2018). Advances in biomarkers, multi-omics technologies, digital health tools, artificial intelligence, and computational methods are creating new opportunities to characterize disease subtypes, stratify patients, and support more individualized approaches to care (Hampel et al., 2018; Chen et al., 2022; Babu and Snyder, 2023).

Frances Jensen, the Arthur Knight Asbury Professor of Neurology and Chair of Neurology at the Perelman School of Medicine at the University of Pennsylvania, noted that advances in neuroscience are translating increasingly into practical applications in research and clinical care, making this an opportune time to examine how precision medicine tools, translational pathways, and implementation strategies can support more individualized approaches to treatment. Deanna Barch, vice dean of Research and the Gregory B. Couch Professor of Psychiatry at Washington University in St. Louis, emphasized that expanding datasets and analytic capabilities are creating new opportunities to address longstanding questions in precision neuroscience.

To explore these opportunities and challenges, the National Academies of Sciences, Engineering, and Medicine's Forum on Neuroscience and Nervous System Disorders, in collaboration with the Forum on Drug Discovery, Development, and Translation and the Roundtable on Genomics and Precision Health, hosted a workshop on March 4–5, 2026. Gayle Wittenberg, vice president of Precision Measures, Neuroscience Research, and Development at Johnson & Johnson Innovative Medicine, emphasized that the workshop would trace the full arc of precision medicine in neuroscience—from emerging tools that deepen biological understanding to the practical realities of implementation (see Figure 1-1). The workshop was organized around a translational continuum spanning biological discovery, biomarker development and validation, demonstration of clinical utility for patient identification and treatment selection, regulatory qualification of biomarkers and other drug development tools, and implementation in clinical trials and clinical practice, with real-world evidence feeding back to accelerate future discovery. Wittenberg also situated the meeting within a broader lineage of prior activities by the National Academies' Neuroscience Forum. The current workshop built on a series of previous activities convened by the Neuroscience Forum that explored topics relevant to precision neuroscience, including biomarkers and biosignatures, patient stratification, therapeutic development, disease modeling, and the application of artificial intelligence to neuroscience. Collectively, these workshops examined many of the scientific, translational, and methodological issues that underpin efforts to develop more individualized approaches to the prevention, diagnosis, and treatment of neurological and psychiatric disorders (IOM, 2008a, 2008b, 2013, 2014; NASEM, 2016, 2018, 2019, 2020, 2024, 2025). Wittenberg encouraged participants to think across sessions

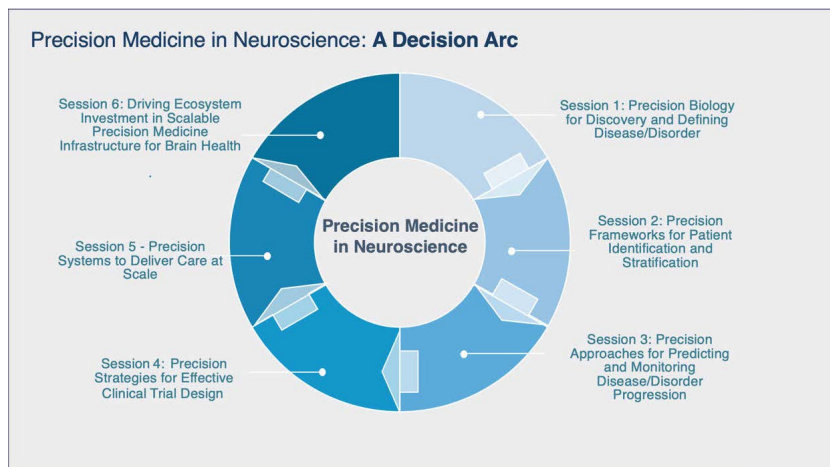


FIGURE 1-1 Overview of workshop sessions.

NOTE: This figure depicts six of the seven workshop sessions outlining the continuum of precision medicine in neuroscience. The arc progresses from precision biology and patient stratification through predictive monitoring, clinical trial design, and care delivery systems, culminating in ecosystem investment to scale precision medicine infrastructure for brain health.

SOURCE: Presented by Gayle Wittenberg and Rosa Canet-Avilés, March 4–5, 2026.

rather than in silos, highlighting the continuous “end-to-end and back again” nature of precision medicine, where real-world data refine biological insight and guide the next generation of interventions. Wittenberg described the workshop as a compass rather than an exhaustive review, urging attendees to consider what future reflections on the field might say about the decisions made today. Jensen highlighted the workshop’s interdisciplinary foundation, bringing together public–private partnerships, lived-experience perspectives, industry, nonprofit, and federal partners as well as expertise spanning basic science and clinical care. Against this backdrop, Barch encouraged participants not only to assess current progress but also to think prospectively about how to accelerate discovery, innovation, and—critically—the implementation of these advances in real-world settings.

WORKSHOP OBJECTIVES

The workshop examined how precision medicine can meaningfully advance neuroscience by tracing its influence across research, diagnosis, and treatment (see Box 1-1). Participants explored emerging tools and technologies—including biomarkers, multi-omics platforms, mobile health technologies, artificial intelligence, and the conceptual and analytic frameworks

of computational psychiatry—and considered how these developments are beginning to shape both scientific discovery and clinical care. The discussions also addressed the practical barriers and opportunities that determine whether precision approaches can be implemented at scale, such as provider education, patient engagement, payer and regulatory models, data privacy, and integration into clinical workflows. Finally, the workshop highlighted the importance of cross-disease and holistic frameworks, emphasizing how precision medicine can illuminate comorbidities and support a broader, population-level brain-health model. Together, these objectives underscore the workshop's central aim to clarify what it will take for precision neuroscience to move from conceptual promise to real-world impact. Given the breadth of the field, the workshop focused on selected topics and was intended to provide a high-level overview of emerging advances, challenges, and opportunities rather than a comprehensive review of all aspects of precision medicine for brain disorders.

ORGANIZATION OF PROCEEDINGS

This Proceedings of a Workshop provides a summary of the presentations and discussions that took place over the 1.5-day meeting. Chapter 2 provides a lived-experience researcher perspective on integrating the patient voice into precision neuroscience. Chapter 3 examines precision biology for discovery and the evolving definition of disease. Chapter 4 explores precision frameworks for patient identification and stratification. Chapter 5 focuses on precision measures used to monitor disease progression and treatment response. Chapter 6 reviews precision strategies for effective clinical trial design, and Chapter 7 considers the systems required to deliver precision care at scale. Chapter 8 discusses ecosystem-level investment needed to build scalable precision-medicine infrastructure, while Chapter 9 provides a synthesis of cross-cutting themes and future opportunities for precision medicine in neuroscience. Keynote presentations are integrated throughout the chapters. Appendix A contains references cited in the proceedings, and Appendix B provides the workshop agenda.

BOX 1-1
Statement of Task

A planning committee of the National Academies of Sciences, Engineering, and Medicine hosted a 1.5-day public workshop to examine opportunities and challenges in applying precision medicine approaches to understanding and treating brain disorders. The workshop brought together experts and stakeholders from across sectors and disciplines to explore how advances in biology, data science, drug development, and clinical practice are shaping the future of individualized care for neurological and psychiatric conditions.

Invited presentations and discussions will:

- Highlight case examples where precision medicine approaches have informed research, diagnosis, treatment, and disease reclassification in neuroscience.
- Examine emerging tools and technologies—including biomarkers, multi-omics, computational psychiatry, and artificial intelligence—and their applications across neuroscience research and clinical care.
- Consider barriers and opportunities for implementation, including provider education, patient engagement, payer and regulatory models, data privacy, clinical integration, and potential risks.
- Explore cross-disease and holistic frameworks, including how precision medicine approaches can address comorbidities and support a broader brain health model.

A planning committee developed the agenda for the workshop, selected and invited speakers and discussants, and moderated the discussions. Following the workshop, a proceedings of the presentations and discussions will be prepared by a designated rapporteur in accordance with institutional guidelines.

2

Integrating Lived Experience Perspectives Across the Precision Neuroscience Continuum

Highlights

- Precision neuroscience cannot achieve its full potential without becoming a continuous learning system that values and integrates the patient voice (Carras).
- Lived-experience researchers strengthen the development of precision tools and care models by grounding scientific innovation in the realities of daily life and ensuring that patient priorities shape research and clinical decision making (Carras).
- Agile, learning-focused care models—guided by patient insight, lived-experience expertise, and new digital measures—offer a more responsive and humane way to advance precision psychiatry (Carras).

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

As precision medicine approaches become increasingly integrated into research and clinical care, there is growing recognition that scientific and technological advances alone may not be sufficient to improve health outcomes. Understanding and incorporating the experiences, priorities, and preferences of patients is increasingly viewed as an important component of developing and implementing individualized approaches to care. To explore this perspective, Gayle Wittenberg introduced Michelle Colder Carras,

founder and CEO of Carras Colder Carras, LLC, as a public health scientist whose research spans epidemiology, public mental health, evidence development, and mental health services program design and evaluation. As one of the workshop's four keynote speakers, Carras offered a perspective that directly complemented Wittenberg's framing for an iterative bench-to-bed-side-and-back process in precision neuroscience (see Chapter 1). Drawing on both her professional expertise and lived experience with bipolar disorder, she underscored a theme that resonates across the neuroscience field—precision medicine in neuroscience cannot advance without systematically valuing, measuring, and integrating the patient voice.

A LIVED EXPERIENCE PERSPECTIVE TO PRECISION NEUROSCIENCE

Carras framed her keynote through the lens of her dual roles as a researcher and a person with lived experience of bipolar disorder. Her professional work focuses on digital mental health, epidemiology and public health program design, while her perspective is shaped by more than 20 years of mental health advocacy, her experience living with bipolar disorder, as a family member of individuals with mental health challenges, and a suicide loss survivor. Carras co-leads an international coalition of lived-experience researchers seeking to transform mental health science by embedding people with lived experience at every stage of research development and design. This grounding, she explained, shapes how she understands both the promise and the limitations of current precision medicine efforts.

Carras emphasized that while precision medicine in other fields draws on biomarkers, imaging, and continuous physiological monitoring, psychiatry relies almost entirely on patient-reported information. She noted that this primary data source is often undervalued, treated as subjective or unreliable compared with clinician observations or system-level metrics. This creates a fundamental barrier. She explained that this skepticism persists even though treatment is usually structured to provide brief and widely spaced clinical encounters, leaving little opportunity for systematic measurement or longitudinal tracking. She stressed that without routine, high-frequency, patient-centered data, the field lacks the rapid feedback loops needed to support iterative learning, timely course correction, and individualized care. She added that this challenge is not unique to psychiatry; across many brain disorders represented at the workshop, patient-generated information remains an underused but essential component of precision neuroscience.

She illustrated the consequences of these gaps through her own personal experiences in which the absence of systematic measurement and biological insight led to preventable harm. Thirty years ago, after a hospitalization,

she was prescribed a selective serotonin reuptake inhibitor (SSRI), a type of antidepressant, that caused her nightly vomiting. Her concerns were dismissed as normal side effects that she should just “push through” despite its debilitating effects and led to the iatrogenic harm of development of a very disabling emetophobia. She reflected that when patients raise concerns in psychiatric settings, they can sometimes be labeled as difficult or nonadherent, and side effects are often minimized, as she experienced over the years, in ways that would be unthinkable in other areas of medicine; in contrast, a person receiving chemotherapy would typically be given preventive treatment for nausea rather than being told to simply endure it. Fifteen years later, she finally learned through pharmacogenomic testing that she was unable to metabolize medications processed through a liver enzyme called cytochrome P450 2D6, often abbreviated CYP2D6, which is involved in the metabolism of many commonly used medications, including several antidepressants, and required for metabolism of some pain-relieving drugs. This meant that the SSRI she was prescribed was unlikely to be effective and could even accumulate to toxic levels, as her nausea symptoms suggested over the weeks, and that if she ever required pain relief, commonly used medications would not work at all. Having this information earlier could have prevented years of avoidable harm, said Carras.

More recently, Carras started hormone-replacement therapy and her depression worsened. She initially assumed it was aging or menopause. Only when she asked a pharmacist did she learn that her hormone replacement therapy reduced her mood stabilizer levels by 50 percent, contributing to her worsening depression. For two years, not one of her health care providers had caught the problem. She reflected that it was fortunate she had the scientific training to think to ask her pharmacist to check for potential drug interactions. She added that, just days earlier, she had used her own financial resources to obtain a brand-name stimulant medication that had long served as an important adjunctive treatment for her mood but is not covered by her insurance. As soon as she started the medication her depression lifted almost immediately, revealing how much she had missed—emotionally, cognitively, and socially—during the preceding months. The first day, she felt compassion for the version of herself who had been struggling without understanding why. The second day, her scientist brain questioned: *How could I have known sooner? How could anyone? What cognitive signs did I miss? How could we measure them?*

Carras’ experience reflects systemic gaps in how patient reported changes are captured, interpreted, and acted upon. She raised questions about equity: *If this was the experience of a privileged scientist educated in public mental health with decades of advocacy background, what happens to the average person who lacks the privilege of scientific training, resources, or stability? What about people who are unhoused, marginalized,*

or affected by structural racism? She urged the field to recognize how many opportunities for prevention and treatment are currently missed.

Having underscored how these systemic gaps fall hardest on those with the least support, she noted that qualitative patient information is sometimes dismissed as “noisy” or “nuisance data,” even in clinical trials, which further limits the field’s ability to act on what patients report. She emphasized that, in psychiatry—as in some neurodevelopmental conditions—patients may be treated involuntarily, which gives clinicians extraordinary authority over their lives. Because of that power imbalance, she argued that the field has an ethical obligation to ensure that diagnoses, decisions, and treatments are as accurate and well-informed as possible. She argued that the field’s ethical obligations are often understated. If payers and regulators insist on diagnosis-based requirements, Carras asked why those requirements should carry such weight when the Diagnostic and Statistical Manual (DSM)—now nearly a century old—was created as a descriptive field guide rather than a biologically-validated system. She questioned why medications must be approved for a diagnostic indication rather than for the symptoms they actually treat, given that many psychiatric indications are themselves constructed categories. She highlighted that organizations, such as the National Alliance on Mental Illness (NAMI), have played an important role in her own recovery, yet the ways in which nonprofessional patients are engaged in these settings can be complex. She observed that these relationships sometimes raise ethical questions about power, representation, and the responsibilities placed on people with lived experience.

With these concerns in mind, Carras shifted from diagnosis to solutions, outlining how the field might begin to change course. To transform the system, she proposed that precision neuroscience must embrace agile methods—team based, iterative approaches that emphasize continuous feedback, rapid learning, and judgment free adaptation. In fields where biological targets remain incomplete or heterogeneous, agile frameworks may offer a more realistic and humane pathway than waiting for perfect mechanistic understanding. Precision care, in this view, becomes a learning system rather than a static diagnostic exercise—one in which clinical experiences, such as unexpected medication side effects, treatment interactions, or subtle longitudinal changes in cognition or function, become actionable signals that inform additional testing, refine treatment decisions, and support earlier intervention. She encouraged clinicians to involve patients more deeply in decision making, cultivate curiosity, and adopt iterative treatment approaches that adjust based on patient-reported changes rather than rigid diagnostic categories.

Taken together, these research ecosystem shifts point toward a more responsive and participatory model of care. Carras shared her long-standing interest in digital phenotyping, particularly the potential of video games to

reveal meaningful behavioral information. She noted that gameplay naturally captures patterns of social interaction and motivational dynamics and argued that these data streams could offer rich, low-burden insights into how people function in daily life. She added that, unlike many clinical measures, most people would likely feel comfortable sharing this type of information. She emphasized that livedexperience researchers bring essential insight to the development of these tools, grounding scientific innovation in realworld needs and experiences. Carras closed with the central message that precision neuroscience must become a continuous learning system that values and integrates the patient voice.

Turning to system readiness, Wittenberg asked where the bottleneck lies for implementing precision medicine in psychiatry. Carras argued that a key bottleneck lies in how the field defines the biological evidence needed before adopting new treatments or measurements in clinical practice. She cautioned that the pursuit of perfect proof can delay translation for years or even decades and called for “epistemic humility.” She added that an agile approach to trial-and-error learning that still maintains rigor but avoids paralysis might be the solution.

3

Precision Biology for Discovery and Defining Disease

Highlights

- Achieving precision neuroscience relies heavily on moving beyond symptom-based categories (e.g., dementia/no-dementia) and reconstructing diagnostic frameworks around measurable biological mechanisms (Hyman, Gabbito).
- Advancing precision neuroscience depends on deep, longitudinal phenotyping—linking behavior, biology, and development over time—to identify the mechanisms that truly differentiate individuals and overcome the temporal and conceptual limitations of current diagnostic labels (Gabbito, Heywood, Simmons).
- Precision neuroscience has the potential to define itself on its own terms—building biologically and clinically meaningful mechanistic pathways while adapting, rather than replicating, lessons learned from oncology’s template or relying on inherited diagnostic conventions (Canet-Avilés).
- Brain disorders cannot be understood through symptoms alone; instead, they reflect underlying genetic networks that interact with life experiences across development, underscoring the need for new biologically grounded definitions of disease (Geschwind).
- Open science approaches that disseminate methods, harmonize data, and connect cellular, genomic, and digital measures across institutions are critical for accelerating discovery and translation (Gabbito).
- The field’s central challenge is determining which biological signals are truly decisionshaping, amid rapidly expanding multiomic and artificial intelligence (AI)enabled datasets and distinguishing actionable insight from noise (Harris).

NOTE: This list is the rapporteurs’ summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Rosa Canet-Avilés, the chief science officer at the California Institute for Regenerative Medicine, opened the first session of the workshop by posing two foundational questions: What do we mean by precision medicine in neuroscience, and how do we move from aspiration to real-world impact? She framed this inquiry as the starting point for the discussions that follow, emphasizing that clarifying the definition and trajectory of precision neuroscience is essential for guiding the field's next steps. She also clarified that precision neuroscience cannot simply replicate the oncology model; rather, the field must confront its own diagnostic limitations and build mechanistic pathways where they are most biologically and clinically meaningful. Canet-Avilés noted that biological insight alone will not drive progress, underscoring the importance of redesigning systems to support translation.

Julie Harris, the vice president of Science Initiatives at the Allen Institute, outlined the session's purpose to examine how precision biology is advancing discovery and reshaping the definition of neurological and psychiatric disorders. She noted that the field now operates with a sophisticated technological toolkit—spanning multi-omics, digital measures, and AI-enabled analytics—that is generating unprecedented volumes of biological data. These capabilities allow researchers to characterize disease mechanisms with increasing resolution, yet they also raise a central question for the session: When is biological understanding strong enough to justify decisions that influence clinical development? To guide discussion, she highlighted three framing questions: 1) Which biological data are most likely to shape downstream decisions; 2) when do correlations or basic-science insights become actionable; and 3) which data meaningfully contribute to redefining disease versus adding noise? She emphasized that determining what is truly informative—and what will only be understood in hindsight—remains a core challenge for precision neuroscience.

REBUILDING DIAGNOSTIC FRAMEWORKS FOR BIOLOGICAL VALIDITY

Steve Hyman, the Harald McPike Professor of Stem Cell and Regenerative Biology and the Distinguished Service Professor at Harvard University, a core institute member and director of the Program in Brain Health at the Broad Institute of Massachusetts Institute of Technology (MIT) and Harvard, opened his keynote by outlining the key challenges, barriers, and a strategy needed to shape the future of precision medicine. To demonstrate what is possible in precision medicine, Hyman pointed to early successes in cancer research. He described how non-small cell lung cancer was once treated as a single disease until researchers discovered that about 80 percent of cases overexpressed the epidermal growth factor receptor (EGFR) (Lynch et al., 2004). Drugs, such as gefitinib, were designed to target this receptor,

but clinical trials initially failed (Giaccone et al., 2004). He explained that researchers eventually noticed a small subset of patients—about 10 percent—were clinically responsive to gefitinib due to an EGFR mutation (Lynch et al., 2004). He emphasized that studies of this mutation transformed lung cancer care and led to routine genetic testing.

However, Hyman argued that neuroscience is an even more complex problem than cancer because the human brain is extraordinarily intricate, highly variable across individuals, and offers only limited access to living tissue, in contrast to cancers and other organ diseases where biopsies provide access to the pathological tissue. He explained that the field still lacks reliable animal models that truly mirror human diseases. Hyman added that the genetics behind these conditions are extremely complicated and the environmental influences are almost limitless, creating what he called an “infinite search space.” He noted that despite major advances in genomic technologies and proteomic methods, progress is constrained by the field’s reliance on descriptive, syndromal diagnoses. Hyman found the claim that there is no other choice unconvincing, urging the field to dismantle current diagnostic categories and reconstruct them around biological mechanisms.

He emphasized that this challenge is universal in psychiatry, where every Diagnostic and Statistical Manual of Mental Disorders (DSM) category groups biologically dissimilar people together into a “made-up syndrome” rather than a biologically validated disease entity. According to Hyman, trial-and-error prescribing is still the norm in psychiatry. He noted that many people cycle through multiple antidepressants without clarity about whether improvement comes from the medication, the passage of time. When clinicians label someone as having “treatment resistant depression,” he argued, the problem often lies not with the patient but with the mismatch between the treatment and the true underlying biology.

Hyman stressed that current diagnostic labels—such as depression, migraine, and seizure disorders—are syndromes, not scientific categories. They group together people who share outward symptoms but may have entirely different biological mechanisms. He explained that this conceptual error leads to highly variable treatment responses, strong placebo effects, and high failure rates in late-stage clinical trials. Regulators, he noted, acknowledge this problem and have been clear that “depression is not a science term,” even though clinical trials still enroll participants based on these broad, heterogeneous labels.

Hyman recalled that when he was director of the National Institute of Mental Health, people with lived experience consistently stated that symptom reduction alone was not their primary goal—functional improvement mattered more. He emphasized that biology is essential but not the whole story; however, without biological clarity, progress stalls. Hyman shared that 35 years of structural magnetic resonance imaging (MRI) research has

produced no clinically actionable imaging test for psychiatric disorders. The problem, he argued, is not the imaging technology but the heterogeneity of the patient groups being studied against a background of vast normal diversity of brain structure and function. He illustrated the consequences through the story of a young patient from a Finnish cohort. Hyman explained that the patient had received a series of shifting diagnoses—beginning with an adjustment disorder at 16 and followed over time by major depression, substance use disorder, conduct disorder, bipolar disorder at age 24, and ultimately schizophrenia at age 32 (Kampe et al., 2024). He emphasized that this was the same patient with the same genome, yet depending on the year, he could be recruited into entirely different studies, each treating him as if he represented a distinct disease. Hyman argued that the common scenario of diagnostic instability contributes to smaller observed effect sizes and slows progress in understanding disease mechanisms and developing effective treatments while also demoralizing patients and families.

He pointed to a recent genome-wide association study (GWAS) of depression involving nearly 700,000 cases and more than 4 million controls (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2025). The study identified hundreds of genetic loci, but without deep, and ideally longitudinal phenotyping or biobanking, researchers lack the basic information to determine how many phenocopies were lumped as depression, now or in future research. Moreover, the information is not available to learn which variants and thus which disease relevant molecular mechanisms belong together in any one person, Hyman shared (Cai et al., 2026). “This is on us to fix,” he said; the technology exists, what’s missing is the right approach and investment.

Hyman then shifted toward hope and action. He described a new multi-institutional effort, called the Psychiatric Biomarkers Network,¹ to study the full psychosis spectrum, from schizophrenia to bipolar I disorder, by sequencing every participant’s genome, collecting cerebrospinal fluid, as well as blood, and following participants longitudinally for phenotyping. Hyman added that their goal is not to validate existing labels but to rebuild understanding from the bottom up, identifying biological patterns that cut across or subdivide traditional diagnoses. He noted that United Kingdom (UK) Biobank² is a strong example of a large data collection effort but its

¹ The Psychiatric Biomarkers Network is a collaboration of academic and industry investigators dedicated to identifying robust, replicable biological markers to support clinical trials in schizophrenia and bipolar spectrum disorders. For more information, see: <https://psychiatricbiomarkers.org/> (accessed June 10, 2026).

² UK Biobank is a large population resource containing extensive biological, health, and lifestyle data from 500,000 participants, made available (after de-identification) to researchers worldwide for studies serving the public interest. For more information, see: <https://www.ukbiobank.ac.uk/about-us/who-we-are/> (accessed June 10, 2026).

mid-life recruitment limits neuropsychiatric insights. He emphasized that data collection must begin early in life given onset of most psychiatric disorders before age 20. He also emphasized that AI cannot deconvolute current syndromes without appropriate training datasets which are biologically grounded.

Canet-Avilés asked Hyman what psychiatry should be targeting if precision neuroscience is to move beyond DSM defined diagnoses. Hyman responded that the psychiatry field has “not done its homework.” He argued that the DSM, while necessary for insurance and disability systems, is not scientifically defensible as a biological framework. He described its historical expansion—from roughly 10 descriptive diagnoses proposed by empirically rigorous early innovators in the early 1970’s to 265 categories in DSM III only a few years later, as evidence that now reified DSM-5 categories were never grounded in data. He emphasized that progress requires grouping patients based on meaningful biological and behavioral measures, starting early in life, and following them longitudinally. Continuing to run case control studies or genome-wide association studies (GWAS) based on DSM categories, he warned, will keep producing uninterpretable and misleading results. Hyman also added that while researchers can map GWAS signals to cells, they still cannot map them effectively to humans.

In support, Jamie Heywood, the chief executive officer and founder of Alden Scientific, agreed and added that each diagnostic grouping carries its own “temporal challenge.” He highlighted the UK Biobank as an unprecedented resource—600,000 deeply characterized individuals—but noted that its full value depends on making new data compatible with older datasets. He also pointed to emerging protein quantitative trait locus (pQTL) approaches that may help identify the biological features that truly differentiate individuals, reducing reliance on compromised clinical labels.

During the discussion, Walter Koroshetz, former director of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH), asked if psychiatric symptoms reflect disordered brain circuits, why are current technologies—such as functional MRI—not routinely used in clinical evaluation. He also asked what causes these circuit disruptions and why symptoms shift across circuits over time. Hyman replied that the limitation is not the scanner itself—“7T is enough,” he said, referring to a 7-tesla MRI, an ultra-high-field imaging system capable of exceptionally fine spatial resolution—but rather who is being scanned and what is known about them. He cautioned against expecting single mechanisms for each condition; instead, multiple interacting mechanisms shape symptoms across development. As an example, he illustrated that a person with late-life depression who develops psychosis may carry a somewhat elevated polygenic score for schizophrenia, while someone with frequently recurrent depression may carry somewhat elevated bipolar related genetic

loading. Circuits change over time, and mechanisms interact with developmental trajectories and exposures. He concluded that the field needs to identify mechanisms and understand how they interact across the lifespan. The technology will continue to improve, but researchers must ask better, biologically grounded questions in appropriate longitudinal cohorts with samples from biobanks.

Janine Simmons, the deputy director of the Office of Behavioral and Social Science Research at NIH, emphasized that in neurology and psychiatry, the health outcome is behavior. She noted that investing in genomics, transcriptomics, and proteomics will not yield meaningful associations unless behavior is measured precisely and continuously. She framed this as both a question and a statement: Are we measuring the right outcomes? Hyman agreed unequivocally. He explained that current studies enroll people based on DSM categories like intermittent explosive disorder or depression rather than on carefully measured behavioral, cognitive, and symptom profiles. Hyman added that without deep behavioral phenotyping, biological data cannot be interpreted and GWAS findings remain obscure. He reiterated that participants must be followed longitudinally, with repeated behavioral and biological assessments, to understand how symptoms and mechanisms evolve.

RECLASSIFYING BRAIN DISORDERS ALONG THE GENETIC SPECTRUM

Following Hyman's argument for replacing DSM categories with mechanistic ones, Daniel Geschwind, the Gordon and Virginia MacDonald Distinguished Professor of Neurology, Psychiatry, and Human Genetics at the University of California, Los Angeles (UCLA), extended the critique by arguing that many failures in neurology and psychiatry stem not from missed targets but from flawed conceptual models and taxonomy that treat symptom-based conditions as single diseases, even though their underlying genetic architecture and longitudinal biology varies widely. For example, he explained that neurologists often call conditions like Alzheimer's and Parkinson's "diseases," but they behave clinically and biologically differently across individuals due to many factors, including genetic and environmental influences. He noted that neurologists have traditionally equated specific pathology with a definitive disease, while psychiatry has long recognized conditions like depression and autism as syndromes. Geschwind emphasized that postmortem pathology remains valuable for revealing cellular and molecular changes, but genetic studies show that inherited and non-inherited diseases can look identical in brain tissue. He suggested that many different upstream biological disruptions can lead to similar end-stage pathological patterns and cautioned that pathology alone should not drive therapeutic decisions.

