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## Feature Review

## The foundation and architecture of precision medicine in neurology and psychiatry

Harald Hampel <sup>1,\*</sup> Peng Gao,<sup>1</sup> Jeffrey Cummings,<sup>2</sup> Nicola Toschi,<sup>3,4</sup> Paul M. Thompson,<sup>5</sup> Yan Hu,<sup>1</sup> Min Cho <sup>1</sup> and Andrea Vergallo <sup>1</sup>

**Neurological and psychiatric diseases have high degrees of genetic and pathophysiological heterogeneity, irrespective of clinical manifestations. Traditional medical paradigms have focused on late-stage syndromic aspects of these diseases, with little consideration of the underlying biology. Advances in disease modeling and methodological design have paved the way for the development of precision medicine (PM), an established concept in oncology with growing attention from other medical specialties. We propose a PM architecture for central nervous system diseases built on four converging pillars: multimodal biomarkers, systems medicine, digital health technologies, and data science. We discuss Alzheimer's disease (AD), an area of significant unmet medical need, as a case-in-point for the proposed framework. AD can be seen as one of the most advanced PM-oriented disease models and as a compelling catalyzer towards PM-oriented neuroscience drug development and advanced healthcare practice.**

### Conceptual overview of precision medicine

The term 'precision medicine' (PM) has been on the lips and minds of scientists and clinicians alike in recent years. Yet the exact scope and scientific theoretical framework of PM is complex and escapes static boundaries. Despite the landmark announcement of the US Precision Medicine Initiative (PMI) in 2015 [1], how PM should be applied at the individual level, and translated from one disease to another, continues to be debated. The fundamental concept of PM is defined as 'prevention and treatment strategies that take individual variability into account' [1]. Despite this seemingly clear-cut definition, the biomedical communities are grappling with the implementation of transformational programs in real-world settings and whether traditionally defined disease entities require redefinition.

The human brain is a highly complex system and is inherently difficult to model due to the dynamic and intricate interactions among its parts. Many of the properties that characterize complex and dynamical systems are relevant in the context of the brain, such as nonlinearity, emergence, spontaneous order, adaptation, and feedback loops. Neurological and psychiatric diseases are often multifactorial, involving different biological systems within a single disease spectrum and resulting from nonlinear interplay of risk genes, dynamic biological determinants, and environmental factors [2–5]. From this complex systems dynamic arise significant individual variabilities in the underlying biology, even when symptomatic and syndromic phenotypes are similar [2–5]. A PM paradigm is pivotal for tackling unmet needs in neurological and psychiatric diseases, which often lack effective treatments and represent a growing burden to healthcare systems and societies worldwide [6,7]. Pharmacological standard-of-care for complex brain disorders is very limited; in the case of brain proteinopathies (including protein misfolding disorders), or pathologically defined 'primary neurodegenerative diseases', approved treatments have been mostly drugs with time-limited efficacy and high interindividual variability in response. Moreover, no disease prediction

### Highlights

Many CNS diseases lack curative or disease-modifying treatments and represent a growing burden to healthcare systems and societies worldwide. These diseases are often multifactorial and complex in nature, with significant individual variability in the underlying genetics and biology.

We posit that the solution to tackling the unmet needs in neurological and psychiatric diseases requires a paradigm shift from a focus on late-stage syndromic phenotypes to targeting preclinical/early prodromal stages.

Precision medicine (PM) approaches in neurology and psychiatry could provide screening solutions, deploy time-sensitive detection/diagnosis, and tailor treatment strategies to an individual's specific clinical–genetic–biological characteristics and risk factors.

We highlight Alzheimer's disease as a case in point for PM oriented across neurology and psychiatry and as a compelling model towards PM-oriented drug R&D and healthcare practices.

<sup>1</sup>Alzheimer's Disease & Brain Health, Eisai Inc., Nutley, NJ, USA

<sup>2</sup>Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV), Las Vegas, NV, USA

<sup>3</sup>Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

<sup>4</sup>Athinoula A. Martinos Center for Biomedical Imaging and Harvard Medical School, Boston, MA, USA

or preventive strategies are available. These issues highlight the need for an evidence-driven revision of the current medical theory and strategies to develop effective biomarker-guided targeted and disease-modifying drugs alongside effective early detection, screening, diagnostic, and therapeutic algorithms.

Reflecting on the modern history of medicine and guided by the framework of the PMI as well as the associated ‘All of Us’ research program (Box 1), here we propose an evidence-based conceptual framework for the transformation to PM in the fields of neuroscience, neurology, and psychiatry. We describe a PM framework as a rational and integrative approach to medical conceptualization, therapy development, and clinical care for multifactorial brain diseases and describe how such a holistic approach can greatly benefit progress in disease characterization and therapeutic development and, ultimately, the individual patient.

### Current models in medicine and their limitations

For a long time, the prevailing model in medicine and drug research and development (R&D) has focused on charting clinically descriptive phenotypic commonalities of large patient populations to identify characteristic signs and symptoms of diseases [4]. This approach falls short of considering the underlying etiology (i.e., genetic and biological dynamics essential to capture the complexity, heterogeneity, and individual progression of neurological and psychiatric diseases). In this context, complexity refers to nonlinear associations, biological crosstalks, molecular mediation pathways [3,8,9]. Another limitation is that past models typically

<sup>5</sup>Imaging Genetics Center, Mark & Mary Stevens Institute for Neuroimaging & Informatics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

\*Correspondence:  
[harald\\_hampel@eisai.com](mailto:harald_hampel@eisai.com) (H. Hampel).

#### Box 1. Precision Medicine Initiatives (PMIs) as a hallmark of an emerging modern era in medicine

The Human Genome Project and the subsequent technological advances in the past few decades have catalyzed rapid progress in human genetics and genomics, yielding new insights into the biological basis of a wide range of health and disease states [2,20]. Recent progress in omics (genomics, transcriptomics, epigenomics, proteomics, lipidomics, metabolomics) and related clinical research applications hold the potential for comprehensive molecular profiling of complex diseases to track their biological evolution across spatial and temporal scales and through different clinical stages. In this context, systems theory as the study of systems composed of interrelated, interdependent parts and its applied sciences (systems biology, systems neurophysiology, and quantitative systems pharmacology) provide a conceptual and analytical framework to generate explainable and biologically clinically meaningful readouts. Large and multidimensional datasets are increasingly available for single or multi-omics studies; several global working groups and societies have formed to accelerate the translation of omics signatures to pharmacological research and/or clinical practice [18,19,179,180].