Geschwind described a study from his lab led by Mike Gandal and Jill Haney that integrated large transcriptomic datasets of more than 2,000 postmortem brain samples generated by other groups, using gene-expression profiles and genomic measurements as quantitative phenotypes to compare across bipolar disorder, schizophrenia, autism, and healthy controls (Gandal et al., 2018). He noted that earlier work had already defined the molecular pathology of autism, and this broader integration showed that those molecular signatures aligned with underlying genetic risk—evidence that the findings were not simply post-mortem artifacts. Geschwind shared that his team and colleagues at the PsychENCODE Consortium³ built integrative maps linking molecular patterns and gene networks. He advocated that, when combined with genetic data, these maps provided a causal anchor and revealed distinct neural-immune trajectories across psychiatric conditions throughout development. He emphasized that large-scale genomic profiling studies offer a strong starting point for mechanistic insight and that gene-network approaches help organize this complexity (Gandal et al., 2018, 2022; Parikshak et al., 2016; Voineagu et al., 2011; Wamsley et al., 2024; Wang et al., 2018). He added that this example focused on transcriptomic data, though the field has since advanced far beyond transcriptomics alone.

Geschwind proposed that brain disorders span a spectrum of genetic architectures, from monogenic conditions—such as certain forms of syndromic autism or dominant neurodegenerative diseases—that allow targeted, mutation-specific studies to highly polygenic disorders, like depression or substance-use disorders, where vulnerability reflects network-level biology, environmental influences, and differences in resilience. These polygenic conditions require large cohorts, real-world longitudinal data, and biomarker- or polygenic score-guided clinical trial designs. He emphasized that this spectrum underscores the need to update the current classification of brain disorders using genetic and biological signatures drawing on genomic networks, molecular and physiologic markers, and longitudinal trajectories. However, Geschwind explained that genetic characterization remains challenging because findings blur boundaries between disease states and normal variation, revealing variable expressivity and reduced penetrance influenced by environmental, network, and epigenetic modifiers (see Figure 3-1; Geschwind and Flint, 2015).

³ The PsychENCODE Consortium, supported by the National Institute of Mental Health, integrates multidisciplinary efforts to define the molecular basis of neuropsychiatric disease. Its work addresses the highly polygenic and predominantly non-coding genetic architecture of brain disorders by generating large-scale gene-expression and regulatory datasets from human postmortem brain tissue across development. The consortium's goal is to map and functionally validate disease-associated genetic variants, regulatory elements, genes, and cell types. For more information, see: <https://www.psychencode.org/> (accessed June 10, 2026).

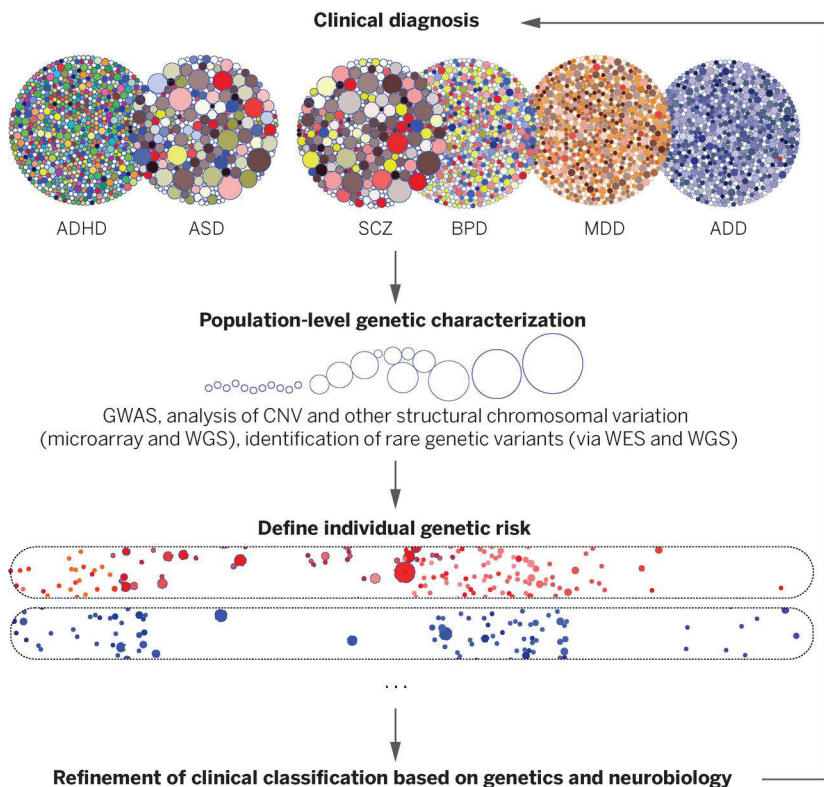


FIGURE 3-1 Redefining brain disorders as biologically stratified syndromes.

NOTES: The figure illustrates refinement of clinical classification through integration of population-level genetic characterization and individual genetic risk, emphasizing the need to define brain disorders as genetically and biologically stratified syndromes. Symptom-based clusters, such as ADHD, schizophrenia, bipolar disorder, and major depression, would be replaced by frameworks grounded in genomic signatures, molecular networks, and longitudinal biomarkers. The same genetic change can lead to different conditions in different people—for example, the gene variants, *NRXN1* and 22q11.13, appear in both schizophrenia and autism; the gene *C9ORF72* can cause either frontotemporal dementia or amyotrophic lateral sclerosis; and *MAPT* mutations are found across progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia. ADD = attention deficit disorder; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; BPD = bipolar disorder; CNV = copy number variant; MDD = major depressive disorder; SCZ = schizophrenia; WES = whole-exome sequencing; and WGS = whole-genome sequencing.

SOURCE: Presented by Daniel Geschwind, March 4, 2026; Geschwind and Flint, 2015. Reproduced with permission from AAAS.

Geschwind underscored that reduced penetrance—when a mutation does not always cause disease—is a biological signal, not a statistical inconvenience, that reflects genes acting within broader network systems, where buffering mechanisms, variable expressivity, and environmental or developmental modifiers shape outcomes across both mendelian (single-gene) and highly polygenic disorders. Although, he highlighted that this variability is even greater in highly polygenic disorders compared to mendelian disorders. Geschwind suggested that understanding the factors that shape penetrance or progression may offer more therapeutic leverage than focusing solely on primary risk genes. He noted that the field is approaching a genomic inflection point as whole-genome sequencing becomes increasingly inexpensive but stressed that genetic data must be interpreted alongside environmental context. He reinforced Hyman’s point of shifting from fixed research cohorts to following patients across the full spectrum of their real-world environments using scalable electronic health record-based phenotypes that provide continuous, rather than episodic, data. Geschwind’s vision is a future model that integrates genomics, multi-omics, and wearable-derived longitudinal data to enable network-topology-aware classification, genetic-architecture-informed subtyping, and trajectory-based stratification that can support mechanism-aligned clinical trials, as illustrated by ongoing work in depression through the Depression Grand Challenge⁴ at UCLA.

CHARACTERIZING DISEASE PROGRESSION AT THE CELLULAR LEVEL

Mariano Gabitto, an associate investigator at the Allen Institute for Brain Science and affiliated assistant professor at the Statistics Department at the University of Washington, introduced a concrete example of precision-biology in action, showing how his team at the Allen Institute is using cellular-level approaches to redefine the current understanding of Alzheimer’s disease. He began by noting that Alzheimer’s is usually defined by brain pathologies—amyloid plaques and neurofibrillary tangles (Drew, 2018). But he emphasized that these changes build up slowly over decades, spreading from one brain region to another in a spatiotemporal pattern (see Figure 3-2). Because of this long timeline of disease progression, Gabitto argued the need for more detailed biological tools to understand how the disease actually unfolds.

⁴ The Depression Grand Challenge is a university-wide initiative launched by UCLA to accelerate progress in understanding and reducing the global burden of depression. The effort mobilizes multidisciplinary expertise and multi-sector partnerships to advance large-scale research, with the long-term goal of cutting the worldwide impact of depression on health and well-being in half by 2050.

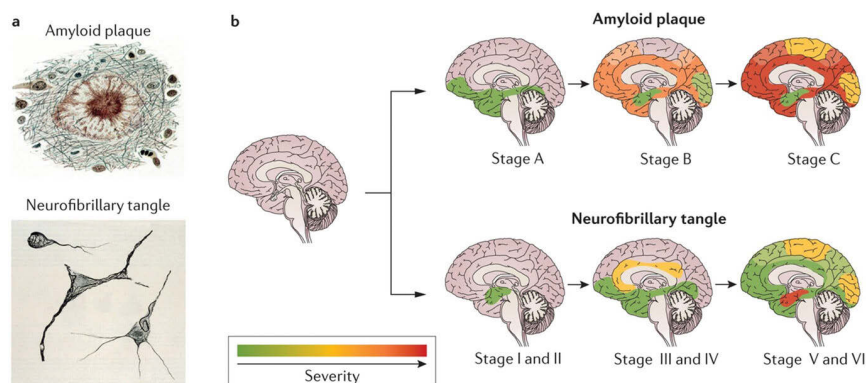


FIGURE 3-2 Spatiotemporal progression of Alzheimer's disease pathology.

NOTE: This schematic illustrates the biologically grounded progression of Alzheimer's disease, showing how amyloid- β plaques and neurofibrillary tangles accumulate through defined anatomical stages. Disease severity increases from early (Stage A; I–II) to advanced (Stage C; V–VI) phases, following stereotypical spatiotemporal trajectories across cortical and subcortical regions.

SOURCE: Presented by Mariano Gabitto, March 4, 2026; Masters et al., 2015. Reproduced with permission from Springer Nature.

To do this, Gabitto described the Seattle Alzheimer's Disease Brain Cell Atlas,⁵ a major collaboration designed to identify the cell types most vulnerable in Alzheimer's disease, map how the disease progresses, and distinguish this trajectory from normal aging. The SEA-AD team redesigned how donated brain tissue is preserved so they could use advanced methods like single cell genomics, which measures what each cell is doing, and spatial transcriptomics, which shows where those cells sit in the brain using the reference cell-type taxonomies generated by the NIH-funded BRAIN Initiative,⁶ to selectively pinpoint the molecular pathways disrupted as the disease advances and to shift from descriptive pathology toward a mechanistic, cell type–resolved understanding (BICCN, 2021). Gabitto explained that they studied one brain region first—the middle temporal gyrus—from 84 donors whose medical histories were well documented and profiled

⁵ The Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD) consortium is a multi-institutional collaboration bringing together multiple investigators from the Allen Institute, University of Washington Medicine, and Kaiser Permanente, aimed at generating an open, high-resolution molecular and cellular map of aging and Alzheimer's disease by using advanced analyses of well-characterized human brain tissue to clarify early disease mechanisms. For more information, see: <https://brain-map.org/consortia/sea-ad> (accessed June 10, 2026).

⁶ The Brain Research Through Advancing Innovative Neurotechnologies® Initiative, or The BRAIN Initiative®, a public–private partnership aimed at accelerating the development of innovative neurotechnologies to transform neuroscience. For more information, see: <https://braininitiative.nih.gov/> (accessed June 10, 2026).

all postmortem modalities in this tissue (Gabbitto et al., 2024). They used statistical machine learning algorithms to turn traditional pathology (like number of amyloid beta plaques or neurofibrillary tangles per unit area), and quantitative cellular measurements, into a precise, numerical scale of disease severity (Agrawal et al., 2026) . This scale assigns each brain donor a number between 0 to 1 , where 0 means very little Alzheimer’s pathology and 1 means the most severe (Agrawal et al 2026). He showed that this scale closely tracked people’s cognitive decline (see Figure 3-3). Gabbitto’s team created an algorithm to analyze the transcriptional landscape of

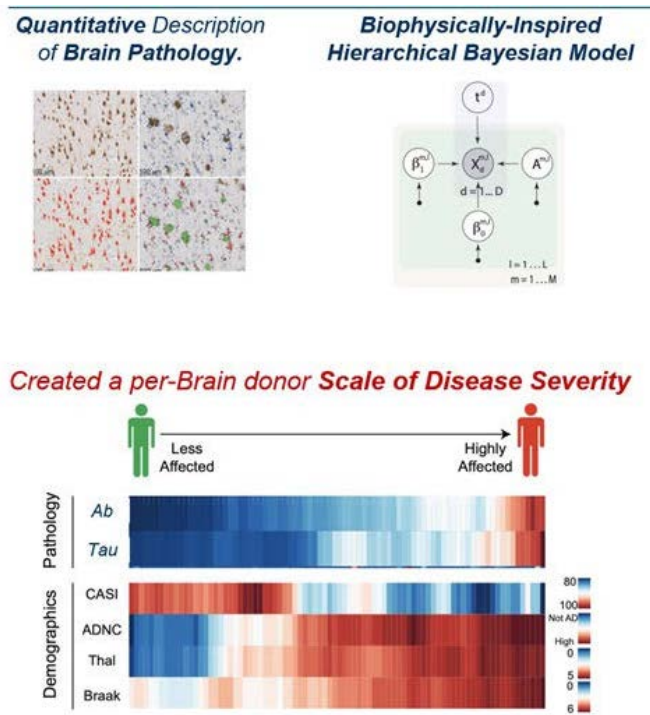


FIGURE 3-3 Quantitative modeling of brain pathology and disease severity. **NOTE:** This figure illustrates a biophysically inspired hierarchical Bayesian framework that integrates quantitative measures of brain pathology—such as amyloid- β and tau burden—with demographic and cognitive data to generate a per-donor scale of disease severity ranging from low to high pathology. Each brain donor is assigned a continuous value between 0 and 1, representing a one-dimensional trajectory from minimal to maximal regional pathology. This construct enables the mapping of emergent properties, such as cognitive proficiency across the trajectory, recapitulating cognitive decline as pathology accumulates. **SOURCES:** Presented by Mariano Gabbitto, March 4, 2026; Gabbitto et al., 2024 and Agrawal et al., 2026. CC BY 4.0.

individual cells (a measurement called single-cell RNA-seq) and create a representation of these cells that biologist can use to understand the underlying biological processes happening in the tissues where those cells originated. Gabitto noted that the algorithms were powerful enough that his team was able to merge ten publicly available studies—despite their differing experimental designs—into a single, consensus representation. This work allowed his team to annotate the type of cell that was analyzed and create and propagate unified cellular taxonomies across the field, enabling researchers to “speak the same cellular language.” Using these algorithms, Gabitto showed that a particular type of local cortical interneurons are the populations of cells that decline earliest and most prominently as Alzheimer’s disease progresses. He noted that the key question is how early loss of a critical cell type that balances excitation and inhibition shapes disease onset and what its downstream consequences are. Gabitto explained that the data reveal a recurring motif of cortical vulnerability, with the same cell types repeatedly affected in the cerebral cortex across individuals. More specifically, he reported that the most vulnerable cell type is the somatostatin expressing neuron—not just in one region but across the cerebral cortex. This process, Gabitto shared, helps the field shift the focus from simply cataloging protein aggregates toward defining the cellular and circuit-level substrates that drive disease susceptibility.

He concluded that Alzheimer’s should not be viewed as a simple “yes/no” diagnosis. Instead, it is a long, multi-layered biological process involving changes in cells, circuits, and brain regions over time. Gabitto argued that to make evidence actionable, researchers must measure many types of data at once—pathology, cell types, brain regions, and digital biomarkers—and integrate them to understand how the disease truly progresses. He emphasized that making evidence clinically actionable demands a new framework for defining disease, staging donors and patients, and building precision-ready cohorts with robust *in vivo* measures. He noted that their integration of longitudinal data with postmortem tissue offers a unique ground truth reference. Looking ahead, he stressed that multimodal and digital biomarkers will produce unprecedented data volumes, requiring new data architectures and new modes of algorithmic learning. Gabitto argued that federated learning—a privacy-preserving computation that enables models to learn across distributed datasets without moving or centralizing the underlying data, thereby achieving precision at scale without copying sensitive information—will be a necessary approach for handling data at this scale.

Hyman asked whether Gabitto’s work at the Allen Institute could eventually rely on brain donations that include serial clinical phenotyping, biomarkers, and stored biofluids rather than relying solely on diagnostic labels assigned at death. He emphasized that the cellular insights Gabitto

presented would be even more powerful if they could be tied to rich, longitudinal upstream data. In response, Gabitto stated that the SEA-AD initiative has developed new methods for preserving postmortem brain tissue so it can support advanced cellular analyses. He explained that the Allen Institute is working with ten Alzheimer's Disease Research Centers⁷ to disseminate these methods, though they have not yet identified the ideal organizational structure to scale this effort. He confirmed that one of these centers is part of the CLARITY Study⁸ that already has MRI, blood biomarkers, and immune profiling *in vivo*, allowing the cellular data to be linked to extensive clinical histories. Gabitto added that their design includes both a "pure Alzheimer's Disease" cohort without co-pathologies or comorbidities and a second cohort with genetic diversity and comorbidities, enabling broader biological comparisons.

GENE-ENVIRONMENT VARIATION ACROSS POPULATIONS

Gabitto's framework for mechanistic, cell-type-resolved disease staging naturally opened into a wider conversation about the forces that shape biological diversity, prompting participants to examine how environmental context modulates genetic risk across populations. Adama Tall, a registered nurse, asked whether differences in upbringing, personality, and resilience could explain why two people exposed to the same stressors respond so differently. She also asked whether gastrointestinal factors might contribute to depression. In response, Geschwind stated that the influence of life stressors on mental health has been extensively studied and that environmental adversity clearly interacts with genetic risk. He emphasized that these interactions are real and important, even if they are difficult to measure precisely. Rhoda Au, professor of anatomy and neurobiology, neurology, medicine, and epidemiology at the Boston University Chobanian and Avedisian School of Medicine and School of Public Health and principal investigator of the Framingham Heart Study Brain Aging Program, shared that her work incorporates the exposome, which includes environmental and social factors like those Tall described. She stressed that to understand

⁷ The Alzheimer's Foundation of America (AFA) is a national nonprofit organization whose mission is to provide support, services, and education to individuals living with Alzheimer's disease and related dementias, to the families and caregivers who support them, and to fund research aimed at improving treatment and advancing toward a cure. For more information, see: <https://alzfdn.org/> (accessed June 10, 2026).

⁸ The CLARITY Study is an Intramural Research Program effort led by the National Cancer Institute to integrate liver cancer clinical trial data, biospecimens, and correlative analyses to understand why immunotherapy benefits some patients but not others and to guide development of new therapies. For more information, see: <https://ccr.cancer.gov/liver-cancer-program/nci-clarity-study> (accessed June 10, 2026).

health outcomes, researchers must collect data from all populations, not just those who are easiest to reach. Au emphasized the need for global data collection, noting that life circumstances vary dramatically across countries and that precision neuroscience must reflect this diversity. Dimitri Krainc, the Aaron Montgomery Ward Professor, chair of the Department of Neurology, director of the Feinberg Neuroscience Institute at Northwestern University, added that the same principle applies to genetic studies in precision medicine that should include diverse genetic ancestries from around the world. Geschwind reinforced that understanding genetic variation requires measuring it across diverse human populations.

4

Precision Frameworks for Patient Identification and Stratification

Highlights

- Biology-based definitions are reshaping how neurodegenerative diseases are diagnosed and studied, with synuclein assays revealing that clinical symptoms alone often mask distinct underlying pathologies (Poston).
- Precision neuroscience rests on a shift from legacy diagnostic categories to measurement-driven mechanistic frameworks that can reliably stratify patients across biological, cognitive, and phenotypic dimensions (Bustamante, Fiske, Heywood).
- Achieving population-level precision demands end-to-end, quality-managed infrastructure that integrates longitudinal biospecimens, digital measures, and representative cohorts to generate scalable, regulatory-ready data (Au).
- Biologically anchored stratification in neurodegeneration shows how pathologically-linked biomarkers can outperform syndromic diagnosis, enabling more accurate trial enrollment and mechanistically defined subgroups (Poston).
- Psychiatry's precision challenge stems from uninformative inputs and coarse outcomes, driving a shift toward deep, mechanistic phenotyping and longitudinal measurement systems that capture latent brain processes rather than surface-level symptoms (Petzschner).
- Regulatory progress depends on shared tools, transparent data, and cross-disease learning, with agencies and consortia building fieldwide evidentiary standards that integrate biomarkers better, including digital endpoints, and patient voice to make precision stratification operational rather than aspirational (Ferguson, Fiske, Hyman, Stephenson).

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Laura Bustamante, staff scientist at Washington University in St. Louis at the time of the workshop, opened the session by noting that the discussion would shift from foundational biology to the development of precision frameworks for patient identification and stratification, a stage that sits between discovery and clinical development. She emphasized the challenge of assembling biological, cognitive, and phenotypic data into frameworks that can reliably distinguish subgroups in both neurological and psychiatric conditions. Speakers, she explained, would address issues such as determining when a phenotype signal is clinically meaningful, how much reliability and uncertainty can be tolerated for use in practice, and how these choices influence regulatory relevance and integration into clinical trial design.

Brian Fiske, chief scientist at the Michael J. Fox Foundation for Parkinson's Research, added that the session would explore both the opportunities and the practical challenges of building biological frameworks, including where to begin—at the level of biology or clinical phenotype—how to manage noise in complex datasets, and how such frameworks should evolve over time. He underscored that these questions are central to advancing precision approaches that can ultimately guide therapeutic development.

MEASUREMENT AS THE FOUNDATION OF PRECISION NEUROSCIENCE

Jamie Heywood opened his keynote by challenging the way medicine relies on diagnosis. He argued that “diagnosis is a word we use to throw out the information that would effectively help us treat someone,” suggesting that broad diagnostic categories can obscure important differences among individuals that may be relevant to treatment. His career in amyotrophic lateral sclerosis (ALS) taught him that what truly transforms outcomes is not just biological insight but the ability to measure the right things quickly. He described how, early in his ALS work, he looked to three medical breakthroughs as sources of hope: insulin for diabetes, combination antiretroviral therapy for human immunodeficiency virus (HIV), and imatinib (Gleevec) for chronic myeloid leukemia. Each transformed a once lethal disease into a manageable condition that allowed people to live normal lifespans. He highlighted the dramatic story of Elizabeth, a 14-year-old girl with severe diabetes who weighed only 45 pounds before receiving insulin and ultimately lived to age 70. But Heywood said he had originally missed the real lesson—if it can be measured, it can be fixed.

The problem, he argued, is that in many diseases—ALS, Alzheimer's disease, schizophrenia, chronic myeloid leukemia, and HIV—the measurements are so imprecise that it takes years to know whether a treatment works. Proxy markers, when they exist, collapse that timeline and accelerate discovery. Without them, progress slows to a crawl.

He then challenged the traditional separation between neuroscience, psychiatry, cardiology, and other specialties. He argued that the mind body divide is artificial: “I don’t believe there is a difference between cancer and heart disease and the brain. I think there is one system.” From this perspective, Heywood argued that medicine should stop anchoring itself in diagnoses and instead measure everything about everyone repeatedly—biology, environment, function, resilience, strengths, and aging. He described Alden Scientific’s system for doing this. The company collects high quality blood samples, runs them across many platforms, normalizes the data, and uses machine learning to compare each person to large population datasets such as the UK Biobank. This produces what he calls a digital twin, generated by their “Serenity AI” platform.¹

Using himself as an example, Heywood showed that standard cardiology tools—such as the American College of Cardiology’s machine learning risk calculator—classified him as the lowest possible cardiovascular risk. Yet, he required heart surgery nine months earlier. By contrast, Alden’s AI, using far more biological parameters, flagged him as high risk. He illustrated how stress spikes and the moment his valve failed were visible in his biological data. After surgery, his heart failure risk curve declined exactly as expected, reinforcing his confidence in the measurement system.

Heywood then showed his Alzheimer’s disease risk profile. He noted that their artificial intelligence sometimes “hallucinates” but said the platform is improving. He referenced Dean Ornish’s clinical trial, which reported symptom improvement in Alzheimer’s disease through lifestyle interventions including diet, exercise, meditation, fish oil, and social support (Ornish et al., 2024). Heywood said Alden’s system classified 90 percent of the trial participants as having Alzheimer’s based solely on their biological signatures, even though they were clinically labeled as having mild cognitive impairment. To him, this suggests the platform is beginning to capture meaningful biological differences.

He closed by sharing Lord Kelvin’s maxim: “When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind.” (Thomson, 1883). As other speakers shared throughout the workshop, Heywood argued that psychiatry and neuroscience still fall short of this standard. His call to action is: Measure far more, far better, because measurement is the engine that makes precision medicine real.

¹ Alden Scientific’s Serenity AI is an artificial intelligencedriven biological state model designed to predict individual health trajectories and simulate personalized interventions. For more information, see: <https://www.jamieheywood.com/innovations> (accessed June 10, 2026).

BUILDING SCALABLE INFRASTRUCTURE FOR PRECISION STRATIFICATION

In agreement with Heywood's call for continuous measurement, Au turned to the population-scale infrastructure required to generate those measurements reliably and at national scale, highlighting the Framingham Heart Study—an ongoing, 78-year, multigenerational, cohort study that ultimately reshaped preventive medicine through its seminal papers that defined risk factors for cardiovascular disease (Dawber et al., 1957; Kannel et al., 1961; Schnabel et al., 2009; Tsao and Vasan, 2015; Wilson et al., 1998; Wolf et al., 1991). Au used Framingham as a benchmark for thinking about how to design and interpret studies of brain aging, but she urged researchers considering a “Framingham study” to focus on the concept rather than attempting to replicate it.

Au explained that Framingham's Brain Aging Program² began in the late 1970s with brief neuropsychological testing and expanded dramatically in 1999, when new funding allowed the team to enroll all three initial cohorts and follow them longitudinally. She noted that the study has used the standard Alzheimer's disease research protocol, supported by a brain donation program, and has steadily incorporated new tools. Over time, Framingham also began collecting digital data, starting with digital voice in 2005, digital pen data to capture written responses in 2011, and smartphone-based assessments in 2022, which complements the traditional clinical and pathological measures.

Au emphasized that Framingham now holds a rare combination of decades of blood samples—about 30,000 suitable for analysis—and large-scale digital data. She argued that linking these two data streams creates a major opportunity for precision medicine at scale, especially now that Framingham has begun measuring Alzheimer's biomarkers in roughly 15,000 samples using the Roche platform.

She noted that the demographic reality of having an aging population with more adults over 65 than under 65 underscores the scale of the challenge. Yet, she observed, the field continues to rely on small-scale studies despite dementia being a life course disease affecting a global population of more than eight billion. Au questioned how the field can study brain health at the precision level when the underlying research is not representative of the populations at risk. She argued that solving this requires end-to-end infrastructure, not just data collection. She suggested that if one

² The Framingham Heart Study Brain Aging Program (FHS-BAP) extends the long-running Framingham cohorts to advance research on brain aging and Alzheimer's disease through dementia surveillance, brain donation, and studies of vascular, inflammatory, genetic, and immune contributors to disease. For more information, see: <https://www.bumc.bu.edu/fhs-bap/> (accessed June 10, 2026).

were starting today—especially in the brain aging space, where far more is known about the brain and its many influences—modern analytics and AI would be essential. She noted that when she first began collecting digital voice data, there was no infrastructure to process, store, or share it; the data sat untouched for years. Au argued that collecting digital data is not enough unless the systems exist to turn it into something meaningful.

Her team's solution is incorporating a quality management system (QMS)—standard in biotech but rare in academia—to ensure data are reliable, regulatory ready, reproducible, and quickly translated into clinical use. It includes a digital engagement platform that she calls “the Facebook of brain health,” an inclusive virtual brain cohort that accepts anyone interested in research, and a customizable, multilingual brain health smartphone app coupled with the back-end systems to manage, process, and access those data. Au explained that her team is now putting this end-to-end framework into practice through the IGNITE Study³ (Butler et al., 2025). She noted that from 2021 to 2023, Apple and Biogen conducted the Intuition Study,⁴ enrolling 23,000 geographically representative participants—30 percent from minoritized populations—and collecting continuous data from iPhones, Apple Watches, HealthKit, SensorKit, questionnaires, and Cambridge Neuropsychological Test Automated Battery assessments. When Biogen terminated the study early, she secured the opportunity to take it over. She reported that they are now relaunching it as the IGNITE Study, re-consenting participants, integrating the previously collected data, and extending follow-up within a U.S. Food and Drug Administration (FDA)-aligned QMS (Butler et al., 2025). She emphasized that this approach would create a nationwide, longitudinal resource.

Au acknowledged the challenge of keeping academic research relevant in an artificial intelligence (AI)-driven landscape, noting that academic timelines lag far behind the pace of technological innovation. She argued that by operating within an FDA-aligned QMS, academic groups can contribute what AI systems most need—trusted, high-quality data. She emphasized that her role is not to generate the solutions but to make the data

³ The IGNITE Study is an NIH-funded Phase III randomized clinical trial testing whether aerobic exercise improves cognitive and brain function in adults ages 65–80, using cognitive assessments, neuroimaging, fitness measures, and blood-based biomarkers to evaluate outcomes and mechanisms. For more information, see: <https://cbh.northeastern.edu/ignite/> (accessed June 10, 2026).