There is rapid growth of enriched and systematized clinical data in electronic health records (EHRs) and other health-related information databases via digital technologies, such as wearable devices, smartphones, and edge computing [181]. In parallel, tremendous growth and maturation of computational science has stimulated the field of bioinformatics and applied artificial intelligence (AI) in the past decade. These converging theoretical and scientific advances have catalyzed the conceptual and technical foundation for PM as a core element of a new era of medicine [178].

In 2015, the PMI was launched in the USA with a near-term focus on oncology [1]. Its long-term vision is to generate knowledge across health and disease that will ultimately enable a more complete understanding of disease mechanisms, better assessment of disease risk, and improved prediction of optimal therapy [1]. A key element of the PMI is the ‘All of Us’ research program, which aims to collect, including from ethnically diverse individuals in the USA, biospecimens, physical measurements, and other health-related information and link these to EHRs with plans to follow the participants longitudinally for decades [182]. The large-scale ‘All of Us’ clinical research program offers unprecedented opportunities to investigate a broad medical spectrum and identify health outcomes for integrative and holistic evaluation, accurate diagnosis, development of biomarker-guided targeted therapies of diverse subsets of individuals, treatment selection, real-world and outcome research, and evidence-based prevention [182]. A similar initiative in the UK, the UK Biobank, has created a robust biomedical database that can be accessed globally by different stakeholders for clinical and public health research [183]. With whole-genome sequencing, neuroimaging, and extensive medical characterization for over half a million UK residents, the UK Biobank has become a platform to discover primary factors that affect short- and long-term health outcomes. This success has stimulated parallel developments in national biobanks worldwide and efforts to harmonize, merge, and compare biobank data across countries and continents [19].

overlooked the long preclinical/prodromal stages of brain diseases, which is arguably the most suitable therapeutic window for recovering and preserving brain homeostasis [3,8,9]. In fact, translational and clinical studies have identified an expanding list of central and peripheral/autonomic nervous systems diseases that are potentially druggable at preclinical and early symptomatic (prodromal) stages. These diseases include, but are not limited to, the traditionally defined cognitive, movement, motoneuron spectrum disorders [e.g., Alzheimer's disease (AD), dementia with Lewy bodies, Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), as well as idiopathic muscular and peripheral disorders (e.g., Duchenne muscular dystrophy, Charcot-Marie-Tooth disease) and multisystemic disorders (e.g., genetic ataxias and paraparesis)]. Neuropsychiatric and neurodevelopmental conditions such as schizophrenia, autism spectrum disorders (ASDs), anorexia, and suicidality are also examples of major unmet needs, with evidence of the potential for intervention at preclinical stages. An additional level of complexity in neurology and psychiatry clinical research is the methodological constraints posed by the anatomy of the central nervous system (CNS), which precludes regular tissue biopsies. Because of these limitations, hypotheses regarding etiology, pathogenesis, and pathophysiological mechanism(s) of CNS diseases are often based on *a priori* assumptions and precipitous translation of preclinical models to human research. For instance, translational models of the neurodegenerative disease spectrum indicate a prominent role of inflammatory and immune responses in the pathophysiological process, and preclinical data support a potential role for anti-inflammatory treatments in AD and ALS, among others [10]. Of note, clinical trials with non-steroidal anti-inflammatory drugs have failed to prove efficacy so far [11] (detailed examination of the potential factors accounting for the lack of success are beyond the scope of the discussion here). Recently, clinical research paradigms and blueprints have introduced systematic assessment of biomarkers, which broadened the understanding of the molecular mechanisms behind neuroinflammation. Such implementation has facilitated the development of promising compounds [9,12].

Clinical evidence suggests that neurological and psychiatric diseases often transcend the strict dichotomous distinction between health and disease. Rather, health and disease exist in an evolving dynamic continuum, especially for conditions that do not follow a linear course (of continuous progression) and that involve a chronic natural history. During the preclinical stages of these diseases, genetic, environmental, and stochastic factors trigger and drive aberrant biological pathways that unfold at different rates across genetic-, epigenetic-, molecular-, cellular-, tissue-, and macro-scale networks, while relevant physiological functions exhibit only subtle changes due to compensation mechanisms at different biological system levels [3,5,13,14]. For instance, studies in AD suggest that the early preclinical stages have homeostatic and cellular adaptation mechanisms that afford resilience to the incipient pathophysiological changes, a compensation mechanism that may be lost as the disease progresses [15].

Along the continuum of health and disease, there is a prodromal phase when pathophysiological changes become detectable and syndromic phenotypes start to manifest. At this point, homeostasis, with the underlying core biological feedback loops and networks and systems have been overwhelmed and begin to break down at varying points along the spatial and temporal continuum with decompensation and subsequent system failure in an individual manner [16,17]. This process culminates in an ultimate and potentially irreversible multiscale system failure stage (i.e., the clinically overt late phase of the disease). During this stage, therapeutic intervention is increasingly unlikely to substantially modulate biological pathways and pathophysiology and has little chance to produce significant and meaningful benefits in patients [9,18–20].

### PM: the rise of a paradigm shift and the pioneering model of oncology

PM is an emerging translational science paradigm related to the evolutionarily developed, complex multidimensional health–disease homeostasis and continuum, which aims to optimize the effectiveness of disease prevention. It deploys time-sensitive detection/diagnosis and treatment strategies tailored to the individual's specific clinical–genetic–biological characteristics, psychosocial environment, and lifestyle risk factors [1]. Such a holistic healthcare approach is actionable only through deep understanding of the clinical–biological trajectories of disease and the identification of at-risk populations. Following this crucial step of clinical research, the development of stage-dependent and pathway-based therapies that target critical causal factors and upstream molecular and cellular alterations can be attained. Eventually, PM-oriented strategies are hoped to lead to effective integration of nonpharmacological (i.e., lifestyle-related) interventions and individualized pharmacological treatments, for primary and secondary prevention and treatment of asymptomatic preclinical and prodromal disease stages.