⁴ The Intuition Study was a large-scale, virtual observational brain-health study sponsored by Biogen in collaboration with Apple to evaluate whether data from Apple Watches and iPhones could be used to develop digital biomarkers of cognitive performance and support early detection of mild cognitive impairment. For more information, see: <https://investors.biogen.com/news-releases/news-release-details/biogen-launch-pioneering-study-develop-digital-biomarkers> (accessed June 10, 2026).

broadly available so others can build on it. By making datasets openly available for benchmarking and iterative data challenges, the field can advance more rapidly. However, accelerating longitudinal cohort studies will require compressing timelines by restructuring how work moves between sectors. Rather than having academics complete their portion and industry restart the process from scratch, Au argued that academic teams should hand off directly to industry so the work can advance without duplication, enabling faster progress toward solutions.

Au closed by positioning the IGNITE Study as an initial step toward a broader framework that could guide future studies. She underscored that “digital [data] is the new blood,” noting that digital measures serve multiple purposes and, in the context of AI, function as its essential input. She argued that reaching true clinical precision will require moving beyond static measurements to dynamic combinations of digital signals and noted this shift as essential for advancing accurate characterization in brain-health research.

A participant asked how Au’s team is addressing the ethical tensions inherent in passive digital monitoring, especially in global settings where resources and protections vary. She asked whether Au had established advisory mechanisms for the IGNITE Study and the Apple Biogen collaboration, similar to those used in the Framingham Heart Study. In response, Au stated that her team has created a small volunteer advisory group that tests all technologies before deployment. This group provides feedback on privacy, confidentiality, and usability and can reject tools that raise concerns. Au highlighted the challenge of voice data, which contain identifiable “voiceprints.” She explained that her team is working with collaborators at MIT to develop methods for de-identifying voiceprints while preserving the acoustic features needed for analysis. She emphasized that they think deeply about all forms of personally identifying information, including ways AI might triangulate identity from multiple data sources. The participant added that ethical issues arise not only from how technologies function but also from how people relate to them, especially when non-medical data begin to reveal medically relevant insights. She encouraged continued further dialogue as these studies expand.

BIOMARKER-DRIVEN STRATIFICATION IN NEURODEGENERATION

Building on Au’s call for end-to-end systems, Kathleen Poston, the Edward F. and Irene Thiele Pimley Professor in Neurology and Neurological Sciences, the division director in the division of Movement Disorders, and the vice chair for Research in Neurology at Stanford University, showed how biologic biomarkers can be operationalized within those systems to

improve patient stratification in neurodegenerative disease. As discussed in chapter 3, she noted that clinicians aim to identify individuals who at least meet the minimal pathology believed to underlie a given syndrome. Yet, in practice, when diagnosing Parkinson's disease (PD) and related parkinsonian syndromes, Poston often still relies on motor features such as bradykinesia, rigidity, and tremor—criteria derived from definitions more than 200 years old to categorize these disorders (Parkinson, 2002). She emphasized that despite these limitations, accurate classification remains essential for enrolling the patients who truly have the targeted disease into clinical trials.

Poston illustrated the limits of clinical diagnosis by noting that 10 to 23 percent of individuals labeled as having Alzheimer's disease lack amyloid pathology on their positron emission tomography (PET) scans. She shared that early anti-amyloid trials showed similar misclassification rates—often one in five to one in four participants—particularly when enrolling people closer to symptom onset. Poston added that Parkinson's disease and dementia with Lewy bodies face similar diagnostic challenges, as patients often present with complex constellations of motor, cognitive, neuropsychiatric, sleep, autonomic, and sensory symptoms (Weintraub, 2023). She explained that overlapping clinical terminology—such as isolated rapid eye movement (REM) sleep behavior disorder and primary autonomic failure—further complicate classification. Although these syndromes are typically assumed to reflect underlying synuclein pathology, she emphasized that many individuals instead could harbor other pathologies, including the glial cytoplasmic clumps, or inclusions, found in multiple system atrophy or the abnormal tau⁵ protein build-ups characteristic of the tau-repeat pathologies seen in progressive supranuclear palsy and corticobasal degeneration (Spillantini et al., 1997).

To address this clinical diagnosis gap, recent breakthroughs in alpha synuclein seed amplification assays—a spinal fluid test that detects misfolded synuclein—allow researchers to classify individuals as synuclein positive or synuclein negative (Siderowf et al., 2023). Poston emphasized that although this binary test is simple, it represents a major step toward the development of a biologically based framework for identifying individuals with neuronal synuclein disease. She noted that the presence of predominantly neuronal alpha-synuclein pathology together with dopaminergic degeneration can be recognized in life and corresponds to what is confirmed at autopsy, independent of whether patients first present with dementia, tremor, or autonomic symptoms (Simuni et al., 2024). She emphasized that

⁵ Tau is a microtubule-associated protein that becomes abnormally phosphorylated, then called p-tau, and forms neurofibrillary tangles in Alzheimer's disease, tightly tracking with neuronal injury and cognitive decline.

this approach moves the field from syndrome-based labels toward biologically defined disease (Höglinger et al., 2024; Simuni et al., 2024).

Poston reported that this biologic framework of using their most advanced clinically syndromic definitions shows greater sensitivity than traditional clinical diagnosis in predicting Lewy body pathology at autopsy. She observed that traditional syndromic criteria prioritize specificity and often perform poorly on sensitivity, particularly during the first five years of symptom onset (Nelson et al., 2010; Virameteekul et al., 2023). By contrast, biomarker- and pathology-based classifications better match final pathology while maintaining specificity (Bargar et al., 2021; Hall et al., 2022; Garrido et al., 2023). According to Poston, these biologic definitions may improve diagnostic accuracy and support more effective participant selection for clinical trials.

To illustrate this point, Poston's findings from the Parkinson's Progression Markers Initiative (PPMI) study in which a cohort of over 900 recruited individuals where 79 who were biomarker negative showed different patterns of disease progression and had their diagnoses changed far more often (more than 14 percent) than biomarker positive individuals (less than 1 percent), despite clinicians being blinded to biomarker status (Brooker et al., 2026). She underscored that, although the available data remain limited, biomarker-based classifications appear to align more closely with underlying pathology than clinical diagnosis alone, even when biomarkers are measured at the earliest stages of clinical presentation.

She explained that individuals with the gene leucinerich repeat kinase 2 (LRRK2)-associated Parkinson's disease were excluded because nearly one-third do not show Lewy bodies at final pathology. Follow-up studies comparing LRRK2 carriers with and without synuclein biomarker positivity revealed distinct clinical trajectories, suggesting the need for three biologically defined trial cohorts: (1) individuals without a genetic variant but with a positive synuclein biomarker; (2) LRRK2 carriers who are biomarker-positive; and (3) LRRK2 carriers who are biomarker-negative.

Poston emphasized that this biomarker-based definition approach still has a long way to go before “getting the right therapy to the right person at the right time.” She added that the original yes/no biomarkers were insufficient, noting that they failed to capture common co-pathologies, such as amyloid or tau, did not convey the range or degree of progression, and did not measure drug-related biological activity—all features, she argued, must be incorporated going forward. She emphasized that precision frameworks should expand in a stepwise, data-driven manner, incorporating additional layers of biological complexity over time to improve trial enrollment and better match interventions to the underlying disease biology.

DEEP DATA FRAMEWORK FOR PATIENT STRATIFICATION

Where Poston benefits from validated biomarkers, Frederike H. Petzschner, assistant professor at the Department of Cognitive and Psychological Sciences and codirector of the BRAINSTORM Program at the Carney Institute for Brain Science at Brown University, described psychiatry's ongoing measurement challenge. Petzschner noted that treatment selection often remains a process of trial and error because clinicians lack reliable biomarkers that can predict which intervention is most likely to benefit a given individual. As an example, she observed that when a first antidepressant fails, clinicians currently have few biologically informed tools to guide the next treatment decision.

She explained that many hoped machine learning would solve this by training algorithms on large datasets—electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and behavior—to identify features that predict who will respond to a given treatment. In single clinical trials, these models often perform well (Gordon et al., 2024). But Petzschner emphasized that the real benchmark is whether a model can predict outcomes in patients it has never seen before. When evaluated this way, most models fail. She cited research showing that a model trained on one antipsychotic trial predicted outcomes well within that trial but performed no better than chance when tested on a different trial (Chekroud et al., 2024). She explained that the model was essentially reacting to patterns specific to the dataset rather than learning anything that genuinely reflects the underlying disorder. Petzschner emphasized that the poor generalizability of current models stems from several factors, including the pronounced heterogeneity, binary biomarkers, and lack of biology-based measures discussed by several others throughout the workshop. She challenged the common view that larger datasets are the solution, contending that progress depends on more deliberate choices about which data are appropriate and informative.

Petzschner argued that many psychiatric models fail because they are built on uninformative inputs: “garbage in, garbage out.” She noted that large datasets often contain only demographics, socioeconomic variables, or brief resting state scans, none of which capture underlying mechanisms. She advocated shifting from “big data” to “deep data,” including targeted cognitive paradigms, symptom provocation tasks, and computational model parameters that reflect latent brain processes as shown by several past studies (Brodersen et al., 2011; Stephan et al., 2015; Wiecki et al., 2015, 2016; Huys, et al., 2016). She emphasized such model-based features consistently outperform raw behavioral or fMRI data by improving signal to noise and better indexing the mechanisms relevant to prediction.

She then turned to the output problem: how we measure whether someone improved. She discussed her team’s longitudinal pain tracking work, explaining that traditional single time point questionnaires misclassify responders in one out of four cases (see Figure 4-1). Daily smartphone-based assessments revealed large natural fluctuations in pain, driven by mood and daily activities. Petzschner highlighted research showing that frequent but strategically timed assessments can capture meaningful changes in symptoms without requiring continuous daily monitoring. She noted that a small number of measurements collected over a two-week period may provide a reliable picture of symptom trajectories, illustrating how smartphone-based ecological momentary assessment could reduce participant burden while preserving data quality. Petzschner concluded that precision medicine suffers from a measurement problem on both the input and output sides. To make reliable predictions, psychiatry needs mechanistically informed data and smarter ways of tracking individual symptom trajectories over time.

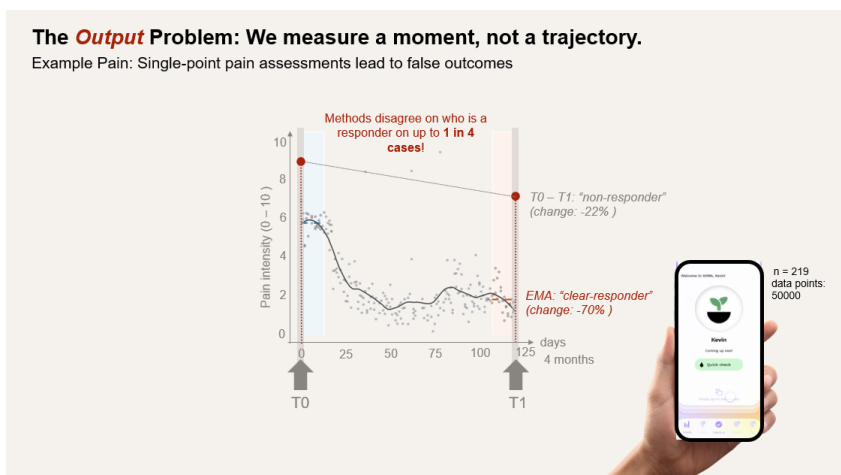


FIGURE 4-1 The Output Problem: Measuring a moment, not a trajectory.

NOTE: This figure illustrates how single-point pain assessments can misclassify treatment response. Over four months of smartphone-based ecological momentary assessment in chronic and acute pain patients, daily ratings of pain, mood, and treatment generated more than 50,000 data points. While retrospective two-time-point measures (T_0 – T_1) classified this patient as a nonresponder (–22 percent), the dense trajectory revealed a rapid and sustained 70 percent reduction in pain intensity, indicating a clear responder. The discrepancy highlights that momentary sampling captures meaningful change that single-point measures miss.

SOURCE: Presented by Frederike H. Petzschner, March 4, 2026; Gunsilius et al., 2024, CC BY 4.0; Gunsilius et al., in prep.

A participant asked whether assessments of pain should incorporate additional dimensions—such as itchiness, sharpness, or other qualitative characteristics—to better capture patients’ experiences. Petzschnner agreed, explaining that dimensions such as unpleasantness and interference reflect aspects of the symptom experience that are fundamentally distinct from pain intensity, as demonstrated through factor analysis. She emphasized that these measures, often treated as secondary or “nuisance” variables, can provide important information about whether a patient is improving.

REGULATORY PARTNERSHIPS DRIVING PRECISION STRATIFICATION

Building on Petzschnner’s call for more meaningful data, Diane Stephenson, the vice president of Neurology at the Critical Path Institute, turned to the regulatory landscape, showing how agencies and consortia are shaping the standards that make precision stratification feasible by integrating biomarker evidence into decision making in ways that make precision medicine not just aspirational but operational. She contrasted this system-level progress with her own experience, noting that despite more than 25 years of laboratory work in major pharmaceutical companies, nothing prepared her for the impact of these diseases when they affected her own family. She emphasized that FDA guidance has fundamentally reshaped how the field thinks and said that if she could restart her career, she would begin with the patient voice. She argued that many past trial failures might have succeeded had patient perspectives been incorporated early and interventions delivered sooner.

She highlighted the growing influence of the patient voice, noting that regulators are now actively encouraging forms of patient-focused drug development that elevate patient experience in shaping research priorities (Cummings et al., 2025; Ferretti et al., 2025). She pointed to the Roadmap to Precision Psychiatry conference⁶ and acknowledged FDA’s role with Dr. Valentina Mantua as senior author of a paper that lays out a concrete plan—rather than an aspiration—to integrate the kinds of data that enabled progress in Alzheimer’s disease (Kas et al., 2025b). Stephenson added that neuronal synuclein disease provides a clear example of how regulators are steering the field, building on the work presented by Poston (Simuni et al., 2024). She also cited parallel developments in Alzheimer’s disease, where leaders in the FDA’s Office of Neuroscience have outlined approaches on

⁶ The Roadmap to Precision Psychiatry conference, hosted by ECNP, is a 1.5-day meeting focused on advancing the clinical implementation of precision psychiatry and emphasized biomarker-driven strategies to translate scientific progress into improved psychiatric drug development and patient care. For more information, see: <https://www.ecnp.eu/meetings/roadmap-meeting-on-precision-psychiatry/> (accessed June 10, 2026).

defining clinically meaningful change, and the European Medicines Agency is seeking community input to update its Horizon Report guidance (EMA, 2024; Buracchio, et al., 2025; FDA 2024c). She emphasized that these are not simply academic publications but regulatory frameworks that will shape how future clinical trials are designed.

This evolving regulatory landscape underscores why shared, field-wide tool development is essential—precisely the need the Critical Path Institute (C-Path) was created to meet. Stephenson explained that C-Path is a non-profit created through the leadership of Janet Woodcock, whose 2005 Critical Path Innovation Report addressed a central question raised earlier in the workshop: Who is responsible for developing the biomarker, modeling, and outcome measure tools needed across the field (Woodcock and Woosley, 2008)? She noted that no single sponsor—and not even the FDA—can shoulder this work alone. With FDA funding, C-Path convenes nonprofits, patient advocacy groups, academic centers, and industry partners to collaboratively generate the tools needed across therapeutic areas.

Stephenson noted that when she joined the C-Path, the organization operated five programs, beginning with Alzheimer’s disease; it has since expanded to 26 programs supported by substantial FDA funding. She explained that C-Path’s five core competencies enable the integration of diverse data types—clinical trial, real world, imaging, digital, omics, and preclinical—to improve predictive accuracy and extract lessons from failed trials. This infrastructure, she said, has allowed C-Path to assemble evidence packages that have led to multiple regulatory endorsements across nervous system and neuromuscular disorders (Stephenson et al., 2023). She emphasized that each endorsement reflects rigorous, multi-source evidence, particularly from clinical trials, because such data ultimately determine how tools will perform in placebo-controlled settings.

Stephenson emphasized that progress in neuronal synuclein disease and other neurodegenerative disorders depends on expanding the available data, particularly in rare conditions such as Huntington’s disease where every sample is critical (Simuni et al., 2024; Tabrizi et al., 2022). She noted that staging frameworks require robust disease-progression modeling and the integration of multiple biomarkers, as no single measure can reliably predict diagnosis or progression. Regulators, she said, are urging the field not to wait for perfect alignment across datasets but to engage them early so they can help define evidentiary expectations.

She illustrated this with work from C-Path’s Alzheimer’s consortium,⁷ which harmonizes tau imaging data across tracers leveraging the strong link

⁷ The Critical Path for Alzheimer’s Disease (CPAD), established in 2008, develops regulatory-grade tools to advance Alzheimer’s disease drug development and support improved outcomes for individuals living with Alzheimer’s disease and related dementias. For more information, see: <https://c-path.org/program/critical-path-for-alzheimers-disease/> (accessed June 10, 2026).

between tau spread and cognitive decline to support regulatory confidence in potential biomarkers used as proxies for clinical outcomes (Leuzy et al., 2019). She also described the institute's efforts in Parkinson's disease, where extensive evaluation of synuclein seeding assay data—spanning six observational studies and two clinical trials—led to an FDA biomarker letter of support (Bellomo et al., 2022; Spillantini et al., 1997, Stephenson et al., in press). She noted that the agency completed its review in only three months, reflecting strong confidence in the assay's predictive accuracy (PPMI). Stephenson emphasized that the FDA's letter of support for the synuclein seeding assay is notable because it recognizes this assay as a susceptibility and risk biomarker for a broad class of degenerative disorders defined by shared synuclein biology (FDA, 2024b). Building on Poston's presentation, she noted that this opens the door to enrolling participants with well characterized biology into trials, including prevention studies. She highlighted that regulators, together with partners such as the Michael J. Fox Foundation for Parkinson's Research, have been engaged throughout this process, enabling the first prodromal platform trial in synuclein disease and supporting the inclusion of pre-symptomatic individuals.

Stephenson closed by outlining several initiatives on C-Path's horizon. She highlighted ongoing work in digital health technologies, including the Wearable Assessment in The Clinic and at Home in PD (WATCH-PD) study, which is generating qualitative and quantitative insights into tracking early Parkinson's disease (FDA, 2023b; Hill et al., 2025, Adams et al., 2024). She also noted a new project focused on women with Parkinson's disease, aligned with recent FDA guidance encouraging greater attention to women's health across disorders (FDA, 2025; Grace, 2026). She emphasized growing momentum around mechanistic modeling, referencing recent calls to action—including a *Nature Medicine* paper—urging the field to share data and adopt quantitative systems pharmacology approaches to ensure target engagement and pharmacologic proof in trials (EMA, 2025; Nature Medicine, 2026). She added that regulatory agencies remain deeply engaged in evaluating AI-based tools as the evidence base evolves (EMA, 2026; Podichetty et al., 2025).

SCALING BIOLOGICALLY GROUNDED PATIENT CHARACTERIZATION

While Stephenson highlighted emerging tools and methodologies that could support more precise approaches to Parkinson's disease research and care, participants also emphasized the practical challenges of implementing these advances at scale. Dimitri Krainc noted that the vast majority of patients living with PD in the U.S. do not receive genetic testing, even when reimbursed by insurance. He emphasized that this gap undermines enrollment for trials targeting genetic subgroups, such as LRRK2 or GBA1,

arguing that scaling genetic testing is essential for practical progress. Poston agreed with Krainc, highlighting the Parkinson's Foundation's PD Gene project as a major step toward making clinical genetic testing easy and feasible. She noted, however, that only about 10 percent of Parkinson's patients ever see a movement disorder specialist, meaning PD Gene reaches only a small subset. Poston described this as structural funnel because PD Gene exists only in specialty clinics, leaving most patients outside its reach.

More broadly, the discussion highlighted a central challenge for precision medicine: generating biologically meaningful patient classifications requires both access to molecular data and frameworks for interpreting those data. Hyman then turned to the limitations of the overreliance on surface-level clinical phenotypes, such as symptom clusters derived from electronic medical records, where the record is devoid of biological data. He explained that many of the clinical syndromes that Poston described, that may or may not have alpha-synuclein pathology, would affect clinical trials and clinical decision making. Hyman argued that clinical scales have limited value for treatment development unless tied to underlying biology and asked whether the field could develop both deep biology and longitudinal cohorts to create a "Rosetta Stone" linking symptoms and mechanisms. Poston agreed that integrating biology and phenotyping is ideal, but current biomarkers such as cerebrospinal fluid (CSF) seed amplification assays are difficult to scale. She explained that plasma-based markers could eventually allow large cohorts, such as Framingham, to be analyzed biologically to look at longitudinal integration of synuclein positivity. She stated that until scalable biomarkers become available, researchers will need to work with clinically defined cohorts that likely contain individuals with different underlying pathologies and biomarker profiles, revisiting those data as more precise biological measures become available.

Toby Ferguson, the senior vice president of the Neuroscience Therapeutic Area at Alnylam Pharmaceuticals, reinforced the need to reach PD patients who currently lack genetic testing. Drawing on ALS, he noted that ALS clinics routinely test patients compared to Parkinson's disease clinics, enabling successful enrollment of rare disease subgroups. Ferguson argued that waiting for an approved therapy to motivate testing is backwards; widespread testing must come first. He also asked the panel whether digital phenotyping can reflect underlying biology or whether such measures are merely endophenotypes that must always be paired with biological samples.

Petzschner answered that digital tasks can indeed infer underlying mechanisms. She described behavioral paradigms that estimate connectivity between brain regions such as the prefrontal cortex and basal ganglia. She emphasized that these tasks can be deployed via smartphones, enabling large-scale mechanistic phenotyping as suggested by Au in the first session,

digital screening first, biological phenotyping second. Petzschner argued that the “low hanging fruit” lies in deploying validated cognitive tasks digitally rather than relying on simple symptom checklists.

DATA GOVERNANCE, SHARING, AND REGULATORY EVIDENCE STANDARDS

A recurring challenge discussed throughout the workshop was how to generate, share, and evaluate the evidence needed to support precision medicine approaches at scale. Stephenson commented that vast amounts of exploratory biomarker and omics data remain hidden within industry and never reach regulators. She argued that even imperfect translational data from clinical trials should be shared because the field cannot advance without learning from real-world performance.

A participant asked what data governance and IP models at C-Path best support academic-industry sharing while protecting participants. Stephenson explained that C-Path operates as a neutral environment where data contributors choose their level of sharing. All data are de-identified, and access is tightly governed. She noted that patients increasingly request broader sharing of their data, but data governance is very strict. She added that publications using C-Path data undergo oversight to ensure responsible interpretation and emphasized that FDA funding has enabled major advances, especially in rare disease platforms.

Another participant asked what level of evidence regulators expect for digital endpoints—such as passive sensors, voice, or smartphone data—to qualify as secondary or exploratory endpoints, and what would be required for them to become primary endpoints. Stephenson responded that C-Path’s Parkinson’s Consortium has been working closely with regulators through the WATCH-PD flagship study.⁸ She emphasized that regulators insist digital endpoints must be tied to the patient voice, not just data driven discovery. She explained that the biggest barrier is the lack of data sharing across digital platforms, unlike tau imaging or synuclein assays, digital tools lack harmonized methods. She encouraged learning from efforts such as Au’s on integrating data sharing across studies. She emphasized that progress depends on combining data across devices and enabling broader sharing so evidence can accumulate more quickly.

⁸ Wearable Assessment in The Clinic and at Home in Parkinson’s Disease (WATCH-PD) is a 12-month, multicenter observational study evaluating whether consumer digital devices can objectively and passively assess disease features and progression in individuals with early, untreated Parkinson’s disease. For more information, see: <https://clinicaltrials.gov/study/NCT03681015> (accessed June 10, 2026).

CROSS-DISEASE LEARNING AND STRATEGIC FIELD BUILDING

Beyond sharing data within individual disease areas, participants also discussed the importance of transferring insights, methods, and infrastructure across disease domains. Hyman highlighted the importance of cross-disease learning, noting that Alzheimer's researchers made major progress by sharing paired CSF and blood samples, which enabled the development of blood-based biomarkers. He observed that psychiatry is now "stealing their playbook," suggesting that Parkinson's research should similarly adopt strategies that have succeeded in other fields. This reflects a broader opportunity for cross-disease strategic borrowing.

Ferguson added a complementary field-level perspective, arguing that the PD community must work collectively to expand genetic testing access. He contrasted PD with ALS, where routine genetic testing is embedded in clinical culture, enabling efficient enrollment of rare genetic subgroups. His comments point to the need for community-level action and cultural change across clinics, foundations, and industry partners.

Fiske added a complementary field-level perspective, arguing that the challenge is not merely operational but structural, reflecting a global infrastructural gap: the field lacks coordinated systems capable of delivering large-scale, multimodal biological data collection across clinical, genetic, and digital domains.

5

Precision Measures to Monitor Disease and Treatment

Highlights

- Early biological markers now allow researchers to detect Alzheimer's disease years before symptoms, with amyloid and p-tau trajectories offering increasingly precise estimates of future cognitive decline (Sperling).
- New assays that detect abnormal alpha-synuclein are enabling biologically based definitions of synuclein disorders and revealing long pre-symptomatic periods during which changes in olfaction, rapid eye movement (REM) sleep behavior, and dopaminergic function may emerge in a predictable sequence (Marek).
- Psychosis-risk research shows that subtle early symptoms, combined with magnetic resonance imaging (MRI) changes, polygenic risk scores, and cognitive performance can help distinguish which young people are most likely to progress to full psychosis (Woods).
- Across disorders, multimodal biomarker "clocks" are emerging that map disease timing by linking biological change, genetics, and clinical features to more accurate predictions of who will decline and when (Marek, Sperling, Woods).
- Large longitudinal cohorts and prevention-focused initiatives, including the Parkinson's Precision Medicine Initiative, Alzheimer Prevention Platform, and Accelerating Medicines Partnership® Schizophrenia, are generating the scale of data needed to validate biomarkers and support early-stage therapeutic trials (Marek, Sperling, Woods).
- Genetic modifiers, vascular factors, and immune pathways appear to influence why some individuals accumulate pathology while others remain resilient, highlighting new frontiers for precision medicine (Marek, Sperling).

continued

- Patient-centered measures—such as digital cognitive tools, olfactory assessments, and clinical high-risk (CHR)-specific symptom scales—are becoming essential for capturing lived experience and evaluating early-stage treatment effects (Marek, Sperling, Woods).
- The convergence of imaging, fluid biomarkers, genetics, and digital measures is reshaping how brain disorders are staged, monitored, and ultimately prevented across the lifespan (Marek, Sperling, Woods).

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Monitoring disease progression and treatment response remains a critical challenge for precision medicine, particularly in neurological and psychiatric disorders where symptoms often evolve over time and prognostic and longitudinal assessment remain difficult, a context that Linda Brady, director of the Division of Neuroscience and Basic Behavioral Science at the National Institute of Mental Health, described when opening a session of the workshop. She emphasized that the session would examine how multimodal measures—including imaging, biofluid, genetic, digital, and clinical data—can be used to predict and track disease progression across different conditions. The discussion, she explained, would address issues of feasibility, heterogeneity, and interpretability, all of which shape both clinical management and therapeutic development. Brady highlighted three guiding inquiries for the session: (1) how biomarker, clinical, and other data can be integrated to support prognosis; (2) what longitudinal biomarker changes reveal about underlying biology; and (3) how initial and evolving biomarker profiles can inform therapeutic decisions, including treatment initiation, dose adjustment, discontinuation, or switching.

REWRITING THE ALZHEIMER'S TIMELINE THROUGH BIOMARKERS

Reisa Sperling, the director of the Center for Alzheimer Research and Treatment at Brigham and Women's Hospital, and professor of Neurology at Harvard Medical School, showed how a shift toward biological precision has transformed Alzheimer's disease research, enabling scientists to identify the disease years before symptoms emerge (see Figure 5-1; FDA, 2024c; Jack et al., 2018; Sperling et al., 2011a). She explained that Alzheimer's progression requires both amyloid, the protein that forms plaques, and

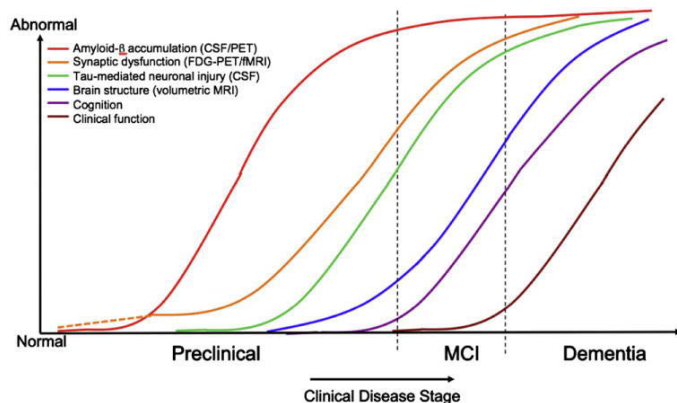


FIGURE 5-1 Stages of Alzheimer's disease prevention and treatment.