In its full deployment, PM in clinical practice will embrace the 'P4' medicine paradigm: (i) stratification of individuals based on the risk of developing the disease (predictive); (ii) large-scale screening and early detection for timely therapeutic interventions (preventive); (iii) tailoring treatment(s) to the patient's social–clinical–biological characteristics (personalized); and (iv) optimizing 'actionable' plans to benefit all patients through patient-centered individualized data collection and utilization such as self-monitoring and self-assessments (participatory) [21,22]. PM would ultimately enable an individualized healthcare workflow and patient journey, skewing the curve of resource investment and success towards prolonging health span over disease management (Figure 1).

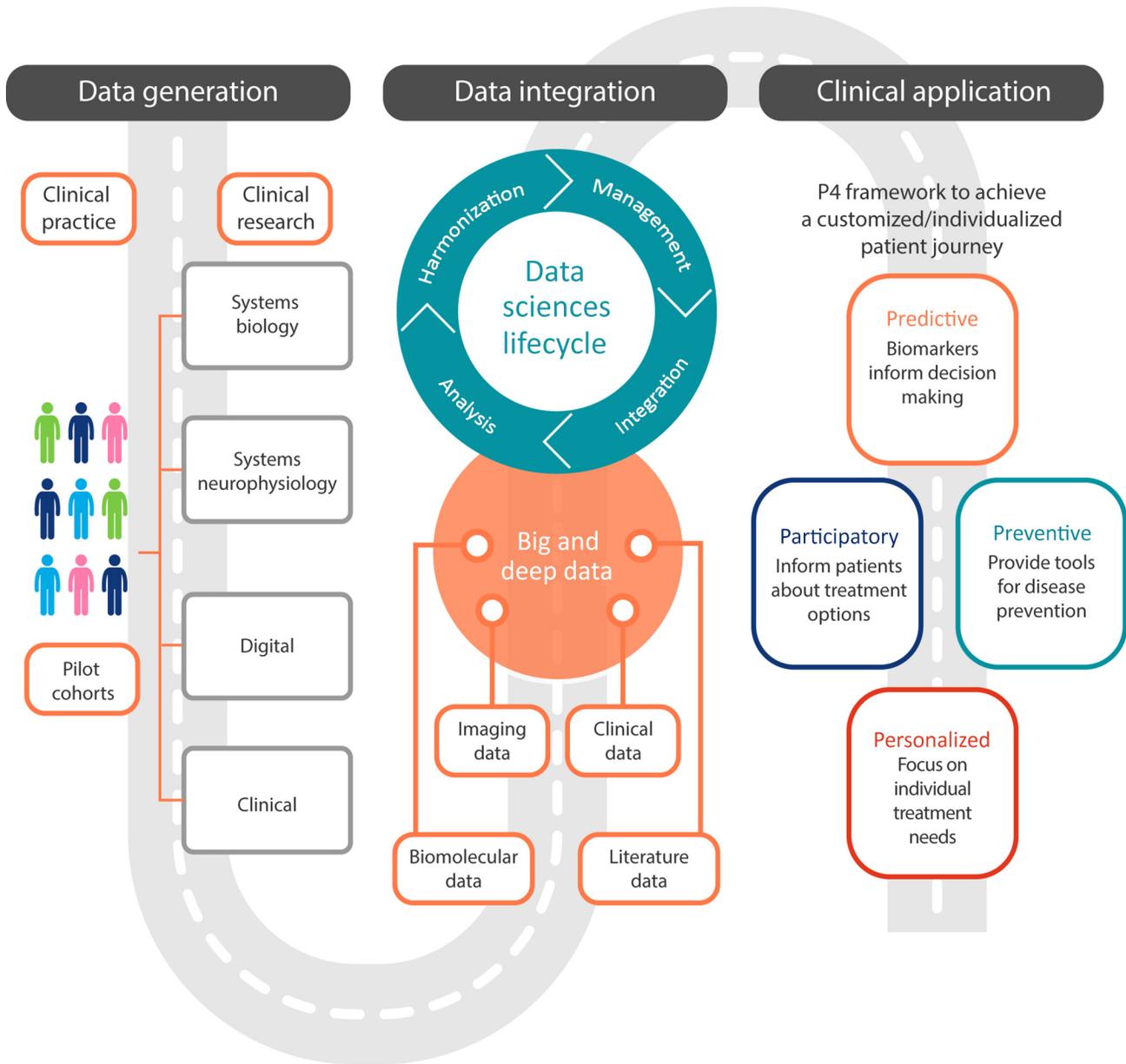
The field of oncology has pioneered the development and implementation of PM-oriented and patient-centered approach in research and clinical care [23]. In the past few years, the US FDA authorized molecular pathway-targeting drugs that can be used in a tissue- and tumor-agnostic fashion. This disruptive innovation has been achieved through exploratory and systematic biomarker profiling studies, identifying the critical (epi)genetic and biological factors rather than focusing solely on traditional assessments such as histology and organ site (Box 2) [24,25]. Capitalizing on key concepts and operating models successfully employed in oncology, one can envision implementation of the PM framework in neuroscience indications, neurology, and psychiatry as well.

### The pillars of PM in neurology and psychiatry

Building on the successful oncology model, we propose an evidence-based conceptual architecture of PM in neurology and psychiatry that is built on four pillars: (i) biomarkers, (ii) systems medicine, (iii) digital technologies, and (iv) data science (Figure 1). This conceptual framework could support the process of redefining diseases according to clinical–biological constructs embedded in a continuum and, crucially, allow the identification of the preclinical stage, a critical time window when restoring brain network homeostasis and prolonging the brain health span are most feasible.

### Biomarkers as a multidimensional description of pathophysiological alterations for different contexts-of-use: genetics and single-/multi-omics profiling

The identification of genetic variants contributing to Mendelian CNS diseases has already transformed clinical care towards genetically informed diagnostic and therapeutic decision-making. One example is deficiency of the *SMN1* gene that results in spinal muscular atrophy [26]. In various neurological and psychiatric conditions, highly penetrant causal variants and risk genes have been identified. This includes monogenic forms of AD or frontotemporal dementia [27], PD and other movement disorders [28,29], ALS and other motoneuron disorders, schizophrenia



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Figure 1. The road to precision medicine (PM) in neurology and psychiatry: towards predictive, participatory, preventive, and personalized (P4) medicine and optimized patient journey. The P4 paradigm envisions a healthcare landscape based on the elements of predictive, participatory, preventive, and personalized medicine [21,90]. The framework outlined in the current article aims to present a path for deploying the P4 paradigm in the fields of neurology and psychiatry. As summarized in the figure, the proposal is grounded on four converging pillars: systems medicine, digital technologies, biomarkers, and big data. Information is gathered from large populations to provide personalized medicine for individuals with neurological and psychiatric diseases. Digital and clinical data generated through systems medicine are gathered and integrated to create big and deep data. A structured data science approach is used to integrate complex data and provide meaningful outputs. This is the necessary substrate to support the P4 framework. This framework integrates the four Ps with the ultimate goal of prolonging health span through early interventions.

[30], and ASD [31]. Insights obtained from genetic studies have provided the crucial entry point and helped identify key biological/pathophysiological processes underlying subtypes of these complex diseases [32].

**Box 2. Precision oncology**

The field of oncology has pioneered the development and implementation of the PM-oriented holistic and patient-centered approach to research and clinical care [23]. Today, PM is being applied throughout the oncology clinical care spectrum, from risk assessment to screening, detection, diagnosis, staging and prognosis, therapy selection, and monitoring.

PM aims to change expectations and behavior toward prevention and prolonging health rather than focusing on diagnostic work-up and therapeutic intervention only when the disease has manifested clinically. Screening represents the most effective strategy for risk prediction and early detection/disease prevention [182]. Noninvasive and globally accessible screening tests that measure the genetic and/or biological variation and risks have been developed, validated, and qualified and are widely available for various types of cancer [184].

In addition to screening, the field of oncology routinely applies genomic and other biomarker analyses on tumor samples and, increasingly, also on bodily fluid samples such as blood (i.e., liquid biopsy) [185], to guide diagnostic and therapeutic decision-making [186]. Moreover, progress in the integration of AI with traditional pathology- or biomarker-based diagnostic work-up holds the promise to address some of the key medical challenges, such as missed or delayed diagnosis and limited resources of healthcare systems [187].

Finally, oncology is a most suitable testing ground for PM-oriented drug R&D, as cancer is a highly heterogeneous biological condition with diverse molecular underpinnings and effective treatments need to target the genomic and other molecular characteristics of patients and their tumors. Drug development under this framework has led to the approval of several tumor- and site-agnostic treatments. In 2017, the US FDA approved pembrolizumab as an immunotherapy treatment for cancers expressing anti-programmed cell death protein 1 regardless of the clinical manifestation such as tumor site or histology. Pembrolizumab indications span a broad set of advanced solid tumors, with a therapeutic work-up guided by the investigation of microsatellite instability-high/DNA mismatch repair-deficient biomarkers rather than clinical phenotypes [24]. Other compounds are in development programs aligned with this approach, such as larotrectinib for TRK fusion-positive cancers [188]. Importantly, these drug development approaches are based on the molecular/biological characteristics of the tumor rather than the overt clinical manifestations such as tumor type/site, increasing the overall clinical benefit and avoiding unnecessary toxicity.

However, familial forms of neurological and psychiatric diseases, caused by hereditary genes, represent only a small fraction of the total disease cases. For the vast majority of patients, genetic risk reflects the cumulative impact of common genetic variants that individually exert a small effect on disease susceptibility [27,28,33]. Large-scale population genomic analyses, such as genome-wide association studies (GWAS), have identified common genetic variants associated with several clinical phenotypes in neurology and psychiatry [33–37]. Importantly, genetic overlap of common brain diseases is increasingly recognized. These observations indicate the presence of highly conserved molecular pathways linked to specific clinical manifestations and pathophysiological commonalities and corroborate findings from experimental models showing that chronic, clinically heterogeneous diseases of the CNS unfold across multiple biological levels and systems [38]. Experimental and clinical evidence indicates that the genetic architecture of neurological and psychiatric diseases can involve pathways that extend beyond the CNS. In this regard, crosstalks between the periphery and CNS have been reported in the context of the immune and inflammatory responses, lipid and glucose metabolism, and functional regulation of the glymphatic and blood–brain barrier systems [34,35,39].

The development of polygenic risk scores (PRS), a combination of genetic variants weighted by their effect sizes, has provided opportunities for translating genomic findings to clinical care [40,41]. Recent studies of AD, schizoaffective disorder, and ASD have shown that PRS can identify individuals with increased susceptibility or risk levels [36,42–45]. Moreover, PRS studies can support investigation of covariance between clusters of genetic factors and clinical (endo)phenotypes [46,47]. Although at present PRS is still used only for research purposes, it is conceivable that in future clinical practice, PRS may inform screening, therapeutic decision-making, and the deployment of preventive strategies [48].

Omic integrative methods that bridge genomics, phenotypes, and function offer an unprecedented opportunity to obtain insights into disease mechanisms and to accelerate the discovery

of molecular biomarkers [49,50]. Epigenomics, the systematic investigation of nonmutational gene expression patterns within the genome, provides a means to systematically explore the effects of gene–exposome interaction [51]. Epigenome-wide association studies point to various gene-regulatory mechanisms and environmentally induced post-translational modifications that account for mechanistic alterations and biological heterogeneity in sporadic diseases [52]. Transcriptomics explores the broad set of RNA transcripts; clinically relevant gene expression signatures of different neurological and psychiatric diseases are being mapped out [53]. Transcriptome-wide association studies have the potential to supply meaningful insights into the spatial and temporal coordinates of causal and secondary mechanisms linked to newly identified genetic and biological risk factors [10,54,55]. Proteomics has been widely used to identify the ultimate pathophysiological mechanisms as well as to develop, validate, and qualify bodily fluid biomarkers in AD, PD, and schizophrenia [56–58]. Albeit still more preliminary than other omic layers, metabolomics and lipidomics hold the potential to provide highly individualized information about bioenergetic, metabolic, and lipid homeostasis processes, relevant to critical pathophysiological pathways that occur in neurological and psychiatric disorders [59–61].