NOTE: This conceptual model illustrates how prevention strategies align with the biological progression of Alzheimer's disease (AD) from no pathology through preclinical, mild cognitive impairment (MCI), and dementia. Colored curves represent increasing abnormality of pathological markers—amyloid-beta ($A\beta$), tau, neurodegeneration, and cognitive decline—across disease stages. Primary prevention aims to avert amyloid or tau positivity altogether by decreasing $A\beta$ production and preventing tangle formation. Secondary prevention, targets individuals with evidence of amyloid (and sometimes tau) pathology to delay cognitive decline and progression to MCI or dementia through interventions that reduce $A\beta$ burden and neurodegeneration. Tertiary prevention and treatment focus on slowing dementia progression via neuroprotection, enhancement of remaining neuronal function, and neurotransmitter repletion. SOURCE: Presented by Reisa Sperling, March 5, 2026; Sperling et al., 2011a. Used with permission of Elsevier.

tau, the protein that forms tangles, noting that high amyloid without tau does not lead to cognitive decline, and tau rarely spreads without amyloid. She emphasized that the amount of each pathology—not just whether it is present—strongly influences prognosis.

Sperling highlighted two landmark studies demonstrating how biomarkers can predict disease progression. She cited a Mayo Clinic study showing that individuals with about 50 centiloids of amyloid on positron emission tomography (PET) scans had a 69 percent chance of developing mild cognitive impairment within ten years (Jack et al., 2025). She also cited a study using plasma phosphorylated tau at threonine-217 (p-tau217)—a blood-based marker of tau pathology that rises early in Alzheimer's disease—which predicted the timing of cognitive decline using a a disease-time-axis “clock” model (Petersen et al., 2026). Her colleague Rachel Buckley further showed that very high p-tau217 levels across multiple cohorts correspond to a 63 percent risk of progressing to mild cognitive impairment within ten years (Buckley et al., 2026).

Turning to clinical trials, Sperling described the A4 prevention trial, which enrolled cognitively unimpaired adults with elevated amyloid (Sperling et al., 2024). Although the drug tested did not reduce amyloid, the study revealed that baseline amyloid and plasma p-tau217 levels were strong predictors of decline, with p-tau217 outperforming amyloid PET (Sperling et al., 2024). She explained that p-tau217 reflects amyloid's early impact on tau at synapses. Sperling then discussed the ongoing AHEAD¹ trials, which use amyloid levels and p-tau217 as biomarkers to tailor enrollment, outcomes, and even precision dosing of lecanemab—an anti-amyloid monoclonal antibody used to treat early Alzheimer's disease. Plasma markers reduced PET screen fail rates dramatically, showing their feasibility for large-scale prevention efforts.

Sperling also highlighted digital cognitive measures, including a smartphone learning test that can identify elevated amyloid by day three of repeated practice (Jutten et al., 2025; Papp et al., 2024). She explained that combining digital measures with p-tau217 improves prediction of decline within just two years. Sperling closed by reiterating that individuals with both high amyloid and high tau remain at very high risk for decline. She emphasized the need to understand currently unexplained variants with additional biomarkers, digital measures, and patient-reported data. She stressed the need for longitudinal datasets—especially from clinical trials—to move beyond predicting who will decline and toward demonstrating meaningful differences over time.

During the discussion, a participant asked Sperling whether high amyloid levels might interfere with p-tau clearance during sleep, potentially explaining why proteinopathies increase with AD progression. Sperling stated that sleep is likely important for clearing proteins such as amyloid and tau, especially during slow wave sleep. She explained that p-tau is actively secreted and may require effective clearance of soluble amyloid and tau to prevent aggregation. While the exact mechanism is not yet known, she emphasized that reduced slow wave sleep is associated with greater protein accumulation. Sperling concluded that although the biology is not fully understood, healthy sleep and exercise are beneficial.

EARLY DETECTION ASSAYS REDEFINING PARKINSON'S DISEASE

Building on the Alzheimer's experience, Kenneth Marek, the president and senior scientist at the Institute for Neurodegenerative Disorders, principal investigator for the Parkinson's Progression Markers Initiative (PPMI), and a scientific advisor at the Michael J. Fox Foundation for Parkinson's

¹ For more information about the AHEAD study, see: <https://www.aheadstudy.org/> (accessed June 14, 2026).

Research, described how Parkinson's disease research is also undergoing a major shift similar to what transformed Alzheimer's disease—scientists can now detect biological changes years before symptoms appear.

Marek explained that the alpha synuclein seed amplification assay now allows the field to detect synuclein pathology directly, transforming the ability to define disease biologically. He noted that Parkinson's disease can now be classified using this measure and introduced the broader term neuronal synuclein disease to encompass Parkinson's disease and related conditions, such as diffuse Lewy body disease. This biological definition has enabled the development of a staging framework that integrates synuclein pathology with dopaminergic imaging, which captures the dopamine dysfunction that typically emerges before clinical symptoms.

Marek noted that these advances have major implications for tracking disease progression and developing therapeutics. He focused on the long pre-symptomatic period, which can now be characterized more clearly: synuclein pathology emerges first, followed by dopaminergic dysfunction, which ultimately leads to symptoms. He emphasized that genetics and other biological factors shape these trajectories, many of which remain poorly understood. This evolving framework, he said, is helping the field better define disease onset, chart progression, and design more effective interventions.

Marek emphasized the importance of identifying individuals at risk before symptoms appear (see Figure 5-2). He noted that Parkinson's disease and other neuronal synuclein disorders offer two early clinical clues—REM sleep behavior disorder and loss of smell (hyposmia)—with olfactory loss showing a particularly strong association with synuclein pathology. He highlighted data demonstrating that adults over age 70 with olfactory dysfunction have roughly a 70 percent likelihood of a positive synuclein assay, even without initial symptoms. These measures, he explained, allow comparisons of olfactory performance, dopaminergic imaging, and synuclein status, revealing that most asymptomatic individuals are synuclein positive, while only about half show dopamine transporter deficits, helping researchers map the timing of disease progression (Siderowf et al., 2023).

Building on Sperling's earlier remarks, this has led to efforts to derive a "clock" that uses dopamine transporter abnormalities to estimate the time to symptom development. Marek noted that a major challenge in longitudinal research is that participants enter studies at very different points along the disease course. He highlighted work led by Roger Gunn to align individuals to a common "time zero," enabling the generation of sigmoidal trajectories that span roughly 40 years—about two decades before symptom onset and two decades after. Marek explained that this modeling approach provides a way to stage early disease by identifying when dopamine transporter measures first become abnormal—provisionally defined

Understanding biology has broad consequences for disease onset, progression, and therapeutics

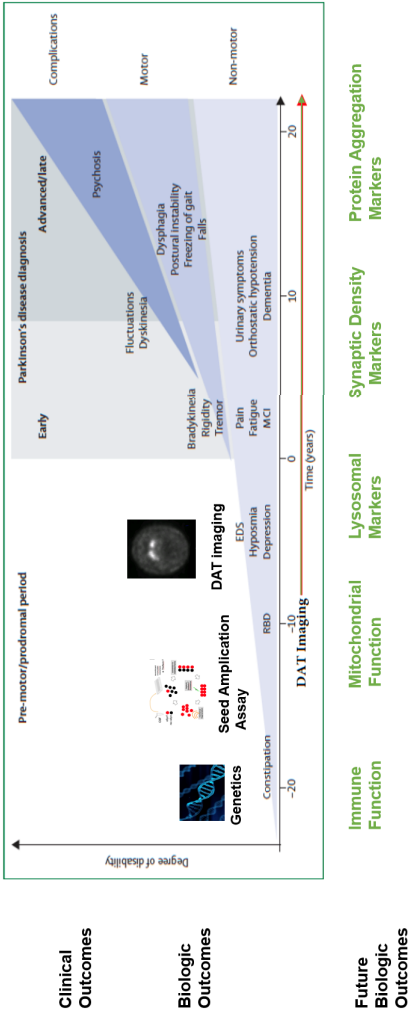


FIGURE 5-2 Model of Parkinson's disease trajectory.

NOTE: This figure illustrates the emerging framework for understanding disease onset and progression in Parkinson's disease and related synucleinopathies. The model depicts the long preclinical or prodromal period—previously a “white space”—now accessible through biomarkers that reveal early synuclein pathology preceding dopamine dysfunction and symptom onset. Genetic influences and other biological factors shape these trajectories, many still incompletely understood. Together, these insights redefine how disease progression is tracked and how therapies can be timed and targeted.

SOURCE: Presented by Kenneth Marek, March 5, 2026. Reprinted from the Lancet and used with permission from Elsevier.

as falling below 80 percent of normal. Among individuals who are already synuclein positive, he noted that this framework may help estimate when those who also become dopamine transporter (DAT) positive are most likely to develop symptoms. Although not yet as advanced as p-tau-based models in Alzheimer's disease, he emphasized that this work represents an important step toward individual level prediction.

Marek outlined a preliminary model suggesting that many individuals are synuclein-positive, but only a subset—perhaps 20–30 percent—progress to dopaminergic dysfunction and ultimately symptomatic neuronal synuclein disease. He noted that this raises fundamental questions about what triggers synuclein aggregation, what drives DAT decline, and why some individuals develop predominantly motor versus cognitive phenotypes. He emphasized that the biology is more complex than the model implies, highlighting data showing that prodromal subgroups differ. Individuals with REM sleep behavior disorder exhibit a much faster decline in DAT measures than those with isolated hyposmia, suggesting either different disease stages or distinct underlying biology.

Marek concluded by emphasizing the need for quantitative biomarkers to map disease trajectories. He noted that this work requires large datasets and highlighted the expansion of the myPPMI² online portal, now involving more than 50,000 participants from whom biomarkers can be collected. He added that biology-based enrollment strategies are being implemented during the preclinical period, including the Path to Prevention project,³ which aims to learn how biomarkers can guide therapeutic development.

FROM BIOMARKERS TO PROOF-OF-PRINCIPLE TRIALS IN SCHIZOPHRENIA

Scott Woods, Elizabeth Mears and House Jameson Professor of Psychiatry at Yale School of Medicine, then extended this framework beyond neurodegeneration, demonstrating that the same principles—early detection, longitudinal biomarkers, and heterogeneity mapping—are now being

² The Parkinson's Progression Markers Initiative (PPMI) is a landmark longitudinal study from the Michael J. Fox Foundation that follows individuals with and without Parkinson's disease to understand disease onset and progression. Its online platform, myPPMI, enables broad participation across the U.S., contributing remote assessments and biospecimens to one of the field's most widely used open datasets, which has informed hundreds of publications and numerous clinical trials. For more information, see: <https://myppmi.org/en-US> (accessed June 10, 2026).

³ The Path to Prevention (P2P) platform trial leverages the infrastructure and longitudinal data of PPMI to enable clinical testing in individuals at risk for Parkinson's disease, aiming to accelerate therapeutic development in the prodromal phase and reduce barriers for industry engagement. For more information, go to: <https://www.ppmi-info.org/study-design/path-to-prevention-platform-trial> (accessed June 10, 2026).

applied to psychosis risk in youth. Woods noted that schizophrenia and other psychoses have been characterized as having three phases: premorbid, prodromal, and psychotic phases. He introduced the clinical high-risk (CHR) syndrome for psychosis, a definition that is designed to detect the prodromal stage of psychosis before full symptoms emerge. He explained that CHR youth show mild, psychosis-like experiences but still recognize these thoughts as unlikely to be real. Woods stressed that CHR individuals are highly heterogeneous, and their outcomes vary widely: some progress rapidly to psychosis, some remain stable, and others improve. Because symptoms alone cannot predict who will follow which path, he argued that the field urgently needs biomarkers to better forecast individual trajectories and inform future schizophrenia prevention-focused clinical trials.

Woods described several early biomarker findings. He cited his team's MRI study, explaining that a rapid decrease in cortical thickness over 2–3 months predicted which CHR individuals later developed psychosis, a change not seen in healthy controls or in CHR individuals who did not progress (Collins et al., 2023). He also cited his polygenic risk score research, explaining that youth with the highest genetic risk scores were more likely to progress to psychosis within six months (Perkins et al., 2020). Woods also noted that cognitive performance, especially executive function, attention, working memory, and declarative memory, can be thought of as biomarkers that help predict progression to psychosis (Seidman et al., 2016). He explained that his team also integrated clinical measures into an individualized risk calculator, showing that those who eventually progressed to psychosis over a 24-month period had higher baseline risk scores than those who did not (Cannon et al., 2016). However, Woods emphasized that these studies were limited by small sample sizes.

To address this limitation, he described the Accelerating Medicines Partnership (AMP) of Schizophrenia, which recruited over 2,000 CHR participants for a two-year follow up study. Woods explained that this study should replicate earlier imaging and genetic findings and broaden them to include digital and language-based biomarkers. He added that combining these measures may offer greater predictive power, help develop tools to parse heterogeneity, and could one day help identify the right participants for clinical trials aimed at preventing schizophrenia. His team is depositing their information in a public archive thanks to public and private partnerships.

Woods introduced the need for precision outcome measures, noting that while precision biomarkers require broad data, outcome measures demand deeper assessment of the specific patients enrolled in trials and how they change over time. He emphasized that existing schizophrenia scales do not capture the clinical experience of CHR youth, prompting development of the Positive Symptoms and Diagnostic Criteria for the

Comprehensive Assessment of at-Risk Mental States harmonized with the Structured Interview for Psychosis-Risk Syndromes (PSYCHS) for both ascertainment and outcomes in the AMP Schizophrenia study (Woods et al., 2023). Using the Food and Drug Administration (FDA) methods of benchmarking, he noted that a five-point reduction in attenuated positive symptoms on the PSYCHS would represent a clinically meaningful change. Drawing on observational data from the AMP Schizophrenia study, he explained that CHR scores decrease on average from about 18 to 14 over three months, suggesting that even after accounting for expected placebo response or natural improvement, there remains sufficient room to detect a clinically meaningful treatment effect before scores approach those of healthy controls. Woods concluded by underscoring the substantial unmet clinical need in CHR, noting that the syndrome is identifiable, relatively common—present in roughly 19 percent of youth undergoing first psychiatric evaluations—and often missed despite causing distress and impairment (Seidman et al., 2016; Salazar de Pablo et al., 2021; Worthington et al., 2021). He emphasized that no pharmacologic treatments are approved for this population. Woods closed with the news that the AMP Schizophrenia study is now moving from observational work to proof of principle clinical trials using tools such as the PSYCHS and reported that the first study has just launched with its initial participant dosed (FNIH, 2026; Monument Therapeutics, 2026).

A workshop participant asked Woods how to distinguish biomarkers of biological dysfunction from responses to environmental stress. In response, Woods stated that psychosis exists on a continuum, and extreme stress can induce psychotic-like experiences even in healthy individuals. He shared a personal example of sleep deprivation–induced hallucinations while in medical school. He emphasized that both environmental and genetic factors shape psychosis risk, and biomarkers must be interpreted within this broader context.

BIOLOGICAL AND GENETIC MODIFIERS OF DISEASE TRAJECTORIES

During the discussion, a participant asked Marek whether loss of smell in alpha synuclein disorders might impair memory, given the strong link between olfaction and memory. In response, Marek stated that although the majority of people with synuclein pathology lose their sense of smell, most people with smell loss do not have synuclein pathology. He noted that while olfactory loss may affect memory, the evidence is not compelling in part because Alzheimer's and synuclein diseases frequently co-occur, making it difficult to isolate effects. Marek also added that approximately 30

percent of people with Alzheimer's disease may also have synuclein pathology, further blurring disease boundaries.

Sperling expanded on the olfaction-memory connection, noting that the entorhinal cortex—which plays a vital role in memory formation and is directly connected to the nose—is affected early in Alzheimer's disease. She referenced Mark Alber's University of Pennsylvania Smell Identification Test (UPSIT) work showing that smell identification and remembering smell may be particularly relevant (Jobin et al., 2025). Luca Pani, professor of clinical psychiatry and medical director at the University of Miami and Professor of Pharmacology at the University of Modena and Reggio Emilia, asked the panel whether olfactory associations, not just odor detection, are studied across diseases, noting the complexity of olfactory processing, the presence of olfactory hallucinations in schizophrenia, and the fact that the olfactory bulb is far more developed in rodents than in humans. In response, Woods stated that olfactory perceptual abnormalities are included in the PSYCHS scale for psychosis risk assessment. Marek stated that olfactory loss is a well-established early feature of Parkinson's disease, but its biological underpinnings remain unclear despite extensive research.

Krainc then shifted the discussion to genetic modifiers of disease onset and progression, asking whether Sperling's cohorts include genetic analyses, offering a rare disease example from Niemann-Pick Type C in which patients develop plaques and neurofibrillary tangles only when carrying apolipoprotein e4 (APOE4) allele, whereas those without APOE4 develop only neurofibrillary tangles but no plaques. Sperling agreed that genetics clearly influence tau spread in Alzheimer's disease, pointing to presenilin-1 carriers with protective variants. However, she emphasized that many people with high amyloid never develop high tau, and rare variants alone cannot explain this. She suggested that vascular and inflammatory pathways may be key modifiers and called this “the new frontier” for understanding why some individuals display a resilience against tau.

Krainc also asked how the Michael J. Fox Foundation for Parkinson's Research is prioritizing efforts to identify genetic modifiers of reduced penetrance in Parkinson's disease, noting that most individuals with pathogenic mutations never develop disease and that expanding the search for disease modifiers would strengthen our understanding of disease penetrance and consequently optimize therapeutic development for PD. In response, Marek stated that genetic modifiers are of “burning importance.” He explained that common variants such as LRRK2 and GBA1, along with many rarer variants, likely influence whether synuclein accumulates, whether dopamine dysfunction emerges, and how fast disease progresses. He noted that all participants in his studies undergo whole genome sequencing and that a collaboration with Andy Singleton and colleagues, a Michael J. Fox

Foundation for Parkinson's Research-funded group called GP2, is under-way to better understand these modifiers.

The discussion then turned to biological modifiers of brain health. Adama Tall shared her hypotheses linking gut bacteria, gamma-aminobutyric acid production, and diabetes to Alzheimer's disease, and asked for the panel's perspective. In response, Sperling stated that the microbiome is under intense study, but findings have not yet converged across studies. She noted that diet, medications, and disease symptoms all alter the microbiome, making cause and effect difficult to determine. She agreed that diabetes and protein glycosylation are important but noted that recent glucagon-like peptide-1 (GLP-1), an incretin hormone involved in glucose regulation, clinical trials have not shown benefits for Alzheimer's biomarkers; instead neurofilament light chain, a marker of axonal injury, and several proteins shifted in the opposite direction from what would be expected. She emphasized that while lifestyle factors such as diet matter for overall brain health, amyloid and tau biology remain dominant drivers. She also highlighted the central role of the innate immune system, particularly microglia, in clearing proteins and maintaining brain health.

INTERPRETING BIOMARKERS IN CLINICAL AND WHOLE-PATIENT CONTEXT

A workshop participant asked how to operationalize the process of interpreting a signal, phenotype, or biomarker in a way that situates it within the full, holistic context of the patient, going beyond multimodal biomarker integration alone. Woods emphasized that biomarkers are tools meant to support—not replace—patients, offering information that helps them better understand themselves and engage more effectively with their clinical providers. Marek added that precision medicine requires integrating genetics, environment, immune function, and personal variability. He envisioned a future where individuals receive biomarker panels early in life to guide monitoring, lifestyle choices, and potential treatments. Sperling agreed with Marek and emphasized that moving earlier in Alzheimer's disease allows clinicians to incorporate the patient's own perspective before memory loss limits self-report. She noted that later stage patients often cannot accurately describe their symptoms, making early engagement essential.

Potter asked Sperling which biomarker (blood-based markers, imaging measures, or tau imaging) she would consider the best candidate to serve as a surrogate for treatment response if she were leading a pharmaceutical company. Sperling replied that she previously would have chosen tau imaging, but recent differences in tau PET responses across drugs, such as lecanemab and donanemab, complicate interpretation. She predicted that

panels of phosphorylated tau markers—a set of blood- or cerebrospinal fluid-based assays that measure tau protein at multiple phosphorylation sites—will likely be most informative, with different markers useful at different disease stages. She noted that despite trontinemab’s substantial amyloid PET reduction, its phosphorylated tau decrease is roughly 50 percent, with lecanemab and donanemab yielding more modest 30–40 percent reductions, which track better with cognitive benefit than the magnitude of amyloid removal itself. She also highlighted that tau markers vary in relevance by disease stage, with aggregated forms like MTBR, the microtubule-binding region of tau, better suited to symptomatic phases than to the 15 years before measurable cognitive symptoms emerge (Doherty et al., 2025). She anticipated that panels of fluid biomarkers will ultimately guide both staging and predictions of treatment response.

6

Precision Strategies for Effective Clinical Trial Design

Highlights

- Precision medicine succeeds when the underlying biology is clearly defined, enabling biomarkers like neurofilament to anchor mechanism-based development and regulatory confidence (Ferguson, Mantua).
- Psychiatric disorders remain limited by syndromic diagnoses, but biologically grounded subtyping, such as immuno-metabolic depression, offers a path toward targeted, mechanism-aligned treatments (Marston).
- Heterogeneity must be embraced rather than erased, with trial designs incorporating multifactorial models, observational data, and computational systems pharmacology to identify meaningful subgroups (Mantua, Marston, Reyderman, Sperling).
- Biomarkers can accelerate development only when supported by disease-specific natural-history data and validated clinical relationships, ensuring they reflect true biological change rather than nonspecific variation (Ferguson, Mantua).
- Preclinical and translational evidence—when tightly aligned with human biology—strengthens confidence in biomarker relevance and supports regulatory decision making across neurodegenerative and psychiatric conditions (Ferguson, Marston, Stephenson).
- Early go/no-go decisions in drug development require trusted biomarkers that reflect target engagement and disease biology, enabling smaller, faster studies without waiting for long clinical endpoints (Ferguson, Mantua, Tillmann).
- Alzheimer's disease demonstrates a mature precision-medicine model, where A/T/N (amyloid, tau, and neurodegeneration) biomarkers guide patient selection, pharmacodynamic readouts, and rational combination therapy strategies (Reyderman).

continued

- Precision neuroscience must integrate biological, contextual, and social determinants of health, recognizing that clinical-trial context effects can meaningfully influence outcomes and should be measured and standardized (Marston).
- The future of precision neuroscience lies in modeling complexity rather than reducing it, leveraging computational tools and AI to capture biological diversity and design more informative trials (Ferguson, Mantua).

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Michael Irizarry, the senior vice president for Clinical Research and the deputy chief clinical officer at Eisai, introduced the session on precision strategies for effective clinical trial design, noting that the discussion would focus on how principles of precision medicine—spanning biology, biomarkers, patient stratification, and outcome measurement—can be applied to the development of new treatments. He highlighted that speakers would draw on examples from Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and psychiatric conditions to illustrate how these approaches are being implemented across different therapeutic areas. Irizarry also underscored the importance of the regulatory framework in shaping precision-based clinical development, emphasizing that regulatory strategy is integral to translating biological insight into viable therapeutic pathways.

VALIDATED BIOMARKERS DRIVING REGULATORY APPROVAL

Toby Ferguson, the senior vice president of the Neuroscience Therapeutic Area at Alnylam Pharmaceuticals, began with the difficult truth that ALS is a devastating, relentlessly progressive motor neuron disease with no natural plateaus or spontaneous improvement (Al-Chalabi and Hardiman, 2013). It was against this backdrop that he described a clinical trial that succeeded precisely because it was built on a deep understanding of the disease's biology. He explained that superoxide dismutase 1 (SOD1) ALS represents a rare genetic subtype that affects fewer than 1,000 people around the U.S. and was made identifiable through discoveries of SOD1 mutations beginning in the early 1990s and the subsequent adoption of genetic testing (CDC, 2026). SOD1 ALS drug development illustrates many of the issues discussed throughout the workshop.

He recalled that there was considerable uncertainty within his company about whether such a rare-disease trial could be operationalized. Ferguson explained that mechanistic work since the discovery SOD1 mutations has

shown that the disease arises from a toxic gain-of-function rather than loss of enzymatic activity, as individuals with widely varying levels of retained SOD1 activity still develop ALS (Benatar et al., 2022). Ferguson explained that neurofilament—an indicator of axonal injury, also known as neurofilament light chain (NfL)—stratifies patients by survival, with higher levels of neurofilament predicting worse outcomes. Ferguson emphasized that this relationship is robust across multiple clinical measures—including the ALS Functional Rating Scale—and that baseline neurofilament levels prospectively predict disease trajectory. He described the ALS therapy being tested by Biogen as an antisense oligonucleotide, called Tofersen, designed to reduce both mutant and normal SOD1 protein levels (McCampbell, 2018). Biogen studied this therapy in a six-month efficacy study called VALOR. It had a formal delayed-start analysis plan, and the primary endpoint was the ALS Functional Rating Scale, a regulatory-accepted endpoint commonly used in the field. Ferguson noted that substantial effort went into developing reliable assays for the key secondary endpoints—total SOD1 protein in cerebrospinal fluid and plasma neurofilament light—emphasizing that achieving regulatory-grade performance was essential to elevating these measures beyond exploratory status. He also acknowledged that the six-month trial duration was short and that the field initially expected mutation status or pre-study progression to help enrich for fast-declining participants, an approach that ultimately failed.

Ferguson noted that the study's primary clinical endpoint did not reach statistical significance, which could be interpreted as a failed trial. He emphasized, however, that the first question is whether the therapy achieved its intended biological effects. Ferguson reported clear target engagement, with meaningful reductions in total SOD1 protein, and highlighted a substantial decrease in neurofilament—larger than had been observed in any prior neurodegenerative disease study at the time (see Figure 6-1; Miller et al., 2022). He explained the importance of this neurofilament finding as they are structural proteins released when neurons are damaged (Wellmann et al., 2024). Ferguson emphasized that neurofilaments are a critical biomarker as “higher neurofilament means worse disease” and can be measured reliably in both spinal fluid and blood (Wellmann et al., 2024). He cited multiple studies showing that baseline neurofilament levels strongly predict survival, functional decline, and other clinical outcomes, noting that this relationship has been “very clear” across the literature (Falzone et al., 2022; Lu et al., 2015; Thompson et al., 2022).

Ferguson explained that the delayed-start results showed a coherent pattern of benefit at 52 weeks across multiple clinical measures (Miller et al., 2022). He underscored that the FDA's decision to approve Tofersen was driven largely by the clear and repeatable drop in neurofilament levels in both early- and late-start groups, combined with the biomarker's

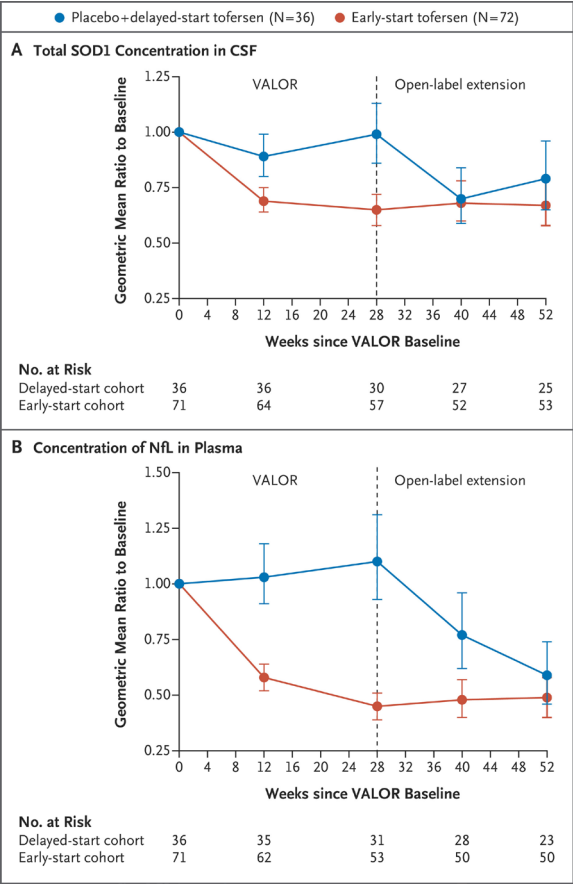


FIGURE 6-1 Tofersen lowers key proteins linked to nerve damage in ALS.