#### Bodily fluid matrixes for biomarker assessment

Various bodily fluids, including cerebrospinal fluid (CSF), blood (plasma, serum), and more recently saliva and urine, have been used as a source to develop biomarkers for different contexts-of-use in several neurological and psychiatric conditions [62–64]. Fluid biomarkers for brain diseases are particularly attractive as they circumvent the physical constraints imposed by the brain’s anatomy for research and healthcare practice (encapsulated in the concept of liquid biopsy, Box 3) [65]. Fluid biomarker analysis also enables simultaneous investigation of multiple biological alterations, which is pivotal for complex diseases with multifaceted pathophysiology and dynamic temporal profiles.

Traditional biomarker discovery has relied on translational research and animal models. Omics science not only facilitates and boosts the accumulation of knowledge about genetics, risk factors, and molecular pathways underlying the biology of neurological and psychiatric diseases in humans [53], but also accelerates the identification of candidate biomarkers. Summarizing advances in this evolving area would be beyond the scope of the current article and we refer

#### Box 3. Liquid biopsy

Minimally invasive and globally accessible tests for different contexts-of-use are urgently needed to address the growing demand for timely diagnosis and management of neurological and psychiatric disease. Blood-based biomarkers are cost-, resource-, and time effective [67]. They hold the potential to enable large-scale biological screening to identify individuals who are likely to have disease-specific pathophysiology and to determine the need for second-level, less accessible or more invasive investigations (e.g., PET or CSF assessment) [64]. Blood-based biomarkers can provide the opportunity for a more efficient, multistep diagnostic work-up. Further, they can facilitate the re-engineering of drug R&D pipelines, from subject enrollment, target engagement, to monitoring of treatment efficacy.

The oncology field has pioneered the approach of liquid biopsy, a concept which could cross-fertilize related practices in neurology and psychiatry programs [185]. According to the US National Cancer Institute, liquid biopsy is defined as ‘a test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood’. Liquid biopsy in oncology allows the detection of various tumor-specific circulating analytes (circulating cell-free DNA and RNA, circulating tumor DNA, extracellular vesicles, etc.) that carry information about the genome/epigenome, transcriptome, proteome, and metabolome of the tumor. Then, these multidimensional big data are integrated through advanced bioinformatics to detect molecular signatures relevant to the disease pathophysiology. Serial liquid biopsies offer clues about the evolution of cancer in individual patients across disease stages, enabling individualized, genetically and biologically guided therapies [185]. In translating such an approach to CNS diseases, the development of novel ultrasensitive, high-throughput techniques has enabled the detection of multidimensional fluid biomarkers that circumvent neuroanatomical barriers and provide comprehensive snapshots of brain pathophysiological processes [65].

readers to recent review articles that have addressed the topic, particularly in the context of neurodegenerative disorders [66–68].

### Neuroimaging biomarkers

Neuroimaging, including molecular and structural/functional imaging, allows noninvasive visualization of the CNS and supplies both qualitative and quantitative data. Molecular imaging methods, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), use radio-ligands that bind to distinct molecular targets implicated in disease-relevant biological pathways. Molecular imaging can directly detect disease-associated molecular and cellular process(es), such as protein misfolding and accumulation (e.g., measured by amyloid and tau PET) [69,70], changes in neuronal metabolism (e.g., measured by fluorodeoxyglucose PET), microglial activation (e.g., detected by translocator protein [TSPO] imaging) [71], and neurochemical dysfunction (e.g., measured using cholinergic, glutamatergic, or dopaminergic system radiotracers) [72,73].

The tight association between the uptake of certain radiotracers and corresponding neuropathological findings has generated core/supportive diagnostic biomarkers for different neurodegenerative diseases [73,74]. Moreover, recent quantitative approaches, leveraging automatic analysis pipelines, allow the *in vivo* tracking of neurobiological pathways, resembling the traditional neuropathological staging and potentially supporting stage-driven therapeutic approaches [69].

Magnetic resonance imaging (MRI) provides a window into the structural and functional organization of the brain. Structural MRI captures cortical and subcortical grey matter volumes, shapes, and surfaces, as well as white matter connections and microstructural properties. Functional MRI reveals activation patterns, including functional integration or segregation among brain areas/networks, both at rest and during cognitive tasks. The resulting maps of brain activity patterns, when combined with structural information, may serve as a fingerprint for each patient [75,76].

Some of the frontiers in human neuroimaging include the development of spatio-temporal maps of short- and long-range connections (connectomes), integration of structural and functional data (structural–functional connectivity coupling), and characterization of the modular organization of the brain. These advances hold the promise to reveal biomarkers in the form of subtle changes in the hierarchical organization of the brain that may underlie altered cognition and behavior [5,77]. Work from recent years has identified structural and functional brain endophenotypes of typical cognition, behavior, and movement, as well as related alterations in neurological and psychiatric diseases [78–80]. For example, the resting state functional connectome of the brain has shown promise in differentiating individuals with specific neurodevelopmental conditions (e.g., ASD) from typically developing controls [80] and predicting an individual's response to treatment in various mental disorders (e.g., anxiety [79] or depression [78]).

Changes in regional and whole-brain functional architecture on the millisecond time scale may reflect physiology- or disease-related alterations in the brain [81–84]. In view of the low temporal resolution of MRI, this methodology can be complemented by electroencephalography (EEG) and magnetoencephalography (MEG), which offer noninvasive albeit indirect assessment of neuronal activity at high temporal resolution. Recent efforts have merged genomic and EEG technologies to discover genomic variants that affect brain synchrony, offering new mechanistic insights into genetic variants associated with alcohol use disorders and epilepsy (see [Outstanding questions](#)) [85].

### Systems medicine

Critical biological factors whose perturbation may lead to systems failure can be uncovered by computational analysis of large, multidimensional datasets under the systems-network theory

[86–88]. Basic and high-level properties of key nodes and modules can be mapped, in static and dynamic conditions, to decipher causative genetic–biological dynamics before they lead to an overt phenotype [86–88]. This provides a mechanistic entry into the complex genetic and pathophysiological landscape that underlies disease signs and symptoms. For neurological and psychiatric diseases, systems biology and systems (neuro)physiology can provide comprehensive models of structural and functional organization of the brain in health and disease [85,89].

#### Systems biology: an overview

We use the term systems biology to refer to approaches aimed at description and quantification of the relationship between molecular biological levels of a given system and for methods intended to generate explainable readouts of causative dynamics, intermediate endophenotypes, or clinical features. According to the concepts in systems biology, physiological functions and pathophysiological changes may be mapped along highly connected networks of genes/proteins/metabolites/lipids with critical connection and intersection [49,53,85,90,91].

Progress in systems biology has been fueled by the recent advances in high-throughput omics science, data mining and modeling approaches, and by the development of accessible classification tools for functional annotation [92,93]. In neurological and psychiatric diseases, omics and multi-omics profiling and systems biology have been widely applied to brain tissues and biofluid samples to gain understanding of disease pathophysiology and dynamics and to identify potential biomarkers (Figure 2). The various omics layers have been described in an earlier section ('Biomarkers as a multidimensional description of pathophysiological alterations for different contexts-of-use: genetics and single-/multi-omics profiling'). As a next step, multi-omics integration could allow different biological organizational levels to be explored simultaneously, resulting in a holistic understanding of genetic-driven or stochastic changes in the CNS [94–96]. For example, genomic, tissue-level and single-cell transcriptomics and epigenetic data have been integrated to identify gene regulatory networks in the brain and predict endo- and syndromic phenotypes of psychiatric disorders [97]. Exploratory systems biology approaches have also been used to map gene-to-phenotype and protein-to-phenotype connections, identifying shared etiologies among different diseases [38].

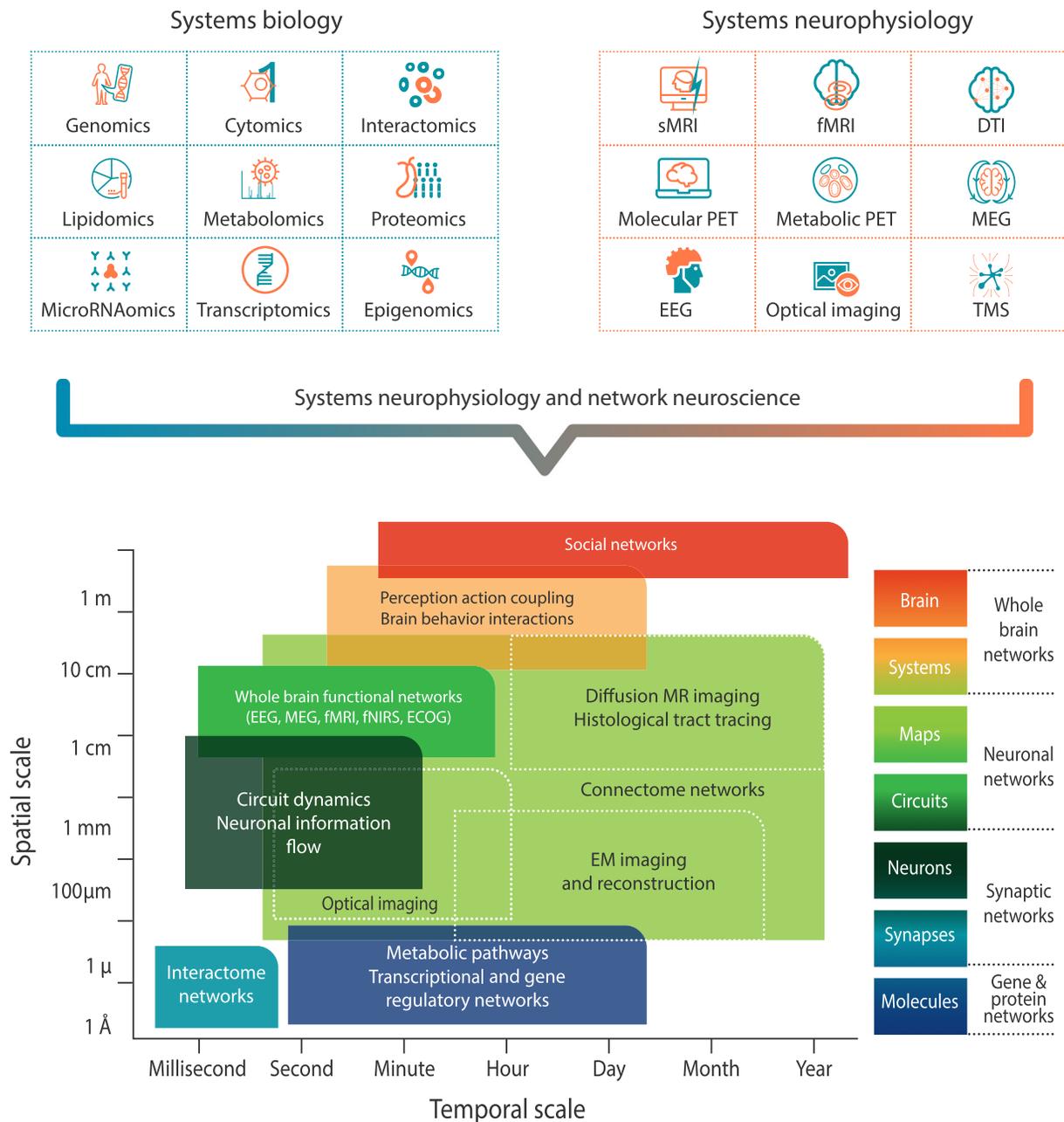
#### Systems neurophysiology: multimodal integrative monitoring of neural activity at different spatial and temporal scales

Systems neurophysiology, as defined here, aims to integrate structural and functional brain activity features across different spatio-temporal scales to generate a functional atlas of neural activities throughout development and aging and in health and disease (Figure 2) [98]. Examples include the reconstruction of the hierarchical organization of the brain in young and aged individuals with normal cognitive/motor functions [99,100] and in several neurological or psychiatric diseases, including AD [101–104], PD and parkinsonism [105], and schizophrenia [106,107].