NOTE: This figure illustrates the target engagement and biological effect of the antisense oligonucleotide Tofersen in individuals with superoxide dismutase 1 gene (SOD1)- amyotrophic lateral sclerosis (ALS). Panel A shows the sustained reduction in total SOD1 concentration in cerebrospinal fluid (CSF) among participants receiving early-start Tofersen compared with those initially on placebo. Panel B depicts a substantial decline in plasma neurofilament light chain (NfL), a marker of axonal injury, in the same early-start group. This neurofilament reduction was greater than previously observed in any other neurodegenerative disease, underscoring its biological importance and predictive relevance for ALS disease trajectory. Together, these results indicate that lowering SOD1 expression with Tofersen leads to downstream reduction of neurofilament, linking molecular target engagement to a measurable effect on neuronal injury and disease course.

SOURCE: Presented by Toby Ferguson, March 5, 2026; Miller et al., 2022. Copyright © 2026 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

known link to disease severity. He pointed to VALOR results showing approximately 27 percent improvement in strength, well outside expected natural history (or the longitudinal, untreated course of ALS), and noted that real-world data have confirmed functional and respiratory benefits alongside consistent neurofilament reductions (Meyer et al., 2024). He noted that this evidence package led to Tofersen's approval as the first disease-modifying therapy for ALS, which has since expanded to several countries.

A participant asked Ferguson whether any mechanistic or quantitative systems pharmacology modeling was used to understand how changes in NfL relate to ALS disease progression and treatment effects and whether what has been learned in SOD1 ALS might also apply to the more sporadic form of ALS. Ferguson explained that formal quantitative systems pharmacology modeling was not used due to time constraints, but the team did develop quantitative models estimating how much NfL reduction would be needed to produce meaningful clinical benefit. This work relied heavily on natural history data from the ALS community, which he described as essential to the drug's eventual approval. He stated that most of what he presented about NfL in SOD1 ALS also applies to broader ALS populations, arguing that NfL's non-specificity is "a feature, not a bug," and that scientists need to determine the implications of neurofilaments in other neurodegenerative diseases.

Valentina Mantua, an associate director for Regulatory Science in the Office of Neuroscience Center for Drug Evaluation and Research Division at the Food and Drug Administration (FDA), noted that Tofersen's approval has reinforced the view that NfL may function as a broadly applicable surrogate endpoint, given that axonal damage—and the resulting rise in NfL—is a common feature across neurodegenerative diseases. She warned that while NfL is broadly useful, each disease shows its own NfL pattern and some show unexpected inverse relationships. She emphasized the need for aligned assays and disease-specific datasets.

BIOLOGY-GUIDED DRUG DEVELOPMENT IN ALZHEIMER'S DISEASE

To expand the lens toward the biomarker ecosystem that supports the maturation of biology-based clinical trial designs, Larisa Reyderman, the vice president and global head of Clinical Pharmacology and Translational Medicine at Eisai, explained how precision medicine is transforming clinical trials in Alzheimer's disease. Today, Alzheimer's disease is defined biology using the A/T/N framework, where amyloid (A), tau (T), and neurodegeneration (N) biomarkers follow a predictable sequence: amyloid rises decades before symptoms, tau increases next and closely tracks cognitive decline,

and neurodegeneration follows (Jack et al., 2013). She emphasized that this sequence enables researchers to stage patients along this disease continuum and define the pathways that can be biologically modifiable.

Reyderman explained that precision medicine in Alzheimer's disease begins with testing a mechanism aligned hypothesis grounded in where a therapy acts along the disease cascade. She emphasized selecting doses based on biomarkers that confirm target engagement and pathway modulation, not drug exposure alone, and measuring pharmacodynamic signals to ensure the biology is moving in the intended direction. She illustrated these principles by contrasting two Alzheimer's disease treatments, Lecanemab and Donanemab: Lecanemab preferentially binds toxic protofibrils while also clearing insoluble fibrils, whereas Donanemab targets pyroglutamate modified A β found only in deposited plaque (Abbott, 2022; Soderberg et al., 2023). Both clear amyloid but at different stages of the cascade, aligning mechanism with the pathology present in the enrolled population (Abbott, 2022; Soderberg et al., 2023). She noted that current trials rely on biomarker-based selection—confirming amyloid positivity, defining early symptomatic stage, and, for Donanemab, assessing Tau burden—to ensure participants have Alzheimer's biology, are early enough to benefit, and will show measurable progression within the trial timeframe.

Reyderman noted that precision medicine depends on tracking the right biological signals. In Lecanemab trials, amyloid positron emission tomography (PET) showed clear target engagement by reducing plaque levels. Plasma markers such as p-tau181, p-tau217, and the A β 42/40 ratio reflected downstream changes in tau activity and amyloid balance, while neurofilament light chain, a marker of axonal injury, indicated effects on neuronal injury. She highlighted tau PET as the most important downstream measure because tau spread is tightly linked to cognitive decline. Taken together, these pharmacodynamic markers provide a broad, multi-layered picture of how the therapy affects the A/T/N system.

Reyderman explained that amyloid-removal therapies do more than clear plaque; by lowering amyloid to negative levels, they appear to alter the Alzheimer's disease trajectory described by the original “Jack Curve,” potentially slowing downstream tau accumulation, and ultimately, cognitive decline (Jack et al., 2013). She noted that modifying the biology upstream motivates investigation of anti-tau therapies to determine whether bending the tau trajectory could further improve cognitive benefit. Given such, she described combination approaches pairing an anti-amyloid agent such as Lecanemab, which clears plaque and protofibrils, with an anti-tau therapy, like Etalaneutug, which is intended to block tau seeding and propagation.

Building on this biological rationale, Reyderman described how these principles are being applied in the ongoing Lecanemab–Etalaneutug combination study (Doherty et al., 2025). Participants are selected using

biomarkers that confirm early Alzheimer's disease, amyloid positivity, and active tau spread. The main biomarker, CSF MTBR Tau243, tracks new tau tangle formation, while tau PET, plasma p tau217, and amyloid PET monitor changes in tau and amyloid biology. She noted that this approach allows the team to see how each drug works on its specific target, how the two therapies interact, and whether their combined effects translate into cognitive improvement.

Reyderman noted that with anti-amyloid therapy now part of routine care, clinical trial designs must evolve to consider these agents as background therapy and to standardize patient populations with respect to safety, titration, and the degree of amyloid clearance. She highlighted the field's move toward quantitative systems pharmacology—mechanistic modeling framework that synthesizes biological knowledge and biomarker data to simulate disease trajectories and treatment responses. This “virtual laboratory” model, she said, is based on a digital twin of the population that enables testing therapeutic hypotheses and projecting outcomes not feasible to evaluate clinically (Cao, et al., 2026). She concluded by emphasizing the need for precision at every stage of Alzheimer's drug development and the promise of more individualized, biology-aligned clinical trials.

PRECLINICAL BIOMARKER EVIDENCE GAPS FOR EFFECTIVE TRIAL DESIGN

Stephenson highlighted a critical gap in nervous system research: a shortage of nonclinical (translational) biomarker data. Drawing on the kidney-safety biomarker project, she noted that extensive preclinical biomarker evidence increased FDA confidence and accelerated clinical acceptance; by contrast, their Alzheimer's dataset—though comprising roughly 100,000 patient-level clinical records and growing clinical biomarker information—lacks supporting nonclinical data. She pointed to the Tofersen review, where SOD-mouse data bolstered confidence in NfL, as an instructive example, and urged a concerted push for sponsors to share preclinical biomarker datasets so that translational modeling, such as quantitative systems pharmacology modeling, and decision making in drug development can be strengthened. She asked for panelists' thoughts on the need for more shared preclinical data, including in psychiatry. In response, Ferguson described how preclinical biomarker data—both electrophysiologic and biochemical—were crucial in the Tofersen development. In SOD1 mouse models, treatment timing determined whether electrophysiologic responses were prevented, repaired, or unchanged, and similar patterns appeared in humans. He cautioned, however, that not all animal models are equally informative, and the key is to measure what truly matters for the disease. Marston added a psychiatry-specific perspective, noting that he dislikes the

term “model” because it is unclear what is being modeled. Instead, he advocated for reverse translation, starting with human biological findings and then creating homologous preclinical measures. He noted that he installed an Innovative Health Initiative program where European industry partners are increasingly willing to share data to enrich future preclinical work.

BEYOND DSM: DESIGNING TRIALS AROUND BIOLOGICAL SUBGROUPS

Hugh Marston, the senior vice president and global head of Neuroscience and Mental Health Discovery Research at Boehringer Ingelheim, addressed what it takes to build a biologically grounded clinical-trial framework in fields where the underlying mechanisms are still being defined. He emphasized that symptoms such as anhedonia and cognitive impairment cut across multiple disorders, suggesting that symptom clusters may offer a clearer path to identifying shared biological mechanisms and therapeutic targets in psychiatry. Marston argued that relying on syndromic Diagnostic and Statistical Manual (DSM) categories leads to heterogeneous trial populations, weakening the ability to test precise hypotheses and limiting insight into patient biology and clinical endpoints (APA, 2022). As a result, treatment decisions often default to trial and error rather than biologically informed strategies as discussed earlier in the workshop.

To illustrate the problem, Marston cited work from Brenda Penninx’s Netherlands Study of Depression and Anxiety cohort, explaining that what DSM labels as “typical” and “atypical” depression actually reflects distinct biological profiles (Lamers et al., 2010, 2013, 2016; Milaneschi et al., 2020; Penninx et al., 2013). Marston noted that the so-called atypical group shows immune metabolic features, such as inflammation, dyslipidemia, leptin and insulin changes, and argued that reframing this subgroup as “immuno metabolic depression” provides a clearer biological target for new therapies. He cited this study to show how symptom clusters can reveal meaningful biology when traditional categories cannot.

Marston also argued that many psychiatric endpoints were never designed to measure change. He noted that the Hamilton Depression Rating Scale was created as a cross-sectional tool; and the Montgomery–Asberg Depression Rating Scale was originally designed to detect antidepressant effects from selective serotonin reuptake inhibitors, not to capture the full experience of depression. This mismatch, Marston said, contributes to failures in late-stage trials and widens the gap between Phase 2 and Phase 3.

He highlighted emerging progress in Europe and the United States, including the European College of Neuropsychopharmacology’s efforts to build neurobiologically informed patient roadmaps (Kas et al., 2025a). Marston also described a 12-year transdiagnostic collaboration, called the

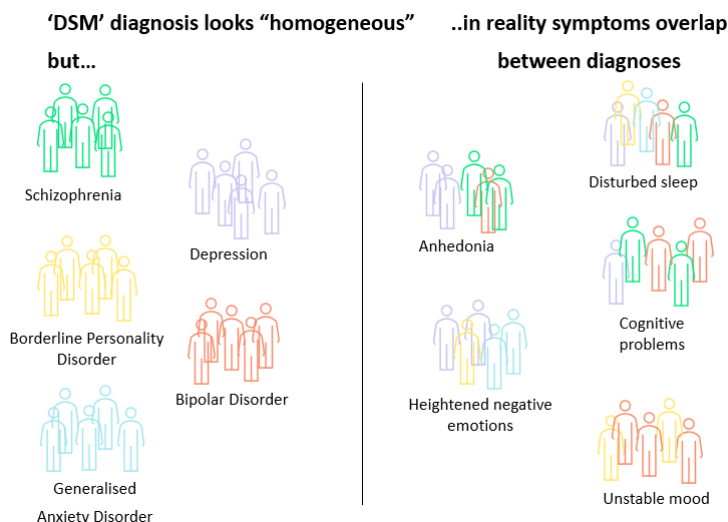


FIGURE 6-2 Symptom overlap challenges the DSM Framework.

NOTE: This figure illustrates how current Diagnostic and Statistical Manual of Mental Disorders diagnostic categories appear homogeneous but mask substantial biological and symptomatic overlap across disorders. While diagnoses such as schizophrenia, depression, bipolar disorder, borderline personality disorder, and generalized anxiety disorder are defined by distinct clinical labels, symptoms like anhedonia, cognitive problems, disturbed sleep, unstable mood, and heightened negative emotions occur across multiple conditions.

SOURCE: Presented by Hugh Marston, March 5, 2026.

Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project which was funded as part of the European Union’s Innovative Medicine Initiative, examining social dysfunction across depression, schizophrenia, Alzheimer’s disease, and healthy controls. He cited this work, explaining that it identified the default mode network structure and function as a key driver and led to new clinical tool recommendations and the development of a passive monitoring digital endpoint.

Marston described a collaboration with researchers at Yale University showing that an unbiased analysis of post-traumatic stress disorder yields two distinct subgroups: the fear profile and the emotional pain profile (Ben-Zion et al., 2025). About 31 percent of patients exhibit a clear “fear” profile marked by impaired regulation of the prefrontal–amygdala circuit and a consistent symptom pattern, providing a tractable neurobiological target for stratification (Ben-Zion et al., 2025). He noted that the more emotionally driven presentation remains less well understood but suggested that

tracking the fear related subgroup may help guide future work to uncover the biology underlying the emotional subtype.

Marston closed by emphasizing that strong biological hypotheses can help trace the pathway from brain mechanisms to individual patients, enabling more precise treatment decisions. Achieving this, he argued, will require validated biomarkers aligned with therapeutic hypotheses, more accurate stratification into biologically coherent subgroups, and clinical endpoints that reflect patient needs and are sensitive to meaningful change.

Larua Bustamante noted that psychiatry faces a high bar when insisting on a strictly biological pathway for precision approaches. She asked whether precision psychiatry is still possible in populations defined primarily by psychiatric symptoms—where psychosocial, contextual, and experiential factors may dominate and a clear biological route may not exist. Mantua described a paradox, despite the need for long, expensive trials and extensive biomarker development, “psychiatry is a winner.” She cautioned that psychiatry’s fast treatment development comes at the cost of not understanding why treatments work for some and not others. She added that although many treatments for depression and bipolar disorder are effective, they remain nonspecific and fail to target cognitive symptoms. Bustamante argued that advancing the field will require moving beyond symptomatic treatments to approaches that directly address cognitive symptoms.

Marston emphasized that psychiatry has made little therapeutic progress over the past 70 years, noting that both pharmacological and non-pharmacological treatments have largely remained unchanged despite substantial unmet clinical need. He argued that progress will require generating new hypotheses and moving beyond the current endpoints. Marston suggested that precision approaches may offer a path forward but only if the field can rigorously quantify biological hypotheses, symptomatic dimensions, drug related biological responses, and whether these changes translate into meaningful patient improvement. He underscored that, as Mantua outlined, advancing precision psychiatry will require building each evidentiary “block” with careful measurement and accuracy. Reflecting on comments from several workshop speakers (see chapter 4), Mantua highlighted need for measurement and that the psychiatry field cannot move forward until those aspects are quantified.

Indida Birto, assistant researcher at Emory University, asked whether trials—especially in behavioral health—should integrate social determinants of health and supportive services (e.g., case management) to distinguish biological effects from contextual ones. Marston responded that in mental health clinical trials, what is often labeled a “placebo effect” is actually a clinical trial effect where simply bringing people into a supportive, structured environment improves outcomes. He predicted that the field will increasingly standardize and optimize the context in which a clinical trial is

conducted to separate contextual benefit from pharmacologic effect. Marston also suggested that in many cases, a pharmacologic agent, or drug, is used not just to treat symptoms but to make a person more responsive to the surrounding therapy or environment—think of the medicine as a plasticizing agent, one that helps the brain become more flexible, so the rest of the treatment works better. He added that many companies and researchers are starting to explore this idea, but it is still hard to measure these “context” effects and determine how to include them properly in clinical trials.

BUILDING A REGULATORY FRAMEWORK FOR PRECISION CLINICAL TRIALS IN NEUROSCIENCE

Building on earlier discussions, Mantua turned to how precision medicine is reshaping the regulatory framework for three pillars of neuroscience clinical trials to be more biology- and measurement-driven. For the first pillar, patient population, the focus shifts from broad clinical diagnoses to defining who has the biology of interest and ensuring that enrolled participants have the biological characteristics the therapy is intended to modify. Biomarkers and genotypes can be used to confirm eligibility, enrich study populations, and manage heterogeneity. For the second pillar, study design and duration, precision approaches seek to align trial design with the underlying disease biology, including following participants long enough to observe meaningful change and incorporate adaptive features or platform designs when appropriate. For the third pillar, outcome assessment, the key question becomes how biomarkers can be integrated with clinical endpoints to improve sensitivity and interpretability, whether as surrogate endpoints—reasonably likely predictors of clinical benefit—or confirmatory evidence supporting treatment effectiveness.

Mantua described population selection as a spectrum. At one end are biologically defined groups, such as genetic or ultra-rare diseases (FDA, 2018). In the middle are neurodegenerative disorders, where enrichment strategies—selecting participants who are more likely to show the biological process the therapy is intended to target—have matured enough to appear in drug labels and guide clinical use. She contrasted this with emerging areas like Parkinson’s disease and other synucleinopathies and tauopathies, where the absence of quantitative biomarkers limits staging—where a patient is along the course of a disease—and early disease identification (Brady et al., 2025; FDA, 2026). The CSF alpha-synuclein seed amplification assay discussed earlier in the workshop, for example, is binary and cannot support the kind of quantitative staging enabled by centiloids in Alzheimer’s disease (Brady et al., 2025). She noted similar challenges in Huntington’s disease, with poorly defined boundaries between clinical stages 2 and 3 of the disease. She raised the question of how enrichment

strategies affect generalizability (Brady et al., 2025). At the opposite end of the spectrum lies psychiatry, where diagnoses still lack biological grounding (Kas et al, 2025b).

Mantua explained that precision medicine can reshape traditional trial design by enabling accelerated-approval pathways (FDA, 2024a). Instead of relying solely on long studies powered to detect clinically meaningful change, precision approaches allow shorter clinical trials supported by biomarkers and followed by confirmatory studies. She pointed to Tofersen as an example of this, where neurofilament light chain served as the “reasonably likely” biomarker supporting accelerated approval, while reductions in SOD1 provided confirmatory evidence in the subsequent SOD1-ALS trial (see Figure 6-1).

Mantua explained that precision neuroscience becomes meaningful only when outcomes can incorporate biomarkers but using biomarkers as endpoints raises the evidentiary bar. She noted that biomarkers are valuable for target engagement, enrichment, and longitudinal safety monitoring, yet their most demanding use is as outcomes, where regulators must determine whether they reliably predict clinical benefit. She distinguished clinically meaningful endpoints from intermediate endpoints that may be “reasonably likely” to predict later benefit, particularly in slowly progressive neurodegenerative diseases. She added that reasonably likely surrogate endpoints require strong mechanistic rationale and supportive epidemiologic data and emphasized that regulators do not accept surrogate proposals without clinical evidence linking the biomarker to patient centered outcomes (FDA, 2023a).

Mantua noted that psychiatry is not yet positioned to apply the precision medicine framework used in other neuroscience areas, but she emphasized that the opportunity is substantial if the field commits to the necessary foundational steps (Kas et al, 2025b). She outlined a sequence of steps to follow: first, prioritizing a biologically grounded and operationally actionable hypothesis to guide population selection and biomarker development; second, validating any proposed measures or biomarkers through work that extends beyond a single trial or program to ensure generalizability and avoid over fitting; and third, scaling these efforts through broad collaboration, data sharing, and sustained investment. Mantua stressed that this ordered progression—biological hypothesis, validation, and collaborative scalability—mirrors what enabled progress in Alzheimer’s disease and is essential for advancing precision approaches in psychiatry.

Mantua suggested that efforts to reduce heterogeneity in clinical trials often reflect development or commercial pressures rather than biological reality. She emphasized that the complexity of heterogeneity is intrinsic to biology and should be measured and modeled rather than minimized. She noted that emerging technologies—including generative artificial

intelligence models designed to learn from nucleotide or single cell data as well as tools like AlphaFold¹ that predict protein structure—illustrate how computational advances may help neuroscience embrace, rather than erase, biological variation (Cui et al., 2024). She encouraged the field to think about scaling future efforts by designing for heterogeneity, not simplifying it, and by leveraging models capable of capturing network level behavior.

Building on Mantua's call to design for heterogeneity rather than simplify it, Julian Tillmann, a principal clinical scientist and industry lead of the AIMS-2-TRIALS in the department of Pharma Research and Early Development at Roche, asked how to practically operationalize the precision medicine steps in clinical development, specifically, how to generate evidence early enough to decide whether to halt or accelerate programs, and how that translates into regulatory interactions and acceptance. Ferguson acknowledged the difficulty of this endeavor, noting that relying solely on clinical endpoints forces long, expensive studies. He argued that researchers must identify biomarkers they trust for early decision making in clinical development. He noted that when researchers identify biomarkers they trust, those markers should inform decision making; he referred to his ALS example, explaining that in a small ALS study a decline in the neurofilament biomarker after six months would be a compelling positive signal, while an absence of change would reduce the likelihood of success. Mantua added that her regulatory evaluation begins with pharmacology: What does the drug do? What is the biological hypothesis? Which biomarkers reflect that mechanism? She emphasized that the FDA now relies heavily on confirmatory evidence, especially mechanistic evidence showing that observed effects on the disease are truly due to the drug (FDA, 2026, 2023a).

INCORPORATING BIOLOGICAL AND CLINICAL HETEROGENEITY INTO TRIAL DESIGN

Sperling appreciated Mantua's earlier remarks about embracing heterogeneity, particularly the importance of matching therapies to disease stage, comorbidities, and individual characteristics. She asked the panel how investigators can realistically build disease heterogeneity into trial designs, noting that doing so may be essential for accelerating therapeutic progress in neurodegenerative diseases. She explained that, in practical terms, the field faces the choice to either undertake a very large Phase 2 study to sort through this heterogeneity—which is challenging—or design Phase

¹ AlphaFold is an artificial intelligence system from Google DeepMind that predicts a protein's three-dimensional structure from its amino-acid sequence quickly and with accuracy comparable to many experimental methods. For more information, see: <https://alphafold.ebi.ac.uk/>.

3 trials that intentionally incorporate heterogeneity but rely on include pre-specified subpopulations hypotheses to preserve interpretability. In response, Mantua explained that Phase 3 trials tend to default to conservative designs, making Phase 2 the better place for hypothesis generation. She emphasized the need for models capable of analyzing relationships across multiple biological pathways, arguing that the field is now ready to use such tools. Reyderman added that observational studies are essential for understanding heterogeneity. She noted that integrating these data into computational models, such as systems pharmacology, can help define better hypotheses and enable smaller, more efficient trials. Sperling followed up, noting that observational data often predict who will decline but do not necessarily predict who will respond to therapy, which complicates trial design. Marston echoed Mantua's point that natural heterogeneity must be embraced because it will always exist but argued that heterogeneity that undermines hypothesis testing must be controlled. He illustrated the distinction by noting that there is no point in giving anti-amyloid therapies to amyloid-negative patients and that glutamate-modulating agents should not be used in individuals with the opposite glutamatergic profile. He agreed with Mantua that bridging Phase 2 to Phase 3 requires multifactorial parameters at scale to manage variance in real-world populations.

7

Precision Systems to Deliver Care at Scale

Highlights

- Genetic discoveries in Alzheimer's disease reveal deep biological heterogeneity, underscoring that precision therapies must account for diverse mechanisms, cell-specific dysfunction, and the need for inclusive data to ensure real-world applicability (Ertekin-Taner).
- The rollout of anti-amyloid therapies demonstrates that scientific breakthroughs cannot succeed without health-system readiness, including diagnostic capacity, workforce expansion, reimbursement clarity, and primary-care engagement to identify early-stage patients (Mattke).
- Pharmacogenomics shows how precision medicine can scale when infrastructure, decision support, and payment models are intentionally aligned but also how misaligned incentives and fragmented care pathways can stall implementation despite strong evidence (Limdi).
- Population-level neurodegenerative diseases require shifting precision approaches beyond specialty centers, demanding new care models, expanded training, and operational redesign to deliver therapies safely and equitably (Mattke, Ertekin-Taner).
- Successful translation depends on integrating strong biology with delivery systems capable of absorbing operational demands, supported by sustainable reimbursement and ethical frameworks that protect patients while enabling timely access to genomic tools (Limdi, Mattke).
- Across conditions, precision medicine fails not because the science is wrong but because clinical systems are unprepared, highlighting the need for coordinated investment in infrastructure, data harmonization, and workforce capacity to achieve scalable, sustained impact (Ertekin-Taner, Mattke, Limdi).

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Throughout the workshop, several participants emphasized that the promise of precision neuroscience depends not only on scientific discovery but on successful implementation and getting treatments to patients. Bruce Korf, Distinguished Professor Emeritus at the University of Alabama, Birmingham, School of Medicine, introduced a session centered on real-world implementation of precision approaches in neuroscience. He observed that, although only a limited number of precision tools have reached clinical practice, these early examples offer important lessons about what happens when systems attempt to adopt them. The session, he explained, would examine what succeeds, what falters, and why, with attention to how clinicians and health systems make adoption decisions and how economic and ethical considerations shape those choices. Korf emphasized that understanding these practical dynamics is essential for translating promising precision strategies into care that can be delivered reliably and at scale.

TURNING BIOLOGICAL DISCOVERY INTO HEALTH-SYSTEM IMPACT

In his keynote, Husseini Manji, a professor at Oxford University, adjunct professor at Yale University, and cochair at the United Kingdom Government's Mental Health Mission, emphasized that extraordinary advances in biological discovery will not translate into patient benefit unless health systems are redesigned to absorb, operationalize, and deliver precision neuroscience at scale. He discussed the shifts required to move from discovery science to the health-system structures that determine whether precision care can be implemented, stressing that discovery alone does not change care (see Figure 7-1).

In some areas of neuroscience, especially Alzheimer's disease, biological innovation is accelerating. He pointed to the expanding Alzheimer's therapeutic pipeline as evidence of what happens when the field "leads with biology." Instead of treating vague symptoms, researchers are now targeting specific mechanisms. He highlighted how neuroimaging and cerebrospinal fluid (CSF) biomarkers have already enabled major progress, and he argued that plasma p217 tau is a "game changing" biomarker because it allows clinicians to detect neuronal injury early through a simple blood test rather than waiting for dementia to appear.

But scientific progress alone is not enough. Manji emphasized that the ecosystem around the science must mature. As he noted, history shows that breakthroughs only reach patients when the surrounding infrastructure—standards, validation, reimbursement, and clinical workflows—keeps pace.

He then turned to the role of artificial intelligence (AI). While AI is not a replacement for biological insight or rigorous thinking, he believes it is becoming an engine that makes complex human biology interpretable.

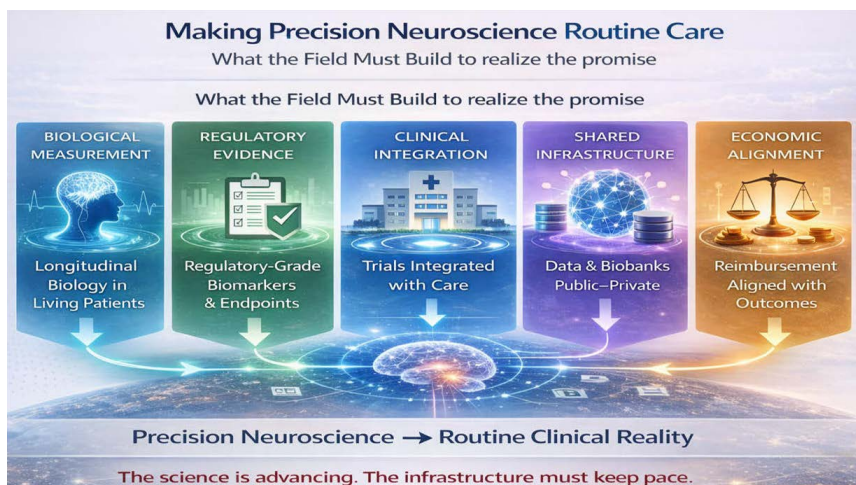


FIGURE 7-1 Making precision neuroscience routine care.

NOTE: This figure illustrates the essential components required to transform precision neuroscience from scientific promise to routine clinical practice. Five interconnected pillars define the infrastructure needed for this transition, emphasizing that while the science of precision neuroscience is advancing rapidly, the supporting infrastructure must evolve in parallel to achieve routine clinical reality.

SOURCE: Presented by Husseini Manji, March 5, 2026.

He credited work from Johnson & Johnson, showing that modern datasets—single cell atlases, proteomics, neuroimaging—are too large and high dimensional for traditional methods. AI can detect structure within this complexity: patterns, dimensions, and subtypes that would otherwise be invisible. According to Manji, AI helps the field move from labels to dimensions, from syndromes to mechanisms, and toward matching interventions to biology.

AI also enables precision approaches that evolve over time. Echoing Heywood’s remarks, Manji argued that precision medicine should be dynamic, tracking biological changes longitudinally so treatments can be adjusted as signals shift.

Manji then summarized that for the current landscape the promise is enormous, but the constraints are real. High dimensional data, multi-omics, digital phenotyping, and circuit-based biomarkers are beginning to define precision subtypes and identify patients most likely to respond to specific mechanisms. Yet translation requires validation, and validation requires standards, infrastructure, and alignment.