The combination of molecular imaging (PET/SPECT) and structural and functional imaging (MRI, fMRI, EEG, MEG) has been refined to show spatial-temporal association of protein aggregate accumulation or regional neurochemical/metabolic alterations overlaid with cortical/white matter damage, network functional activity changes and clinical features [99–102,106,108–113]. This multimodal and multidomain combination allow all of these factors to be investigated jointly and integrated in a system-wide manner, providing insights into their interplay and modulation and how such interplay may become aberrant in neurological and psychiatric diseases [99–102,106,108–113].

New links from multimodal brain imaging to cellular and molecular data have recently been established by the ENIGMA Consortium. Established in 2009, the consortium conducted the most

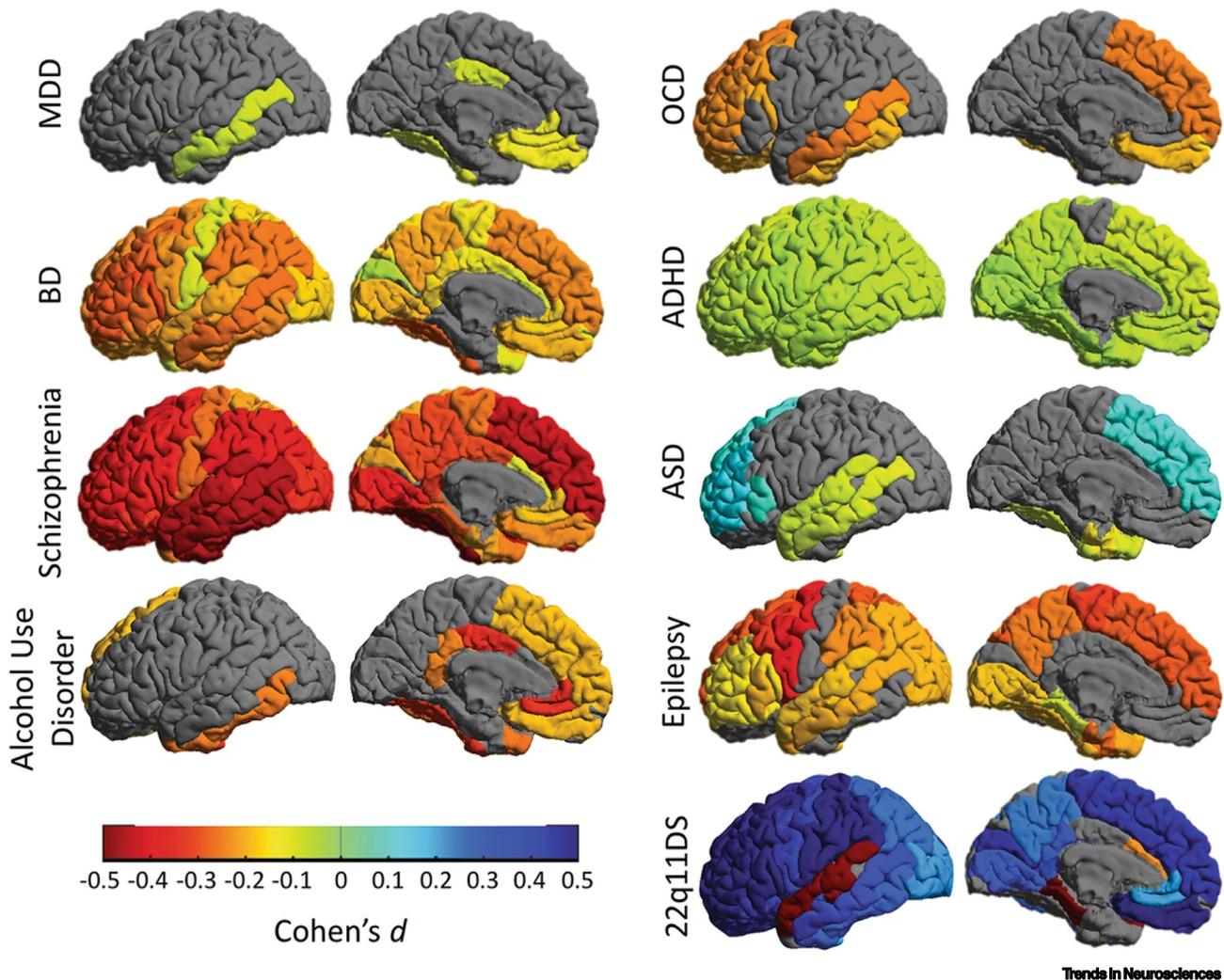
Integrative disease modeling



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Figure 2. Systems biology and systems neurophysiology data provide information across different spatial and temporal scales. Multiple types of data can be obtained from systems biology, including quantification of neurobiological systems at the molecular biology level, and systems neurophysiology, which encompasses multimodal integrative imaging or recording techniques to capture data at different spatial and temporal scales. These data can be integrated for the purpose of systems modeling across spatial and temporal ranging from the atomic and molecular scale to whole brains, and from millisecond-range phenomena to processes progressing over

(Figure legend continued at the bottom of the next page.)