He described the “translational tension” between biological discovery and routine care. On one side, discovery is advancing rapidly. On the

other, the field still lacks validated proxy (surrogate) endpoints, consensus diagnostic thresholds, clear reimbursement pathways, and coherent implementation structures. Most neuroscience disorders cannot yet be measured dynamically in living patients in ways that health systems can operationalize. This gap—between what science can see and what systems can deliver—is the “valley of uncertainty” the field must cross.

Manji then broadened the lens. Precision medicine, he said, begins with molecules, moves to patients, enters clinics, must function inside health systems, and ultimately must improve population outcomes. That journey requires new ecosystem capabilities including workforce readiness, workflow integration, reimbursement alignment, equity, and strong ethical and data privacy governance.

Manji emphasized that confidence in biomarkers matures in stages. Early on, scientists must believe; in the middle, regulators must gain confidence; later, clinicians and payers must trust the measures. He agreed with Rosa Canet-Avilés and Gayle Wittenberg that neuroscience cannot simply copy oncology but oncology does offer lessons. He pointed to the HER2 “no test, no drug” model, which succeeded because diagnostic testing was standardized, labs were certified, guidelines were clear, and reimbursement was linked to testing. Precision oncology worked because the field reformed care delivery to scale it. Neuroscience, he argued, must aspire to do the same.

Wittenberg asked whether psychiatry sets the bar too high or too low when claiming that “biology is the bottleneck.” Manji responded that while rigor is essential, actionable biology does not require perfect mechanistic maps. Instead, the field needs the ability to perturb a mechanism in humans, observe what changes, and iterate. He emphasized that meaningful progress comes from demonstrating that a targeted biological change moves a “key node” in the system, even if it does not correct the entire disease process. Drawing parallels to other areas of medicine, he noted that many successful treatments emerged from partial understanding, refined through learning oriented clinical trials. He argued that psychiatry should adopt similar “learning engine” approaches rather than waiting for complete mechanistic certainty.

BUILDING PRECISION SYSTEMS THROUGH GENETICS AND MULTI-OMICS

Where Manji highlighted the system-level redesign needed to translate discovery into care, Nilüfer Ertekin-Taner, Roy E. and Merle Meyer Professor of Neuroscience, enterprise chair in the Department of Neuroscience, professor of Neurology and Neuroscience at Mayo Clinic, examined the genetic and multi-omics discoveries that form the scientific backbone of

precision systems. Ertekin-Taner noted that much of what is now understood about Alzheimer's disease stems from early work on its two defining pathologic hallmarks—amyloid and tau—and that genetic studies built directly on this biological foundation. She outlined the first major era of Alzheimer's genetics, from the 1980s through 2009, when mutations causing early onset familial Alzheimer's disease were identified (Ertekin-Taner, 2007, 2010, 2011; Is et al.; 2025, Liu et al., 2013). Although these mutations account for less than 1 percent of cases, she emphasized that they are largely fully penetrant and directly influence amyloid production or processing. In the same period, the apolipoprotein E4 risk allele was discovered through family and case control studies; she highlighted its dose dependent and ancestry dependent effects, its contribution to roughly 20 percent of population risk, and its influence across multiple biological pathways. Together, she noted, these early genetic discoveries shaped the field's understanding of Alzheimer's pathophysiology, informed the amyloid cascade hypothesis, and enabled the development of model systems and biomarkers that continue to guide therapeutic research.

Ertekin-Taner noted that early genetic discoveries ultimately moved into clinical practice, shaping how Alzheimer's disease is diagnosed, stratified, and treated (Ertekin-Taner et al., 2000, 2008; Graff-Radford et al., 2007; Klunk et al., 2004). She highlighted that testing for early onset familial Alzheimer's mutations is now used in appropriate clinical scenarios and that amyloid beta biomarkers—whether in CSF or imaging—are routinely applied, as several speakers had discussed. She added that APOE ε4 genotyping now informs risk counseling and treatment decisions for patients considering anti-amyloid therapies. These same discoveries, she emphasized, also established the amyloid pathway as a central therapeutic target and enabled trials that enroll mutation carriers or APOE defined subgroups, as described by earlier industry speakers. Ertekin-Taner told workshop participants that the current wave of monoclonal anti-amyloid antibody therapies—covered by other speakers throughout the workshop—emerged directly from this foundational biochemical, neuropathologic, and genetic work (Heidebrink and Paulson, 2024).

Ertekin-Taner emphasized that early pathology, biochemistry, and rare disease genetics taught the field how studying the right tissue and the right populations can reveal disease driving molecules, generate model systems, and ultimately identify therapeutic targets. She then described the subsequent era of genome-wide association studies, which uncovered more than 80 Alzheimer's risk loci clustered around pathways such as inflammation, lipid metabolism, and cell signaling (Ertekin-Taner, 2010, 2011; Graff-Radford et al., 2007; Is et al., 2025; Liu et al., 2013). While these discoveries were scientifically valuable, as other speakers had also underscored, they did not directly reveal causal genes or mechanisms and highlighted that

most risk variants lie in non-coding but transcriptionally active regions, complicating therapeutic translation. She stressed that this translational gap is driven in part by two funding realities: developing a single Food and Drug Administration (FDA)-approved therapy now exceeds a billion dollars, and despite more than 100 molecules in clinical trials, most efforts remain concentrated on amyloid and tau, even though many additional biological pathways are disrupted (Wouters et al., 2020).

Ertekin-Taner emphasized that the long prodromal phase of neurodegenerative diseases is both a challenge and an opportunity, creating space for earlier intervention if these conditions are treated as distinct biological entities rather than a single aggregated disorder. She outlined a precision medicine framework in which environment, genetics, and epigenetics interact to produce perturbations across multiple omics layers. These signals rarely occur in isolation and interpreting them is further complicated by the comorbidities common in older patients. These upstream perturbations ultimately manifest in measurable outcomes such as cognition, fluid biomarkers, neuroimaging, and neuropathology (Allen et al., 2016; Oatman et al., 2025). She stressed that despite this complexity, current practice still treats Alzheimer's disease as a uniform disorder, when in reality it reflects diverse biological pathways and patient specific drivers.

Ertekin-Taner noted that large scale omics initiatives—many supported by the Foundation for the National Institutes of Health (FNIH), the National Institutes of Health (NIH), and other funders highlighted by earlier speakers—now generate genome, epigenome, and multiple other data layers that can be analyzed through genome -wide scans, differential expression comparisons, and network approaches. She emphasized, however, that data generation and curation alone are insufficient; transforming these datasets into actionable biological insight requires integration, harmonization, and broad data sharing across groups. She added that despite these investments, a major gap remains between accumulating knowledge and achieving truly biology-anchored precision therapies, underscoring the need to prioritize therapeutic targets, and biomarkers prioritization.

Ertekin-Taner outlined four brief case studies to illustrate how integrative omics can move the field toward precision therapies. She described work combining genome, epigenome, and transcriptome data from Alzheimer's disease and progressive supranuclear palsy (PSP) to reveal widespread perturbations in oligodendrocyte and myelin pathways, opening new biological directions beyond the amyloid-tau focus highlighted by earlier speakers. She noted that integrating genomic and transcriptomic data can pinpoint disease genes, uncover regulatory variants, and clarify whether expression changes are therapeutically beneficial or detrimental—insights not possible from association studies alone (Allen et al., 2012, 2014, 2015, 2017; Zou et al., 2012,). She emphasized the importance of resolving cell specific

dysfunction, citing findings of opposite synaptic and immune network changes in neurons versus astrocytes in PSP, and underscoring the need for cell targeted interventions (Allen et al., 2018). Finally, she described a PSP project that layered bulk and single cell transcriptomics with network analyses and model system screening to narrow thousands of perturbed genes to three high confidence therapeutic targets, for which her group has now developed antisense oligonucleotides and advanced toward studies of investigational new drugs (Min et al., 2023).

Ertekin-Taner concluded that multi-omics can reveal additional disease biology, clarify causal genes and regulatory mechanisms, identify cell specific dysfunction, and help prioritize therapeutic targets. However, she underscored the need for inclusive research, noting that most current studies disproportionately sample non-Hispanic white populations and that multi-ancestry cohorts, including special populations such as individuals with Down syndrome, are essential for equitable discovery (see Figure 7-2). She highlighted the central role of biobanking, which requires standardized biospecimen collection, processing, and phenotyping to support reproducible science. Equally important are deep phenotyping and robust data management capable of handling large multimodal datasets, integrating them with electronic health records, and enabling diverse analytic approaches. Together, these layers form the infrastructure necessary to advance precision medicine toward meaningful clinical impact.

HEALTH SYSTEM BARRIERS TO IMPLEMENTING NEW TREATMENTS

Soeren Mattke, a research professor of economics at the University of Southern California (USC) Dornsife Center for Economic and Social Research and director of the USC Brain Health Observatory, contrasted the ambitions of precision neuroscience with the practical constraints of real-world care delivery, underscoring the gap between scientific innovation and health care system readiness. Using the Alzheimer's disease medication called aducanumab as a case study, he argued that even when a therapy demonstrates biological and clinical impact, implementation can fail catastrophically if systems are unprepared. He shared that in 2016, a breakthrough publication showed the Alzheimer's disease treatment aducanumab reduced amyloid plaques and slowed cognitive decline, providing evidence supporting the long-debated amyloid hypothesis that amyloid deposits are on the clinical path (Mattke et al., 2023). He framed this case as a reminder that scientific progress matters only when it leads to interventions that can be successfully delivered within health systems, setting up his broader discussion of the gap between scientific innovation and the operational realities of care.

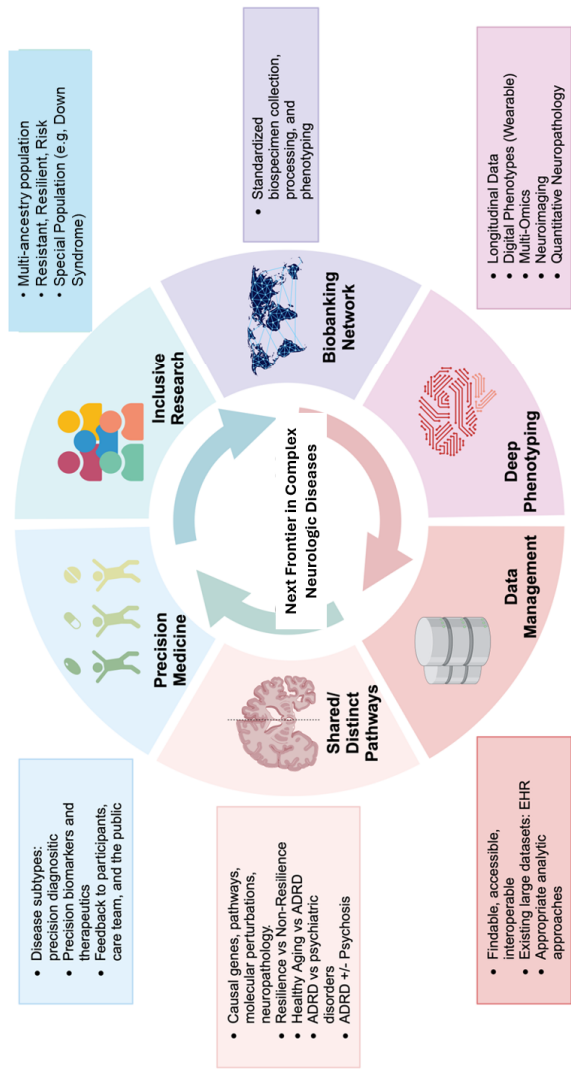


FIGURE 7-2 Next frontier in complex neurologic diseases.

NOTES: This figure presents a conceptual framework for advancing research and care in complex neurologic disorders through six interconnected domains. At the center, the Next Frontier in Complex Neurologic Diseases emphasizes integration across biological, clinical, and data-driven approaches. Surrounding segments highlight the pillars required for progress—including precision medicine, inclusive, multi-ancestry research; standardized biobanking; deep phenotyping; and robust data infrastructure capable of supporting diverse analytic approaches. Together, these domains define a roadmap for precision neuroscience that integrates biological discovery, inclusivity, and data infrastructure to accelerate translation into clinical impact.

SOURCE: Presented by Nilufer Ertekin-Taner, March 5, 2026.

Mattke noted that he and Craig Ritchie each published analyses predicting that the real-world rollout of anti-amyloid therapies would “be nothing short of a disaster,” a warning they now feel was unfortunately validated (Liu et al., 2017; Ritchie et al., 2017). He explained that their concern stemmed from the limited readiness of current memory care systems, which would require transforming memory care from its existing counseling-oriented model into something closer to oncology, with routine use of procedures such as lumbar punctures, advanced imaging, infusion-based treatments, and genetically informed therapeutic decisions—an infrastructure shift far removed from how most memory clinics operate today. This mismatch between existing care structures and the demands of precision neuroscience framed his argument of why health systems were ill-prepared for the introduction of drugs like aducanumab.

Using Medicare data to illustrate the scale of the gap, Mattke noted that although aducanumab received accelerated approval in 2021—followed by lecanemab and donanemab in 2022 and 2023, respectively—aducanumab was withdrawn for lack of commercial viability. By the end of 2023, only 924 Medicare fee-for-service beneficiaries had initiated treatment out of an estimated two million eligible early-stage Alzheimer’s patients (Mattke et al., 2025). He underscored that just 410 clinicians had prescribed these therapies, highlighting the limited activation of the care system, despite substantial disease burden. Compounding the problem, he emphasized that primary care detection of mild cognitive impairment—the stage at which these drugs are intended to be used—has not improved, remaining at roughly 8–10 percent in analyses from 2019 through 2022. In his view, this failure to identify patients upstream effectively blocks them from ever reaching precision neurodegeneration treatments.

Mattke argued that this limited real-world uptake of anti-amyloid therapies reflects a mix of clinical skepticism, safety concerns, and structural barriers. Many specialists remain unsure about the net benefit of these drugs and worry about amyloid-related imaging abnormalities; only a small fraction of the roughly 23,000 clinicians capable of treating Alzheimer’s disease have actually prescribed them; and system level obstacles—such as inconsistent payer coverage for diagnostics, like covering positron emission tomography (PET) scans but not tracers, occasional treatment denials, and health system reluctance to invest in an oncology like infrastructure—create a “doom loop” that suppresses demand and discourages capacity building. He added that primary care clinicians rarely detect mild cognitive impairment, in part because of limited training, which prevents most patients from ever reaching the point where precision neurodegeneration therapies might be considered.

Mattke closed by arguing that the scientific momentum, particularly the shift toward biologically grounded disease definitions and

biomarker-enabled targeting, will only matter if the workforce and care infrastructure can keep pace. He noted that neurodegenerative diseases are far too common to be managed by within a small specialist community, especially since many treatment-oriented neurologists have historically gravitated toward areas like multiple sclerosis (MS) and stroke rather than neurodegeneration. He emphasized that specialist capacity must expand rapidly because scientific progress is outstripping the system's ability to deliver emerging therapies, and he urged the field to develop new care models that can extend scarce expertise rather than being solely reliant on growing the workforce.

Korf reflected that the situation Mattke described was “sobering” and questioned why the difficulties had not been anticipated. He pointed out that the rollout of any new therapy typically involves extensive education of the clinical community and deliberate efforts to ready the system for implementation. In this instance, he observed, that process appears either to have been absent or insufficiently effective. Mattke stated that many in the field had given up on the amyloid hypothesis and doubted disease-modifying treatments would ever succeed. As a result, there was no existing “treatment ecosystem” to build on. He contrasted this with immunology, where clinicians already used steroids, methotrexate, and other treatments, allowing biologics to be adopted gradually. In Alzheimer's disease, he said, there was no comparable foundation, only symptomatic treatments, so the system could not evolve organically. Mattke concluded that without a clear business case—a financial rationale for investing in new diagnostic and treatment infrastructure—health systems did not commit the resources required for implementation.

Ertekin-Taner added that other specialties, such as autoimmune multiple sclerosis, already have established infrastructures with advanced practice providers, fellows, and specialized nursing staff. Because memory clinics lack the staffing and structural support seen in other fields, placing the full burden of a population-level disease on a small group of subspecialists is, as she put it, “doomed for failure.” She asked what infrastructure, education, and personnel are needed to implement new therapies effectively and how some of those responsibilities could be transferred to primary care clinics or other systems. Korf shared that in building the infrastructure, a lot of groundwork must be laid before implementation can be successful. Mattke agreed that precision medicine has historically focused on rare diseases, such as amyotrophic lateral sclerosis (ALS) or spinal muscular atrophy, being managed by specialists and subspecialists. He added that this specialist-centric model breaks down for population-level diseases, just as diabetes cannot be managed solely in endocrinology clinics nor heart failure exclusively in cardiac centers.

ADDRESSING OPERATIONAL BOTTLENECKS IN PRECISION CARE DELIVERY

Building on Mattke's critique of system-level readiness, Nita Limdi, the Dr. Ray L. Watts Heersink Endowed chair and professor of Neurology and Associate Dean for Genomic Medicine, director of the Translational Pharmacogenomics Program, associate director of the Hugh Kaul Precision Medicine Institute at University of Alabama at Birmingham (UAB), examined the practical bottlenecks—laboratory, workflow, ethical, and reimbursement—that must be solved to deliver precision care reliably and at scale.

She first illustrated these operational barriers through apolipoprotein E (APOE) gene genotyping, showing how efforts to integrate this seemingly simple test into routine care exposed gaps in laboratory capacity, workflow, counseling, and reimbursement—gaps that matter because APOE genotyping helps identify patients at higher risk of side effects from Alzheimer's treatments that clear amyloid, the protein that builds up in the brain in Alzheimer's disease. Limdi explained that APOE, now guides treatment decisions because people who carry certain versions of the gene, especially the $\epsilon 4$ form, have a higher chance of developing amyloid-related imaging abnormalities or amyloid-related imaging abnormalities (ARIA) risk, the brain swelling or small brain bleeds that can occur with amyloid-clearing Alzheimer's treatments. She added that clinicians now combine evidence of amyloid buildup—obtained through cerebrospinal fluid testing, positron emission tomography imaging, and baseline magnetic resonance imaging (MRI) scans—with APOE genotyping results to guide shared decisions about safety risks, expected benefits, and the level of monitoring required. She emphasized the operational challenges of implementing this model at scale: laboratories must return results quickly; MRI capacity must accommodate more frequent surveillance for $\epsilon 4$ allele carriers; and genetic counseling must help patients and families navigate the ethical complexities of learning lifelong, inherited risk information. She also highlighted a reimbursement gap, although payers cover anti-amyloid therapies, they do not cover the APOE testing required to use them, leaving manufacturers to provide testing at no cost. At UAB, she leads a large pharmacogenomics and chronic disease genomics program that spans from discovery to delivery. In-house APOE testing has a five-to-seven-day turnaround, she noted, but roughly half of patients are tested outside the system because telemedicine and long referral pathways shift early workup. As health systems consolidate and anti-amyloid use expands beyond academic centers, she argued, these logistical and ethical issues will become increasingly central to scaling precision medicine approaches.

Limdi then shifted from safety to efficacy by describing how testing for cytochrome P450 2C19 (CYP2C19)—a liver enzyme that affects how people respond to antiplatelet therapy and demonstrate how precision medicine works in a learning health system. She noted that the approach illustrates the full translational cycle: discovery of a biologically meaningful variant, evaluation of its clinical impact in real-world care, assessment of cost effectiveness, and eventual incorporation into reimbursement policy and professional guidelines. She traced the story back to coronary stenting, where most patients receive aspirin plus clopidogrel and roughly 70 percent achieve adequate platelet inhibition. The pivotal 2009 discovery showed that CYP2C19 loss of function variants (Shuldiner et al., 2009) impair conversion of clopidogrel to its active metabolite, leading to insufficient platelet inhibition and higher rates of stent thrombosis and major cardiovascular events. Because many antiplatelet trials had banked DNA, investigators were able to return to double blinded, adjudicated datasets and consistently demonstrate increased cardiovascular risk among loss of function carriers (Mega et al., 2010).

Limdi explained that the next step in optimizing efficacy is identifying who should receive CYP2C19-guided antiplatelet therapy, noting that consensus has settled on testing patients with acute coronary syndrome, where genotype guided treatment can reduce coronary events by roughly 30 percent (Pereira et al., 2024). She described how UAB used this evidence to launch its first clinical pharmacogenetics program by building in-house laboratory platforms, testing patients directly in the cardiac catheterization laboratory, embedding genotype triggered decision support in the electronic health record (EHR), and linking implementation to a research protocol that followed all patients for a year (Harada et al., 2017). She emphasized that emerging point-of-care technology, such as buccal swab CYP2C19 testing with a 60-minute turnaround, now enables treatment decisions within the clinical workflow and noted that UAB's health system supported these efforts as part of a learning health system approach (Harada et al., 2017).

Limdi explained that her collaborative efforts allowed investigators across large genomic consortia to pool one year outcome data across institutions, creating the statistical power needed to quantify the clinical impact of CYP2C19-guided antiplatelet therapy. Across these combined cohorts, about 30 percent of patients carried a loss of function allele and switching those individuals to an alternative antiplatelet agent produced a 50 percent reduction in major adverse cardiovascular events—including myocardial infarction, stroke, stent thrombosis, and cardiovascular mortality—representing a twofold risk reduction (Cavallari et al., 2018). The volume of harmonized clinical events also enabled a national level cost effectiveness analysis, which demonstrated that genotype-guided therapy was the most cost-effective strategy (Limdi et al., 2020). Limdi noted that these findings

ultimately informed the development of professional guidelines (Lee et al., 2022).

Limdi noted that regulatory and professional guidance has been slow to align with the evidence for CYP2C19-guided antiplatelet therapy. She pointed out that although the FDA issued a black box warning for clopidogrel in 2013, it took until 2024 for the American Heart Association (Pereira et al., 2024) to recommend testing in acute coronary syndrome, and guidance for ischemic stroke remains equivocal because of limited data. She emphasized that the strength and rigor of the collaborative evidence base ultimately enabled consortia to work directly with Centers for Medicare and Medicaid Services (CMS) to secure reimbursement for CYP2C19 testing.

Limdi noted that emerging evidence—particularly the CHANCE 2 (Clopidogrel with Aspirin in High-risk Patients with Acute Non-disabling Cerebrovascular Events) trial in China, where about 45 percent of patients carry CYP2C19 loss of function alleles—shows that switching ischemic stroke patients from clopidogrel to ticagrelor can reduce recurrent strokes, (Wang et al., 2021) prompting UAB to extend its pharmacogenetic platform to stroke care. She explained that the operational model works well in principle, as patients can be identified, tested, and receive results within two to four hours with real-time decision support. The challenge, she emphasized, is that stroke patients are dispersed across multiple services and physical locations, unlike acute coronary syndrome patients who all pass through the cardiac catheterization lab. As health systems increasingly triage milder strokes to outlying hospitals rather than tertiary centers, she argued that the next task is scaling pharmacogenetic testing across an entire, distributed health system network, including multiple emergency departments and community hospitals.

Limdi used pharmacogenetic panel-guided psychotropic prescribing as an example of how multi-gene prediction can shorten the trial-and-error process in depression care (Hirschtritt et al., 2016). She noted that strong evidence supports using CYP2D6 and CYP2C19 to guide SSRI selection and that psychiatry now has actionable guidance for roughly 44 drug-gene pairs across Canadian, Dutch, U.S., and FDA frameworks. The primary challenge stems from misaligned policies: testing is rarely performed on inpatients, who need it most, because inpatient diagnostics fall under a low-margin, flat-fee Diagnosis-Related Group (DRG) payment. Instead, patients are tested in ambulatory settings, where the testing (technical fee) can be billed separately for reimbursement. Limdi explained that UAB has addressed this gap by funding inpatient pharmacogenetic testing through the health system and a School of Medicine-funded initiative so that hospitalized patients—those with the highest clinical need—can receive timely, genotype informed treatment.

Limdi concluded by emphasizing that successful precision medicine implementation requires clarity about purpose—defining effect sizes, risk thresholds, clinical impact, operational requirements, ethical considerations, and cost. She noted that across health care innovations, translation from discovery to routine practice averages 17 years, (Rubin, 2023) not because the underlying biology is flawed but because delivery systems are often unprepared, especially for heterogeneous, chronic, and resource intensive diseases (see Figure 7-3; [Rubin, 2023]). In her view, the central question is not simply whether an intervention works but whether a system can be built to make it work equitably at scale. She argued that translation succeeds only when strong biology, meaningful clinical benefit, operationally capable delivery systems, and sustainable payment models align; if any one of these elements fails, even the most sophisticated science will not reach patients.

Eric Peterson, workshop attendee, expressed particular interest in Limdi's brief discussion of polygenic statements, arguing this is a major barrier to translating advances into clinical practice, especially in rural areas. Limdi explained that polygenic risk scores are increasingly offered

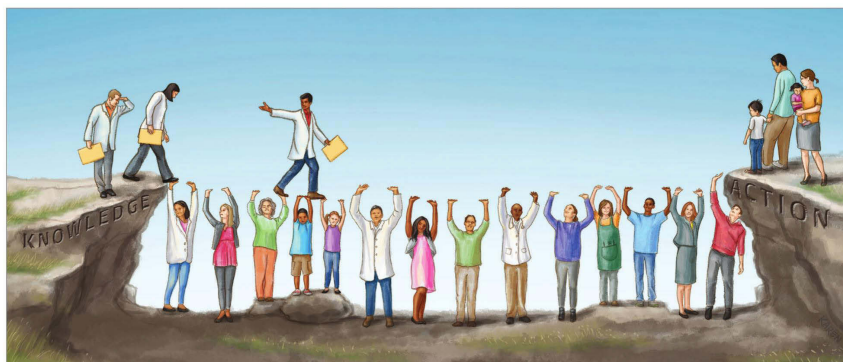


FIGURE 7-3 The knowledge-to-action gap in translating evidence to practice.

NOTE: This illustration depicts the persistent delay between scientific discovery and clinical implementation. On the left, researchers stand on the knowledge side, representing the generation of evidence. On the right, clinicians and patients stand on the action side, symbolizing real-world practice. Between them lies a wide gap bridged by a diverse group of individuals working collaboratively to translate findings into care. The image highlights that, on average, it takes 17 years for evidence to change clinical practice, underscoring the need for more efficient pathways to move validated knowledge into actionable health improvements.

SOURCE: Presented by Nita Limdi, March 5, 2026; Rubin et al., 2023. Reproduced with permission from JAMA Network. Copyright © 2023, American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

by direct-to-consumer companies, but they remain probabilistic and lack clear thresholds for defining “high risk.” She described her work with the eMERGE consortium, which developed and validated polygenic scores for ten conditions across four ancestral groups and enrolled 24,000 participants. She explained that the consortium is now studying how providers and patients act on these results and whether they lead to new diagnoses or treatment changes. She emphasized that health systems are not yet equipped to integrate these scores dynamically since most are delivered as static PDFs, and clinicians lack tools that update risk based on current blood pressure, cholesterol, or other clinical data.

REIMBURSEMENT BARRIERS THAT UNDERMINE SCALED PRECISION CARE

Carras asked what must change when reimbursement systems incentivize delaying genetic testing for psychiatric inpatients, precisely at times when the bar for testing should be lowered. Limdi clarified that the issue is not physician reluctance but the structure of payment models. She explained that inpatient care is reimbursed under a fixed diagnoses-related group (DRG) amount, meaning hospitals absorb the cost of genetic tests performed during admission. Outpatient testing, by contrast, is reimbursed per test. She noted that her team circumvents this by offering inpatient testing free of charge, but this is not sustainable for most systems. Carras described “perverse incentives” as economic features of payment systems that encourage delaying genetic testing for psychiatric inpatients, even when timely testing could inform care and prevent harm. She emphasized that this is not only a reimbursement issue but also an ethical one, asking what changes to payment structures would be needed to ensure that precision testing is available—particularly for patients receiving involuntary treatment, where preventing potential harm is especially important. Mattke answered that DRGs are not fixed; CMS could adjust them to include the cost of genetic testing as part of standard care. While hospitals might still choose not to use the funds, the financial barrier would at least be removed.

PATIENT-CENTERED MEASUREMENT SYSTEMS FOR SCALED PRECISION CARE

The conversation shifted toward the systems required to measure what truly matters to patients at scale. A participant asked what is known about how patients with early-stage dementia perceive the difficulties in their lives and whether the patient’s priorities of what they find helpful align with researchers’ high-value therapeutics. Ertekin-Taner called this question “critically important” and still largely unanswered. She explained that

while anti-amyloid therapies clearly reduce amyloid and slow measurable cognitive decline, researchers do not yet know what these changes mean for daily life—for example, whether patients can “keep their driver’s license a little longer” or “get their books in order.” She also emphasized that meaningful benefit may vary from person to person. She noted that ongoing studies aim to capture patient-centered outcomes, but alignment between scientific priorities and lived experience remains uncertain.

Wittenberg asked how prescribers can better respect patient experience. Carras argued that patient-reported side effects must be treated as meaningful biological data, not dismissed as expected reactions. She shared examples where side effects signaled important underlying mechanisms, such as persistent nausea reflecting a reduced ability to metabolize, and emphasized that clinicians must “peel away judgment” and treat patient observations with the same weight as laboratory measures. Manji agreed, noting that psychiatric conditions arise from complex interactions among genes, environment, cellular biology, and circuits. To make biological findings clinically meaningful, the field must invest in deep clinical phenotyping—far beyond DSM categories. He highlighted the importance of incorporating lived experience into measurement strategies, including identifying treatment areas that matter most to patients, such as motivation or cognitive functioning. He noted that many patients report their mood symptoms improve with treatment while cognitive or motivational deficits persist, and these areas must be measured and targeted.

Bustamante asked how well current systems integrate affective and cognitive symptoms, given that Carras’s lived experience involved both mood changes and cognitive side effects requiring out-of-pocket treatment. Carras explained that diagnosis still dominates clinical decision making. Because she carries a mood disorder diagnosis, her treatment focuses on mood even when cognitive symptoms are more disabling. She described times when medication doses improved mood but severely impaired communication or cognition—tradeoffs clinicians were reluctant to address. Manji agreed that the field has not done enough to integrate cognitive and affective areas. He noted that regulatory frameworks often constrain what companies can measure or target, even when patients identify other areas as more important. He emphasized that interventions may include medications, psychosocial approaches, or digital tools, but regulatory acceptance will determine whether these domains can be formally targeted. He also highlighted the value of off-label prescribing as a flexible tool that has benefited many patients.

DIGITAL MONITORING AND ETHICAL GOVERNANCE SYSTEMS

Participants also examined how digital tools can support precision care at scale and what governance systems are needed to ensure these tools

enhance, rather than undermine, patient autonomy. William Potter, former senior advisor at the National Institute of Mental Health, drew attention to a practical challenge in digital monitoring, asking whether a patient's decision to stop using a symptom-tracking device should be interpreted as a warning sign and what, if anything, clinicians are obligated to do to intervene. He also asked whether any groups, such as Patient-Centered Outcomes Research Institute, are formally testing the impact of digital monitoring with feedback. Manji agreed that digital tools—sensors, smartphones, voice and activity measures—can detect relapse earlier than clinicians. He described prior work showing that speech and sleep changes can signal worsening depression. However, he stressed that digital signals must be interpreted in partnership with the patient. Before monitoring begins, patients should specify whether they want to be contacted, who should be notified, and under what circumstances. He cautioned that digital alerts are only signals; clinicians must contextualize them through conversation. He also noted that large longitudinal initiatives in the UK are testing integrated omics, digital, and clinical phenotyping approaches. Carras emphasized the risks of “just in time” interventions that resemble surveillance. She argued that digital monitoring is most valuable for guiding treatment over time, not triggering immediate responses to every signal. She shared her own experience using a wearable device to understand her symptoms, noting that patients may willingly share data when it helps them make sense of their own health. She underscored the importance of patient driven data collection and personalized applications that reflect what matters to individuals.

8

Driving Ecosystem Investment in Scalable Precision Medicine Infrastructure

Highlights

- Precision mental health requires shifting from symptom-based categories to a living, biologically grounded diagnostic framework that evolves with new data and global alignment (Kas).
- Building integrated data and artificial intelligence (AI) infrastructures—linking research cohorts, clinical pathways, and national-scale data systems—creates the technical backbone needed to operationalize precision mental health in real-world care (Glatard).
- Public–private partnerships can break long-standing research and development (R&D) silos by sharing risks, standardizing methods, co-creating with people with lived experience, and building re-contactable longitudinal cohorts that accelerate biomarker discovery and clinical translation (Tillmann).
- Objective, scalable, multimodal measurement tools are essential for precision psychiatry, enabling rapid detection of clinical change, treatment matching, and real-world deployment through tightly integrated translational and industry partnerships (Mohatt).
- Sustainable progress in precision neuroscience depends on federated data infrastructures, ethical governance, and durable cross-sector collaborations that ensure shared platforms remain accessible, secure, and clinically impactful over time (Kas, Glatard, Tillmann, Mohatt).

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Magali Haas, the founder and board chair of Cohen Veterans Bioscience and the chief medical officer at Psilera, opened the session by noting that the Neuroscience Forum has returned to the topic of precision medicine many times over the past two decades, and the cumulative progress, while sometimes difficult to see in the moment, has been substantial. She emphasized, however, that advances have been concentrated in a limited number of disease areas, despite the more than 600 disorders of the brain. With proof-of-concept now established in both neurological and psychiatric conditions, she argued that the central question is how to scale and accelerate progress across the broader landscape.

Haas highlighted that operationalizing precision medicine will require coordinated movement across multiple levers, including infrastructure, policy, and—critically—sustained public and private investment. She pointed to the need for attention to public health, regulatory pathways, reimbursement, and other system-level factors that determine whether precision approaches can be adopted at scale. She introduced a workshop session that would explore strategies to drive these levers globally, featuring perspectives on roadmaps, alternative clinical-research models, novel funding mechanisms, and emerging approaches to consumer engagement.

As part of this discussion, Elisabetta Vaudano, principal scientific manager at the Innovative Health Initiative (IHI), provided an overview of the IHI (see Box 8-1).

BOX 8-1 **The Innovative Health Initiative**

Innovative Health Initiative (IHI),^a is a cross-sector European public–private partnership that brings together public investment and in-kind contributions from industry active in the healthcare sector, e.g. pharma, diagnostics, imaging, and other health-sector partners. Each IHI project functions as a small ecosystem in which innovators, regulators, health-technology assessment bodies, clinicians, and people with lived experience work collaboratively rather than through traditional sequential models. IHI has built a substantial portfolio in brain-related conditions, spanning neurodegeneration and mental health, and has supported the development of several enabling platforms, including the European Platform for Neurodegenerative Disease as the regional branch of the Alzheimer’s Disease Data Initiative for data and sample sharing. Ongoing and emerging initiatives include efforts to strengthen pediatric trials and improve inclusiveness in clinical research. An IHI precision-medicine platform is currently under evaluation.

^a For more information, see: <https://www.ih.europa.eu/>.
SOURCE: Presented by Elisabetta Vaudano on March 5, 2026.

A PRECISION PSYCHIATRY ROADMAP FOR SCALABLE, BIOLOGY-INFORMED INFRASTRUCTURE

Martien Kas, a professor of behavior and neuroscience at the Groningen Institute for Evolutionary Life Science at the University of Groningen in the Netherlands and former president of the European College of Neuropsychopharmacology (ECNP), explained that the ECNP's precision psychiatry roadmap, developed at its New Frontiers meeting two years ago, reflects a consensus that mental health diagnosis must shift from symptom based categories to an evolving, biology-informed framework (Kas et al., 2025b). He described his collaboration with experts from academia, professional societies, industry, and regulators to outline how such a framework should function, emphasizing that rapid scientific advances require a structure capable of continuously integrating new data and emerging technologies (Kas et al., 2025b). Kas noted that implementing this approach depends on three elements: (1) global alignment on principles and procedures; (2) consensus on predictive validity of emerging data, and (3) operationalization of an iterative framework that links research, clinical practice, and stakeholder engagement (Figure 8-1; Kas et al., 2025b). In his view, progress will require coordinated movement from improved biological understanding through professional society acceptance toward ultimately achieving precision diagnostics and treatments.

Kas explained that the next phase of the precision psychiatry roadmap involves detailing the steps needed for global alignment on principles and procedures. He noted that although the group initially aimed for a five-year plan, the experience in Alzheimer's disease, where similar work took more than 15 years, suggests a longer horizon is realistic (Kas et al., 2025b). The roadmap outlines critical early actions including sustained engagement with stakeholders, including funders and partner organizations; development and harmonization of data platforms to support biological discovery; consensus on quantitative biological measures; and subsequent validation of biomarkers and identification of emerging biotypes. Kas emphasized that these steps must be sequenced across a timeline that brings the correct parts of the ecosystem into the process at the right moment. He highlighted early progress, including outreach to major professional organizations, such as the American College of Neuropsychopharmacology (ACNP) and European Psychiatric Association (EPA), and joint efforts to develop position papers that articulate shared principles for a biology-informed diagnostic framework (Kas et al., 2025b).

Kas emphasized that sustained support from funding agencies is essential. He noted that the Wellcome Trust has recognized the importance of systematically mapping biomarkers and is partnering with ECNP to inventory existing and emerging measures and convene stakeholders to build

consensus papers (Arango et al., 2026; Cevoli et al.; 2026, Khalsa, 2026). He also highlighted the new IHI call focused on developing a platform for transdiagnostic stratification of brain dysfunction, aimed at strengthening mechanistic understanding, improving patient outcomes, reducing stigma, and increasing health system efficiency. Kas underscored that these initiatives build on the model established by the Psychiatric Ratings using Intermediate Stratified Markers (PRISM) and PRISM 2 public-private partnerships, which demonstrate the importance of funding pre-competitive public-private partnerships.

Kas noted that findings from the PRISM and PRISM 2 programs demonstrate how moving beyond traditional diagnostic categories can reveal shared biological mechanisms across disorders (Sarris et al., 2022). He highlighted that social dysfunction, a core feature of many brain disorders, maps onto connectivity within a specific brain network and shows a transdiagnostic biological signature. Importantly, these results were not only observed in the initial PRISM cohort but were replicated and extended across major depression, Alzheimer's disease, and schizophrenia, underscoring the value of identifying mechanistic substrates that cut across diagnostic boundaries (Braak et al., 2026). He emphasized that such work is essential for advancing knowledge about the underlying mechanisms of brain functions in mental health conditions.

Kas reported that last year's ECNP meeting converged on several priorities essential for advancing a biology-informed framework in precision psychiatry, including standardization, collaboration, clinical implementation, digital innovation, long term planning, and sustained engagement of people with lived experience (Kas et al., 2026). He noted that ECNP has launched round table initiatives with industry and network scientists to accelerate biomarker development and pursue regulatory pathways, including current work to validate a digital endpoint for social functioning.

He emphasized that the framework must ultimately be operationalized; biological insights need to be incorporated into diagnostic classification systems and treatment guidelines, and health care delivery models must be prepared to implement precision diagnostics and therapeutics (Kas et al., 2025). He noted that ECNP's DSM working groups have since released five white papers, identifying domains such as biomarkers, biological factors, and diagnostic features, and committing to a living document model that can integrate emerging science in real time (APA, 2026; Ongur et al., 2026).

FROM FRAMEWORK TO IMPLEMENTATION: CLOSING THE LOOP BETWEEN CLINICAL DATA, AI RESEARCH, AND CARE

Building on Kas's call for a living, biologically informed framework, Tristan Glatard, a scientific director at the Krembil Centre for

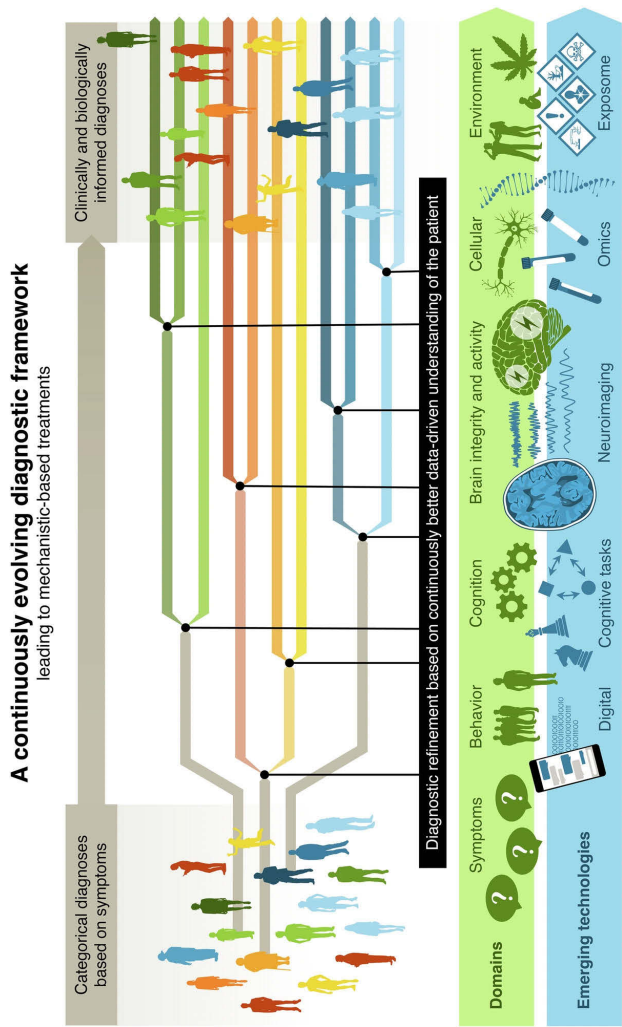


FIGURE 8-1 Proposed framework for precision psychiatry.

NOTE: This figure outlines the vision for a continuously advancing framework that integrates scientific and technological progress to achieve precision psychiatry. The transition from syndromic to biologically informed diagnosis requires coordinated evolution across the mental health ecosystem. Early progress will come from linking symptoms and behaviors to brain circuits and systems, supported by emerging digital technologies that enable large-scale data collection and interpretation. As these foundations mature, the integration of omics data and environmental interactions will unlock a more complete understanding of disease onset, progression, and therapeutic targets.

SOURCE: Presented by Martien Kas, Valentina Mantua, Hugh Marston; Kas et al., 2025b. CC BY NC-ND 4.0.

Neuroinformatics at the Centre for Addiction and Mental Health (CAMH) and BMO chair in Artificial Intelligence for Mental Health, described the data and AI infrastructure required to translate that vision into practice. He outlined how the Krembil Centre is developing a data and AI ecosystem to support precision mental health, using a continuous cycle that moves from clinical data to AI research and back into clinical care. He emphasized that the system is not yet fully connected but major components are now in place.

He explained that CAMH has invested heavily over the past five to six years in data infrastructure, including the BrainHealth Databank,¹ an institutional repository that now contains data from 66 studies and more than 17,000 research participants, spanning MRI, genetics, and clinical assessments. Most of the platform is built on open-source software, and significant effort has gone into harmonized consent language, secondary use protocols, and alignment with the Research Ethics Board. He noted that the databank is already being reused by external partners, including the Cardio-Neuro-Mind Data Platform² in Ottawa and a pan-Canadian youth data platform.

Clinically, he explained, the same infrastructure now supports more than 40 digital care pathways, covering data from more than 50,000 patients. He shared that the main outcomes are dashboards that clinicians can use to understand where patients fall within clinical distributions. Glatard explained that the long-term goal is to enrich these dashboards with predictive tools for risk and treatment response once models become reliable.

He highlighted a major Canadian effort, VITAL,³ and noted that the initiative's long-term ambition is to build the world's largest linked clinical and imaging data repository, integrating data from more than 160 hospitals across three Canadian provinces. Glatard explained that the effort is led by Unity Health Toronto's Amol Verma and Fahad Razak and is designed as a national-scale extension of Gemini, Ontario's established hospital data-sharing infrastructure. The goal, he said, is to replicate Gemini's success and expand it across Canada to create a unified platform capable of supporting large-scale analytics and research.

Glatard described how the emerging national data platform enables two broad classes of AI applications. On the predictive-modeling side, teams are developing models for hospital violence-risk prediction, clinic

¹ For more information about the BrainHealth Databank, see: <https://www.camh.ca/en/science-and-research/discovery-fund/brainhealth-databank> (accessed July 20, 2026).

² For more information about the Cardio-Neuro-Mind Data Platform, see: <https://cnmdp.atlassian.net/wiki/spaces/CNMDP/overview?homepageId=33329>

³ For more information about the VITAL collaborative health platform, see: <https://gemini.medicine.ca/VITAL/> (accessed June 14, 2026).

readmission risk, and treatment-response prediction. He highlighted ongoing work by Fiona Coutts on antipsychotic response and by Daniel Felsky and colleagues on late-life depression treatment response (Heinz et al., 2025).

On the conversational-agent side, he noted rapid growth in chatbot-based mental health tools designed to support talking therapies (Heinz et al., 2025; Mahmood et al., 2025). He pointed to the first randomized trial of a generative-AI mental-health chatbot, published in the *New England Journal of Medicine* in mid-2025, as evidence of the accelerating interest in AI-enabled psychotherapy supports (Heinz et al., 2025).

Glatard noted growing interest in AI-enabled clinical trials and highlighted two examples. The first was CAMH's work on conversational agents, including a chatbot that delivers motivational interviewing for smoking cessation with the goal of expanding access to affordable, 24/7 support (Mahmood et al., 2025). He explained that the system was built using off-the-shelf large language models but incorporates multiple safety layers that monitor interactions and flag responses that deviate from established guardrails. Glatard emphasized that while building such systems has become relatively straightforward from a technical perspective, rigorous evaluation and validation remain the primary bottlenecks. He added that Osnat Melamed and Laura Sikstrom recently secured funding to move this chatbot into a clinical trial focused specifically on women, given sex-based differences in smoking cessation drivers. He then described a second example, the Biotype-assigned Augmentation Approach in Resistant Late-Life Depression (BAARD) trial,⁴ a National Institutes of Health (NIH)-funded study scheduled to begin enrollment in fall 2026. The model, based on eXtreme gradient boosting, a high-performance gradient-boosted decision-tree algorithm widely used in biomedical prediction tasks, aims to predict treatment response in late-life treatment-resistant depression. Current results indicate that it can reliably forecast outcomes for antidepressants bupropion and aripiprazole augmentation strategies, with or without neuroimaging and cognitive profiling inputs. He emphasized that the central challenge for AI in clinical settings is rigorous evaluation and argued that the emerging data infrastructure should be used to strengthen both clinical evaluation through trials and technical evaluation through reliable, reproducible model performance assessments. Glatard highlighted that technical evaluation remains one of the most challenging aspects of AI development, noting pitfalls in data linkage, metric selection, and confounds. To address these issues, his team is building the Brain Health Data Challenge Platform, a Kaggle-platform-like environment tailored to mental-health applications.

⁴ For more information, see: https://reporter.nih.gov/search/Ym09DhMfd0-tUjFN97zw_w/project-details/10954667 (accessed June 14, 2026).

The platform will draw on the BrainHealth Databank to define disease-specific AI problems and invite data scientists worldwide to submit models for standardized, reproducible evaluation and leaderboard ranking.

He added that clinical evaluation is the second essential pillar. CAMH is expanding its infrastructure to support AI-enabled clinical trials—both internal and external—by integrating additional data sources, linking to the EHR, strengthening privacy and de-identification processes, and enhancing data-modeling and harmonization capabilities to better support trial operations.

Glatard closed by underscoring that CAMH's AI work is deliberately grounded in patient and family engagement, supported by formal structures that range from informing participants to empowering them in key decisions—an effort led by Nelson Shen (Santisteban et al., 2025; Shen et al., 2025; Yu et al., 2023). He then summarized the core ingredients needed to advance precision mental health through AI: integrate clinical and research data; establish reliable technical and clinical evaluation pathways; and embed people with lived experience throughout the process. He added that the team is also exploring federated learning approaches to enable collaboration with external partners while protecting privacy, noting that this will be an important area for future development.

BREAKING SILOS THROUGH PUBLIC PRIVATE PARTNERSHIPS

Where Glatard demonstrates the technical backbone required for precision neuroscience, Julian Tillmann turns to the organizational engine of public-private partnerships. He began by noting a striking paradox: while scientific and technological progress has advanced at extraordinary speed (citing Eroom's Law, explaining that DNA sequencing costs have dropped even faster than Moore's Law would predict), these gains have not translated into more productive drug development (Ringel et al., 2020; Scannell et al., 2012). Instead, R&D productivity has steadily declined since the 1950s (Scannell et al., 2012). This disconnect, he argued, underscores why precision approaches and public-private partnerships are urgently needed.

Tillmann emphasized that public-private partnerships are essential because they tackle innovation challenges no single actor can solve alone, enabling stakeholders to share risks and benefits across multiple levels of discovery and translation. He noted that public-private partnerships make it possible to run large, deeply phenotyped longitudinal cohorts, accelerate biomarker development through iterative testing of diverse candidate markers and technologies, and focus resources on foundational biological breakthroughs rather than correlational findings. Because these activities require years of sustained effort, public-private partnerships provide the

scale and coordination needed to generate durable data assets and complex analytical pipelines.

He added that public–private partnerships also facilitate regulatory engagement, helping move emerging tools toward qualification, and ensure that people with lived experience shape research priorities and outcome measures. By developing standardized frameworks and models, public–private partnerships lower barriers to entry for new contributors and help build multidisciplinary expertise and networks of centers of excellence. Taken together, Tillmann argued, these features create a “rising tide” effect—an ecosystem in which shared infrastructure and aligned incentives lift the entire field.

Tillmann described how the AIMS-2-TRIALS,⁵ an IHI funded consortium, offers a pragmatic example of how public–private partnerships can accelerate precision neuroscience and overcome barriers that no single institution can solve alone. The AIMS-2-TRIALS were designed to apply a precision health approach to autism with the goal of improving life outcomes for autistic people. He highlighted three areas where the consortium’s impact has been strongest. First, co-creation with people with lived experience has been central (Loth et al., 2014; Oakley et al., 2022). Advocates and individuals living with autism were involved throughout the consortium’s development, helping shape the research agenda and identify what outcomes and measures are most meaningful. Tillmann noted that this partnership has also supported translation of findings into actionable policy, ensuring the work has real-world impact. Second, he emphasized the consortium’s data and analytics infrastructure. AIMS-2-TRIALS assembled a deeply characterized data lake spanning multiple cohorts and then focused on ensuring its long-term value. The dataset has now been integrated into the EU Data Space, making it accessible for future analysis and establishing a durable legacy beyond the initial project period. Tillmann reported that AIMS-2-TRIALS developed a biomarker research platform that supported European Medicines Agency (EMA) interactions, contributed to the qualification of a biomarker, and ensured that all findings—including negative results—were published in peer reviewed journals to avoid fragmentation and promote transparency across the field (Loth et al., 2014; Oakley et al., 2022). He added that the consortium also strengthened trial capacity by establishing a clinical trial network with recontact capabilities and by conducting several Phase 2 proof of concept studies, positioning the community for more efficient and scalable precision health trials in autism.

Tillmann emphasized that scaling precision health infrastructure requires building biological understanding, new endpoints, and capacity for

⁵ For more information about the AIMS-2-TRIALS, see: <https://www.ih.europa.eu/projects-results/project-factsheets/aims-2-trials> (accessed June 14, 2026).

clinical trial implementation in parallel (Ashwood et al. 2015; Bloomfield et al., 2024). He underscored the importance of assembling deeply phenotyped cohorts with consent for recontact, enabling rapid follow-up when new targets become tractable, and supporting efficient trial recruitment. He noted that biomarker validation pipelines must be designed with an end-to-end perspective, spanning discovery through clinical trial deployment.

Tillmann highlighted the consortium's focus on sustainable data sharing, ensuring that its datasets legacy persist as long-term resources rather than one-off project outputs (Loth et al., 2017). Turning to broader impacts, he argued that public-private partnerships have proven to be a critical lever for precision neuroscience by de-risking innovation through shared platforms, lowering barriers to entry, and supporting standardization and regulatory engagement. He also pointed to the creation of re-contactable, longitudinal cohorts as a major achievement.

Remaining challenges, he noted, include moving from siloed data sharing models toward federated infrastructures, achieving global alignment across regulatory and geographic contexts, and developing mechanisms to ensure that shared assets become durable, sustainable infrastructure capable of driving long-term health system change.

ACCELERATING PRECISION MEASUREMENT AND TRANSLATION: AN ARPA-H EXAMPLE

Extending Tillmann's argument that shared platforms and partnerships are essential, Nathaniel Mohatt, a program manager in the Proactive Health Office at the Advanced Research Projects Agency for Health (ARPA-H), pushes the narrative toward acceleration. Mohatt opened by emphasizing that his motivation for this work is deeply personal, shaped by the loss of multiple family members and friends to addiction and suicide. That experience, he noted, drives his commitment to finding solutions that can change how health care is delivered today, not years from now, and underscoring that "people out there need these solutions now."

Mohatt explained that ARPA-H's mission is to change the course of human health, pursuing breakthroughs with the same transformative impact that Defense Advanced Research Projects Agency (DARPA) achieved through innovations such as the internet, global positioning systems (GPS), and early artificial intelligence. He noted that ARPA-H is intentionally modeled on DARPA's approach—seeking scientific advances that fundamentally reshape what is possible—but with an added imperative that these advances must be translated into practice rapidly, not left to mature over decades. He described the agency as both a disruptor and a time compression engine, designed to take a vision of the future, work at accelerated

speed, and deliver solutions that can be implemented in real-world health care today.

He explained that ARPA-H operates through program managers who propose bold ideas and receive substantial, time-limited funding—often \$30–200 million—to pursue them. Unlike traditional grants, ARPA-H uses actively managed contracts, allowing rapid pivots, redirection, and acceleration when promising results emerge. He stressed the importance of planning from the start for translation into practice, identifying commercial partners, clinical partners, and pathways for real-world deployment.

Mohatt explained that ARPA-H's EVIDENT (Evidence-Based Validation & Innovation for Rapid Therapeutics in Behavioral Health) program⁶ was designed in response to the fundamental barrier in precision neuroscience and psychiatry described in earlier talks; the field lacks predictive, scalable, objective, and standardized measurements, leaving clinicians unable to determine what works, for whom, or when. He noted that this measurement gap contributes directly to delayed or ineffective treatment and, in turn, to rising chronic disease burden (Correll et al., 2017; Gracia-Garcia et al., 2023; Graham et al. 2020; Mannan et al., 2016). EVIDENT focuses specifically on objective measurement. Mohatt described its distinctive approach of treating interventions as perturbations that reveal underlying change. Rather than comparing treatments to determine which is best, the program deploys multiple interventions across multiple disorders and measures multimodal biological, psychological, and social signals to detect what changes when treatment is effective. The goal is to triangulate objective indicators of clinical change, including those that could support continuous passive measurement in daily life and, in-session markers that show whether a therapy is working in real time.

Mohatt noted that ARPA-H is building a shared data repository across all EVIDENT trials and coordinating with related external databases to ensure interoperability. He emphasized that the repository is designed to be different not only because it spans transdiagnostic, multi-trial data but because its common data elements explicitly reflect the biological, psychological, and social dimensions of mental health. Each dimension includes both standardized measures and deep multimodal data, creating a comprehensive structure for future analysis.

He explained that integrating these layers is intended to produce a “Rosetta Stone”-type resource capable of helping the field identify causal biomarkers, improve the predictive performance of mental health models, and support the integration of measurement tools into daily life. Mohatt explained that EVIDENT's core common data elements are intentionally

⁶ For more information about the EVIDENT program, see: <https://arpa-h.gov/explore-funding/initiatives-and-sprints/evident> (accessed June 14, 2026).

minimal, designed to support a diverse set of trials while enabling easy, continuous measurement in daily life. The shared elements include very short patient reported outcome scales, wearable sensor data, and GPS-based mobility measures, which are then complemented by a broader set of study specific data streams contributed by individual projects.

He emphasized that the central question is not simply what data or analytic methods are needed but how to build a data resource that supports sustainable, continually updated discovery. Achieving that, he argued, requires strategic partnerships, including public–private collaborations that ensure these datasets serve a public benefit mission while also being connected to industry so that validated tools can be embedded into clinical practice.

Mohatt noted that EVIDENT’s data resource must be governed in ways that reflect the needs and rights of the people contributing data, emphasizing the importance of nonprofit consumer governance to ensure that data use aligns with what benefits participants now, not decades in the future. He acknowledged that the framework is still being developed but stressed that it is essential for building a resource that supports sustainable, continually updated discovery.

He reminded the workshop participants that EVIDENT is a two-year program aimed at accelerating progress on objective measurement, even if the full solution cannot be achieved within that timeframe. To ensure that breakthroughs can be rapidly tested and translated, the program is also building a network of translation partners. These include additional data partners who can evaluate promising models in independent, large-scale datasets, extending beyond the approximate 10,000 participants in the EVIDENT repository. Mohatt emphasized that if even one research team makes a major breakthrough, the program must have the infrastructure and partnerships in place to quickly determine whether it works as a measurement tool and as a system-level innovation capable of changing how health care is delivered.

Mohatt explained that EVIDENT also requires translation partners embedded in real-world care systems so that promising measurement models can be tested rapidly in two directions: direct to consumer tools that provide actionable continuous health information and clinical practice pipelines that evaluate whether these measures can operate at scale within measurement-based care. He noted that large clinical practice networks are already engaged so that, if a breakthrough emerges, it can be deployed and evaluated quickly.

He emphasized that ARPA-H aims to function as an accelerator alongside the field’s longer horizon of iterative science—taking “home run swings” while ensuring that validated advances move swiftly into practice. To achieve this, the agency is focused on building collaborative structures

for data stewardship, translation networks capable of real-world testing, and an integrated ecosystem that mirrors the DARPA model, where the end user, implementer, and funder are tightly aligned. Mohatt argued that creating this kind of unified ecosystem in health care is essential for moving transformative solutions into practice at the speed patients need.

ECONOMIC AND POLICY DRIVERS OF BRAIN HEALTH INVESTMENT

While Mohatt focused on accelerating the development and translation of precision health tools, participants also emphasized that innovation alone will not be sufficient. Sustained progress will depend on the economic and policy environments that shape investment, adoption, and implementation at scale. Haas asked whether international platforms such as the World Economic Forum, which now emphasize the “brain economy,” could help shift governments and industry toward greater investment in brain health. She noted that even with major funders like IHI and Wellcome Trust, the roadmap described earlier far exceeds current funding levels. She invited Kas and Mohatt to comment on whether economic framing could drive broader investment.

Kas agreed that this framing is powerful, stating that brain health ultimately has economic value and positioning it this way may help attract funding not currently allocated to mental health. He emphasized that solving these problems requires large-scale investment and presenting brain health through a health economic lens is “a clever way forward.” Mohatt noted that while he had not specifically considered the World Economic Forum model, ARPA-H focuses daily on ensuring that its programs produce solutions with demonstrated economic value that attract industry investment. He explained that ARPA-H’s model emphasizes commercialization pathways and identifying companies capable of translating innovations into large-scale clinical practice.

Jamie Heywood added that medicine often asks for funding without demonstrating effectiveness, which can lead to understandable taxpayer skepticism. He argued that self-agency and participant driven research can complement traditional funding. Drawing on his experience founding the ALS Therapy Development Institute, he described how individuals can contribute to research by studying themselves and participating in distributed experiments. He suggested that such innovation could challenge and invigorate academic science.

Rosa Canet-Avilés emphasized that funding challenges fall into two distinct categories: (1) support for discovery research and (2) the separate issues of reimbursement and access required for clinical implementation. In discussing discovery research, she invoked both the Psychiatric Genomics

Consortium and her earlier talk, underscoring that investments to advance the field are already being made, and not only at the federal level.

SUSTAINABLE FUNDING MODELS AND DATA INFRASTRUCTURE FOR PRECISION BRAIN HEALTH

Krainc highlighted a key challenge to the long-term sustainability of precision brain health initiatives. Although clinics manage high patient volumes, precision approaches depend on resource-intensive activities such as biospecimen collection and storage, genomic sequencing, and deep phenotyping. He questioned how these efforts would be financed if insurers do not provide reimbursement. Hyman addressed the research side of the question. He argued that major consortia, such as the Psychiatric Genomics Consortium, continue to invest in large-scale meta-analyses based on shallow phenotyping—including datasets such as 23andMe—that, in his view, offer limited value for advancing precision psychiatry. He recommended reallocating funds toward fewer, deeply phenotyped longitudinal cohorts with biobanking to support future proteomic and molecular analyses. He acknowledged that such reallocation is politically difficult but argued that it is necessary. A participant asked Tillmann whether increasing the use of re-contactable cohorts could build trust, reduce confusion, and even provide therapeutic benefit by maintaining long-term relationships with patients. Tillmann said yes and explained that re-contactable cohorts typically include consent for recontact and information about participant's treatment priorities and needs. This allows researchers to reach out to individuals for studies that align with what they personally care about, making participation a personalized choice. He emphasized that this approach strengthens engagement and should be considered when designing registries and clinical cohorts. He added that public-private partnerships help ensure that patients, families, industry, and researchers remain aligned around shared goals.

Eric Peterson, a workshop participant, asked whether the consortia working with massive multimodal datasets (e.g., genetics, omics, neuroimaging) have strategies to monetize commercial involvement to sustain data resources. Additionally, Peterson asked whether groups are addressing the power and data center limitations emerging in the United States as AI growth outpaces available energy capacity. Tillmann stated that for IHI, data must serve the public good, not monetization. He described a rigorous data access approval pipeline involving people with lived experience to ensure proposals meet ethical and security standards and align with community needs. Peterson expressed concern that relying solely on the government and the goodwill of commercial enterprises is not realistic given the scale of the challenge. Glatard shared that while CAMH is not

currently monetizing data, they are exploring two approaches: (1) synthetic data generation, allowing commercial users to work with modeled data rather than real clinical data and (2) federated learning, enabling external users to train models on hospital hosted data under precise rules and regulations. Mohatt emphasized that while data and results have clear public benefit value, industry must also play a role in sustaining these resources. He described ARPA-H's partnerships with device companies developing scalable multimodal biomarker tools and with large for-profit health care systems that hold extensive behavioral health data. These partnerships allow industry to build products they can commercialize while contributing to the sustainability of shared data resources

SCALING INTEGRATED CLINICAL-RESEARCH ECOSYSTEMS

Building on the closed-loop model described by Mohatt, Haas observed that Glatard has established one of the first truly integrated clinical and research infrastructures outside the U.S. Veterans Administration. She asked whether such a model could be scaled across Canada and other countries and whether broader adoption could create a market for the types of platforms and technologies envisioned by ARPA-H.

Glatard explained that scaling becomes more challenging when crossing institutional boundaries. Within CAMH, data systems are harmonized, but extending data sharing across Ontario introduces questions related to patient identification, governance, and interoperability. He pointed to the national VITAL initiative—under which each province maintains its own data warehouse without a central registry—as an example of the balance required between centralized coordination and decentralized data stewardship. He added that psychiatry has lagged behind other areas of neuroscience in data sharing and identified clinical notes as a major unresolved frontier with significant research potential.

9

Opportunities for Precision Medicine in Neuroscience

Highlights

- Fragmentation across precompetitive initiatives underscores the need for interoperability, shared concepts, and aligned infrastructure to enable a cohesive global ecosystem for neuroscience precision medicine (Fiske, Vaudano).
- Strengthening clinical trial infrastructure, engaging payers early, and leveraging national biobanks for scalable genomics and phenotyping represent critical bottlenecks and opportunities for accelerating therapeutic development (Korf, Marston).
- The field needs flexible, biology-grounded disease frameworks that can evolve as new multimodal data and mechanistic insights emerge (Brady, Fiske, Irizarry).
- Public–private partnerships, broad stakeholder coalitions, and trust building are essential for aligning concepts, sharing data, and sustaining global progress in neuroscience precision medicine (Fiske, Haas, Marston, Vaudano).

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

As the workshop concluded, panelists were invited to reflect on the key themes, challenges, and opportunities highlighted throughout the discussions. As the conversation unfolded, Gayle Wittenberg noted several interconnected themes that had emerged throughout the workshop, including framework building, heterogeneity, precision medicine, implementation challenges, global coordination, and the need for shared infrastructure. Expanding on these themes, Wittenberg argued that the field must rethink disease classification. Existing diagnostic frameworks predate contemporary biological insights, and harmonized data collection across populations could fundamentally reshape disorder boundaries. She emphasized that measurement drives knowledge, and accelerating the generation of informative, mechanistically relevant data is essential for expanding global capacity to test hypotheses and develop effective therapies.

BUILDING A PRECISION NEUROSCIENCE ECOSYSTEM

Wittenberg invited the workshop moderators to reflect on the key takeaways from their respective sessions (see Figure 1-1). Fiske revisited discussions about building disease frameworks, emphasizing the need to organize biological insights, genetics, clinical features, and emerging tools into structured staging systems. He highlighted examples from Parkinson's disease, including the idea of reframing it as a neuronal synuclein disease, which could unify related disorders under a shared biological mechanism. He stressed that frameworks must start somewhere, even if imperfect, but must also remain flexible so new biological discoveries can be layered in over time. Fiske also noted the importance of defining inputs and outputs correctly—if researchers measure the wrong things or measure too infrequently, they risk misunderstanding the biology. Finally, he underscored the need for early regulatory engagement and the massive infrastructure demands required to build deeply phenotyped datasets, citing the 15-year Parkinson's Progression Markers Initiative (PPMI) study as an example. Linda Brady highlighted discussions on embracing heterogeneity, emphasizing that diseases such as Alzheimer's disease, Parkinson's disease, and schizophrenia vary widely across individuals. She underscored the need for longitudinal, multimodal datasets that track people over time using clinical assessments, biological markers, and imaging. Such datasets can help identify where individuals fall along the disease continuum, clarifying when to intervene and how to identify early biological targets. She also highlighted the importance of studying prodromal phases, when biological changes occur before symptoms emerge, as early intervention may improve long-term outcomes. Brady further noted the growing role of AI in integrating multimodal data and predicting disease trajectories and stressed the importance of consortia, data sharing, and

flexible staging frameworks that can incorporate new technologies as they emerge. Michael Irizarry recapped discussions on the role of precision medicine in transforming drug development, pointing to Alzheimer's disease and a form of amyotrophic lateral sclerosis (ALS) as examples where biomarker-guided approaches have led to meaningful therapeutic advances. He emphasized the importance of a clear biological hypothesis, a deep understanding of disease mechanisms, and a structured approach to using biomarkers for patient selection, dose finding, target engagement, and the demonstration of biological and clinical effects. He also noted that regulatory agencies are increasingly incorporating biomarker-based precision strategies into drug labels, reflecting the growing real-world impact of these approaches. Finally, he highlighted the unique challenges in psychiatry, where biological mechanisms remain less well understood and symptoms are highly heterogeneous. Focusing on implementation, Bruce Korf shared several prerequisites for bringing precision medicine into routine clinical practice. He emphasized the need to clearly define the target patient population and ensure that patients are adequately educated and engaged in the process. He also stressed the importance of defining the target clinician population, noting that common conditions, such as Alzheimer's disease, cannot rely solely on specialists for implementation. Effective adoption requires clinical infrastructure, including trained staff and streamlined systems that minimize friction in everyday workflows. He added that alignment with professional practice guidelines can support reimbursement and broader uptake. Finally, he discussed the economic considerations involved, including differences between inpatient and outpatient reimbursement structures, underscoring that these issues must be addressed before implementation begins, not after.

Elisabetta Vaudano emphasized the collaborative foundations needed to advance precision brain health, including public-private partnerships, stakeholder trust, and coordinated infrastructure development. She stressed the importance of building trust across stakeholder groups, particularly when proposing new disease classifications in sensitive areas such as psychiatry. She also underscored the need for roadmaps, data integration, standards, and interoperability across systems and countries. In addition, she emphasized the importance of evaluating AI models, sharing both positive and negative results, and ensuring that individuals who contribute data remain informed and engaged. Robust data governance, she noted, is essential for maintaining trust.

Magali Haas expanded on these themes by calling for a global strategy for brain health, akin to the global dementia roadmap that helped accelerate progress in that field. She argued that policymakers respond most effectively to a unified message and that broad coalitions—including insurers and the broader health care enterprise—are necessary for long-term

sustainability. She also emphasized the importance of roadmaps that define actionable steps and track progress over time.

STRENGTHENING COORDINATION ACROSS STAKEHOLDERS AND INFRASTRUCTURES

Rosa Canet-Avilés asked which bottlenecks should be prioritized and whether any important stakeholders were missing from the conversation or underrepresented in ongoing efforts. Responses focused on three interconnected issues: (1) reducing fragmentation across initiatives; (2) engaging stakeholders who influence implementation and reimbursement; and (3) leveraging existing research infrastructure more effectively.

Fiske pointed to the fragmentation of precompetitive initiatives. Many groups are doing similar work in parallel, often separated by disease area or geography. He argued for greater interoperability—not through a single global initiative but by enabling datasets, concepts, and frameworks to “speak to one another.”

Vaudano agreed, noting that fragmentation may never fully disappear and emphasized the need to balance alignment with flexibility, given the wide variation in health care structures and regulatory environments across the globe. Drawing on experience from Alzheimer’s initiatives, she highlighted the value of identifying “big ticket” areas—such as patient engagement, ethical considerations, and data platform design—where conceptual alignment is both feasible and beneficial. Establishing shared principles in these domains, she argued, would make it easier to build infrastructures that can interact and learn from one another, even if a single global system is neither practical nor desirable.

Marston noted that several European initiatives now include governmental clinical agencies as full partners, providing early consumer-level buy-in and public investment. He contrasted this with the United States, where payers remain largely absent from similar discussions despite their central role in determining long-term adoption and reimbursement. He argued that payer engagement is essential not only for signaling future value but also for supporting the clinical infrastructure needed for measurement, hypothesis generation, and therapeutic development. Drawing on a current example, he described a promising therapeutic approach and a well-defined patient population that cannot yet be advanced because many U.S. clinicians lack the trial experience and technical capabilities—including specialized imaging—needed to study those patients. Until this infrastructure gap is addressed, he cautioned, the field will struggle to accelerate innovation. He suggested that payer participation, alongside targeted government support, will be critical to building the systems needed to move new therapies forward.

Korf noted that the workshop repeatedly underscored the need for deep phenotyping paired with multi-omics analysis but observed that large national cohort studies—such as the All of Us Research Program, UK Biobank, and similar efforts worldwide—were mentioned only briefly despite their potential relevance. While these cohorts do not provide the level of phenotyping envisioned in precision neuroscience, he argued that they represent a valuable partnership opportunity. By leveraging existing genome sequencing and other omics data—often already available within these cohorts—researchers could identify relevant patient subgroups and then apply more intensive phenotyping to support mechanistic studies.

CONCLUDING REMARKS

In reflecting on the workshop's discussions, Canet-Avilés emphasized the central message that emerged across both days was that measurement is the engine of precision medicine, but it must evolve as science moves from discovery to real-world care (see Figure 9-1). She illustrated that in early discovery, deep, mechanism-proximal tools such as neuroimaging, cerebrospinal fluid biomarkers, and high-dimensional omics sit close to disease biology and enable detection of mechanisms, subgroup identification, and early proof-of-concept signals yet remain too complex and costly for routine use. The field's core challenge, she explained, is the “bridging” step—linking these biological measures to simpler clinical signals by collecting them together so that scalable tools retain mechanistic meaning. Once treatments reach health care systems, measurements must become simple, deployable, and scalable, while still anchored to the biology uncovered upstream. She stressed that achieving this continuum requires an ecosystem capable of supporting precision science at scale, including shared infrastructure, coordinated investment, regulatory pathways, and multi-stakeholder collaboration such as public-private partnerships. She framed the workshop as a starting point for future thematic meetings.

Wittenberg highlighted advances that now allow researchers to probe disease processes with increasing precision—from cellular vulnerability to circuit-level dysfunction—while acknowledging the persistent challenge that shared pathology does not necessarily imply shared causality. She underscored the importance of enrolling patients who truly reflect the biology being targeted and observed that current clinical trials often collect limited mechanistic data. Across multiple sessions, several speakers emphasized that the value of biomarkers and precision measurements lies in their ability to generate clinically actionable information that informs clinical decision making and improves patient outcomes. Progress, she argued, will require uniting stakeholders across the health care continuum.

In closing, Wittenberg reminded participants that the workshop had

Measurement Evolves along Development

Bridging Measures is Critical to Maintain Mechanistic Meaning

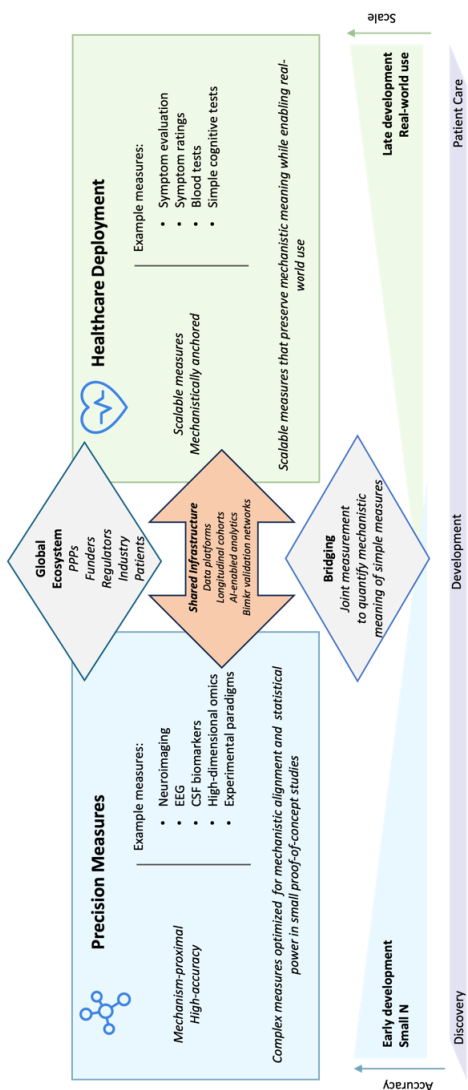


FIGURE 9-1 Visualization of major concepts and relationships discussed by speakers across the workshop.

NOTES: This is a schematic of the core messages that emerged throughout the workshop by individual participants. The left panel (cluster of boxes) shows mechanism-proximal measures—neuroimaging, electroencephalography (EEG), cerebrospinal fluid (CSF) biomarkers, and omics—used in discovery to detect biology and identify subgroups. Arrows lead into a central diamond (rhombus) that reflects the bridging zone—the need to measure complex biological signals alongside simple clinical indicators so mechanistic meaning is preserved. From the diamond, arrows proceed to the right panel of scalable clinical measures—symptom ratings, brief cognitive tests, routine blood assays, and wearables—while an outer frame denotes the enabling ecosystem of data platforms, coordinated investment, regulatory pathways, and multi-stakeholder collaboration required to translate discovery into care.

SOURCE: Adapted by Rosa Canet-Avilés and Gayle Wittenberg from a conceptual framework developed by Gayle Wittenberg; presented by Rosa Canet-Avilés, March 5, 2026.

sought to connect “the complex system of biology” with “the even more complex system of health care.” She acknowledged that bringing these systems together is an inherently challenging undertaking and that fully absorbing the implications of the discussions will take time. She encouraged participants to continue reflecting on the ideas raised during the workshop and to consider the steps needed to move the field forward. The next phase of progress, she added, depends on building the infrastructure, from data standards to clinical pathways, that can carry precision neuroscience from promising concepts to routine practice (see Box 9-1).

BOX 9-1

Ideas for Progress Shared by Individual Workshop Participants

- Achieving precision at scale demands multimodal, longitudinal, and globally diverse data—spanning cellular, behavioral, environmental, and digital measures—to capture real-world variation and support equitable, biologically coherent classification (Au, Geschwind, Krainc, Simmons).
- Scaling access to genetic and biomarker testing remains essential, as most patients still lack the biological characterization needed to match them to emerging precision-based therapies (Krainc, Poston).
- Integrating deep biology with longitudinal phenotyping is critical, as surface-level clinical descriptions have limited value without biomarkers that anchor symptoms to underlying mechanisms (Hyman, Petzschnr, Poston).
- Shared translational datasets, including imperfect or exploratory biomarker data, are urgently needed to accelerate learning across clinical trials and reduce repeated failures in drug development (Hyman, Stephenson).
- Precision medicine requires early and continuous engagement with regulators, clinicians, patients, and payers to ensure feasibility, adoption, and real-world impact (Irizarry, Korf, Mantua, Marston, Vaudano).

Appendix A

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Appendix B

Workshop Agenda

PRECISION MEDICINE IN NEUROSCIENCE: TOOLS, TRANSLATION, AND IMPLEMENTATION: A WORKSHOP

Wednesday, March 4, 2026: 2:00 pm – 5:00 pm ET

Thursday, March 5, 2026: 9:00 am – 4:00 pm ET

WEDNESDAY, MARCH 4, 2026

2:00pm

Introductory Remarks

- Frances Jensen, University of Pennsylvania, *Forum on Neuroscience and Nervous System Disorders Co-chair*
- Deanna Barch, Washington University in St. Louis, *Forum on Neuroscience and Nervous System Disorders Co-chair*

2:05pm

Workshop Overview

- Rosa Canet-Avilés, California Institute for Regenerative Medicine, *Workshop Co-chair*
- Gayle Wittenberg, Johnson & Johnson, *Workshop Co-chair*

2:10pm	Keynote Presentations • Steve Hyman, Harvard University and Broad Institute of MIT, <i>Planning Committee Member</i> • Jamie Heywood, Alden Scientific and ALS Therapy Development Institute
2:40pm	Session 1: Precision Biology for Discovery and Defining Disease/Disorder <i>Objectives:</i> This session examines how emerging tools and technologies—including biomarkers, multi-omics, and artificial intelligence—contribute to a deeper understanding of human neurobiology in health and disease/disorder. Talks explore the strengths and limits of these technologies in tackling the complexity of the human brain and the challenges in distinguishing causal insight from correlation. A central theme is at what point is our biological understanding strong enough to justify moving forward? Key discussion questions: • What kinds of biological evidence actually shape decisions? • When does correlation become actionable insight? • What data are we collecting today that meaningfully shift disease/disorder definitions toward precision, and what data are we collecting that do not?
2:40pm	Session Overview • Julie Harris, Allen Institute, <i>Planning Committee Member</i> • Dimitri Krainc, Northwestern University, <i>Planning Committee Member</i>
2:45pm	Speaker Presentations • Daniel Geschwind (virtual), University of California, Los Angeles • Mariano Gabitto, Allen Institute • Rhoda Au, Boston University
3:20pm	Moderated Panel and Audience Q&A
3:45pm	BREAK

3:55pm

Session 2: Precision Frameworks for Patient Identification and Stratification

Objectives: Positioned between discovery and development, this session explores how precision biology data are assembled into biomarker-driven and composite frameworks for patient stratification across neurological and psychiatric disorders, including threshold selection and uncertainty management, and how these choices impact regulatory relevance and downstream clinical trial design. Speakers highlight contrasts in progress in Alzheimer’s disease and Parkinson’s disease versus psychiatric disorders, where stratification remains challenging.

Key discussion questions:

- Should precision frameworks be biology-first or phenotype-first and are we ready to revise diagnostic categories accordingly?
- How much uncertainty and misclassification are acceptable to ensure a framework is still usable?
- How can frameworks evolve with new biological understanding without losing regulatory confidence?

3:55pm

Session Overview

- Laura Bustamante, Washington University in St. Louis, *Planning Committee Member*
- Brian Fiske, Michael J. Fox Foundation for Parkinson’s Research, *Planning Committee Member*

4:00pm

Speaker Presentations

- Kathleen Poston (*virtual*), Stanford University
- Frederike H. Petzschnner, Brown University
- Diane Stephenson, Critical Path Institute

4:35pm

Moderated Panel and Audience Q&A

4:55pm

Day 1 Concluding Remarks

- Rosa Canet-Avilés, California Institute for Regenerative Medicine, *Workshop Co-chair*
- Gayle Wittenberg, Johnson & Johnson, *Workshop Co-chair*

5:00pm

Adjourn Day 1

THURSDAY, MARCH 5, 2026

- 9:00am** **Review of Day 1 and Preview of Day 2**
- Rosa Canet-Avilés, California Institute for Regenerative Medicine, *Workshop Co-chair*
 - Gayle Wittenberg, Johnson & Johnson, *Workshop Co-chair*
- 9:05am** **Keynote Presentations**
- Hussein Manji (*virtual*), UK Government Mental Health Goals Program, Oxford University, Yale University, Duke University
 - Michelle Colder Carras, Carras Colder Carras, LLC
- 9:35am** **Session 3: Precision Measures to Monitor Disease/ Disorder and Treatment**
- Objectives:* This session focuses on prognostic and longitudinal assessment, a particular area of challenge in brain disorders. Topics include predicting and assessing disease/disorder progression using imaging, biofluid, genetic, and digital markers along with clinical data. Discussion highlights feasibility, heterogeneity, and interpretability across conditions and how these factors influence clinical management and therapeutics.
- Key discussion questions:
- How can biomarker, clinical, and other data be integrated for prognosis and prediction of progression?
 - What do biomarker changes over time tell us about the biology of disease/disorder?
 - How can initial and longitudinal biomarker profiles inform therapeutic interventions, including initiation, dose changes, discontinuation, or switching?
- 9:35am** **Session Overview**
- Linda Brady, National Institute of Mental Health, *Planning Committee Member*

9:40am	Speaker Presentations • Reisa Sperling, Harvard University Medical School • Kenneth Marek, Institute of Neurodegenerative Disorders • Scott Woods, Yale University
10:15am	Moderated Panel and Audience Q&A
10:45am	BREAK
11:00am	Session 4: Precision Strategies for Effective Clinical Trial Design <i>Objectives:</i> This session explores how biological insight informs drug development and therapeutic strategy. Discussion addresses patient stratification and enrichment approaches, trial design, endpoint choice, and biomarker translational medicine strategy. The emphasis is on how precision approaches influence decisions about which intervention is appropriate for which patient and under what evidentiary conditions. • Given a biological hypothesis, what intervention do we choose for which patient population? • How is precision medicine incorporated across the clinical development stages • How do we ensure generalizability of biomarker results from studies?
11:00am	Session Overview • Michael Irizarry, Eisai, <i>Planning Committee Member</i>
11:05am	Speaker Presentations • Toby Ferguson, Alnylam Therapeutics • Hugh Marston, Boehringer Ingelheim • Larisa Reyderman, Eisai • Valentina Mantua, Food and Drug Administration
11:50am	Moderated Panel and Audience Q&A
12:20pm	LUNCH

1:00pm

Session 5: Precision Systems to Deliver Care at Scale

Objectives: This session examines what happens when precision medicine approaches move from trials and centers of excellence into routine clinical care. Discussion focuses on the practical constraints that shape real-world delivery (clinical workflows, workforce capacity, infrastructure, reimbursement, ethical obligations, and health-system readiness) and how these factors determine whether precision approaches can be scaled, sustained, and deliver value to patients and health systems.

Key discussion questions:

- What breaks when precision medicine moves into real-world practice?
- How can implementation barriers be overcome?
- How do health systems decide what is worth adopting and sustaining?
- Where do ethical, economic, and clinical considerations collide?
- Why do some precision approaches stall despite strong biology?

1:00pm

Session Overview

- Bruce Korf, University of Alabama, Birmingham, *Planning Committee Member*

1:05pm

Speaker Presentations

- Nilüfer Ertekin-Taner (*virtual*), Mayo Clinic, Florida
- Soeren Mattke (*virtual*), University of Southern California
- Nita Limdi, University of Alabama, Birmingham

1:40pm

Moderated Panel and Audience Q&A

2:05pm

BREAK

2:15pm

Session 6: Driving Ecosystem Investment in Scalable Precision Medicine Infrastructure for Brain Health

Objectives: This session explores perspectives on the precision medicine infrastructure needed to advance brain care, including shared platforms

that support translation, reduce risk, and improve patient outcomes. The discussion examines structural scientific, regulatory, financial, and governance challenges that limit scale, interoperability, and long-term sustainability and cannot be addressed by individual institutions alone. Participants also consider public–private partnership and investment approaches and what factors may inform future action-oriented efforts to move precision medicine tools from research assets toward broader clinical and public health impact over the next several years.

Key Discussion Questions:

- What shared platforms (e.g., biomarkers, biorepositories, brain banks, AI and real-world data systems) are most critical to accelerate translation, de-risk innovation, and improve patient outcomes, and what cross-cutting scientific, regulatory, financial, and governance constraints limit their interoperability, adoption, scalability, and long-term sustainability—particularly those that cannot be addressed by individual institutions or stakeholders alone?
- What lessons can be drawn from existing partnership and investment models (e.g., ARPA-H, IHI, industry consortia) to mobilize coordinated national investment and leverage international collaboration, share risk, and ensure tools are built as durable, accessible infrastructure rather than fragmented pilots?
- What elements would be important to include in an actionable roadmap that outlines priority investments, partnership structures, key institutions, and policy levers required over the next 3–5 years to scale precision medicine tools from research assets into routine clinical and public health impact?

2:15pm

Session Overview

- Magali Haas, Cohen Veterans Bioscience, Psilera, *Planning Committee Member*
- Elisabetta Vaudano (*virtual*), Innovative Health Initiative

2:20pm	Speaker Presentations • Martien Kas (<i>virtual</i>), University of Groningen • Tristan Glatard, Centre for Addiction and Mental Health • Julian Tillmann, Roche • Nathaniel Mohatt, Advanced Research Projects Agency for Health
3:00pm	Moderated Panel and Audience Q&A
3:25pm	Session 7: Synthesis and Opportunities for Precision Medicine in Neuroscience <i>Objectives:</i> Examine the core themes that have been highlighted during the workshop. Consider next steps to advance precision medicine research and care for brain disorders.
3:25pm	Session Overview • Rosa Canet-Avilés, California Institute for Regenerative Medicine, <i>Workshop Co-chair</i> • Gayle Wittenberg, Johnson & Johnson, <i>Workshop Co-chair</i>
3:30pm	Themes & Future Opportunities Discussion Session Moderators
3:55pm	Concluding Remarks • Rosa Canet-Avilés, California Institute for Regenerative Medicine, <i>Workshop Co-chair</i> • Gayle Wittenberg, Johnson & Johnson, <i>Workshop Co-chair</i>
4:00pm	Adjourn Day 2