**Figure 3.** Large neuroimaging studies of several major neurological, psychiatric, and developmental conditions reveal both overlap and characteristic differences in the profiles of brain alterations. Findings depicted in the figure are by the ENIGMA Consortium [19]. Cortical grey matter thinning is prevalent in a range of conditions examined in the study, except for autism spectrum disorder and 22q11 deletion syndrome, where excess brain tissue is found. Recent work has related some of these patterns to cell-specific gene expression patterns and to neuroreceptor distributions [114], implicating specific cell types and molecular pathways in psychiatric conditions. Reproduced from [19]. Abbreviations: 22q11DS, 22q deletion syndrome; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder.

extensive neuroimaging investigations of several major neurological and psychiatric conditions, from PD, epilepsy, and ataxia to schizophrenia, bipolar disorder, depression, substance use disorders, and post-traumatic stress disorder (Figure 3) [19]. In an approach termed ‘virtual histology’, the characteristic patterns of imaging abnormalities across diverse brain disorders appear to relate to several molecular and cellular features: (i) transcriptomic data and gene expression patterns mapped in the Allen Brain Atlas, and (ii) neurotransmitter distributions mapped in a normative atlas of 18 receptors and transporters across nine different neurotransmitter

years. Abbreviations: DTI, diffusion tensor imaging; ECG, electrocardiogram; EEG, electroencephalography; EM, electron microscopy; fMRI, functional magnetic resonance imaging; fNIRS, functional near infrared spectroscopy; MEG, magnetoencephalography; PET, positron emission tomography; sMRI, structural magnetic resonance imaging; TMS, transcranial magnetic stimulation.

systems [114]. The ENIGMA Toolbox, developed to compare brain disorders with each other and with histologic and molecular data, has facilitated the discovery of specific cell types and systems that may be implicated in major psychiatric conditions, offering new mechanistic leads for research in psychiatry [115].

Brain activity characterized solely in the form of anatomically segregated responses is insufficient to explain the complexity of neurodevelopment, cognition, behavior, aging, and related diseases [116]. A higher order statistical analysis and network-level concept is needed to uncover potential sources of neural and glial dysfunction. In the past two decades, graph theoretical measures applied to neuroimaging have revealed abnormalities of network configurations in clinically defined pathological conditions [89]. One such effort integrated neuroimaging and connectome analysis to identify network associations with atrophy patterns in 1021 adults with epilepsy compared with 1564 healthy controls from 19 international sites; this work identified disease epicenters and hubs, intrinsic features of brain networks that helped explain the patterns of atrophy seen across multiple epilepsy syndromes [117].

### Digital health devices and technologies

Neurological and psychiatric diseases often manifest in several physiological systems and functional domains such as changes in complex behaviors, social interactions, and sleep patterns. Digitally enabled data collection may capture the rich and diverse repertoire of disease-related phenotypes that cannot be readily assessed during clinical visits alone [118]. Digital health technologies hold the unique advantage of being portable and intrinsically quantitative, allowing data collection to be convenient, unobtrusive, and longitudinal. Digital health data can span a multitude of biometrics related to central and peripheral autonomic system functions (e.g., heart rate, body temperature, cardiac rhythms, skin conductance, blood oxygenation) and cover clinically relevant parameters (e.g., motion, gait, pace, sleep, speech and voice patterns) [119,120]. Digital technologies can detect subtle changes during early stages of disease, offering solutions for screening and early diagnosis. They also open new possibilities for longitudinal data collection and have the potential to provide useful information on prognosis and disease progression [118].

There has been a steep increase in pilot studies, multicenter clinical trials, and large-scale observational datasets exploring the performance of various digital health devices that could provide surrogate measures for clinical outcomes [119–121]. The field of movement disorders as traditionally defined has dramatically benefited from digital biomarker development programs; wristwatch-type wearables and smartphones with built-in accelerometer and gyroscope can capture aspects of tremor, bradykinesia, dystonic movements, and impairments in gait and balance [119,122–124]. More broadly, actigraphy, other wearable analytics, and smart technologies are under development to support early detection and management of different behavioral and psychological symptoms, such as psychosis, changes in mood, and circadian rhythm disruption, in several neurological and psychiatric conditions [125–128]. In addition, digital technologies are being explored as therapeutics [129].

### Data science

Generating ‘big data’ is an inevitable outcome of current technology trends, as technologies are evolving to capture increasingly comprehensive datasets of physiological and behavioral measures from individuals [omics data, brain structural and functional data, continuous health data from wearables, electronic medical records (EHRs), etc.]. Massive in quantity and complex and heterogeneous in nature, big data can be challenging to analyze using traditional statistical approaches. Computational models based on artificial intelligence (AI) approaches can generate clinically meaningful readouts using sparse and noisy multidimensional data from different sources [130]. The

widespread use of machine learning (ML), especially in the development of deep learning (DL) algorithms, has revolutionized the application of AI in clinical research and drug R&D [131]. DL methods have been developed to detect AD based on learning patterns in MRI scans from over 200 sites worldwide [132]. Other approaches have synthesized novel image contrasts [133], boosted scan resolution and speed [134], and even learned to infer neuropathology from *in vivo* scans not previously thought to be sensitive to such molecular features [132].

Owing to its predictive abilities, AI is expected to facilitate the time-dependent analysis and serial/longitudinal tracking of patients' clinical and medical data-rich profiles. AI algorithms may support medical data aggregation and filtering, as well as clinical decision-making based on manually curated data (i.e., supervised learning). In addition, AI may help identify clinically relevant subgroups of individuals (e.g., genetic-biological clusters) from large, heterogeneous populations who at the surface level share clinical phenotypes or disease labels [131–133]. This can be accomplished by autonomously searching for association within the high dimensional data space (i.e., unsupervised learning) [132,133]. The resulting clusters or latent dimensions of variation can in turn reveal the latent, long-postulated biological heterogeneity underlying the symptoms that may influence treatment response and clinical-biological trajectories [131,135]. This approach could be applied to AD, other neurodegenerative diseases, and a spectrum of affective disorders [78,136–139]. Unsupervised AI approaches can also finely dissect preclinical stages of diseases to uncover hidden biological signatures [78,140–142]. In clinical trials, unsupervised algorithms trained on clinical or biomarker data have already been shown to predict treatment response in depression and AD [142,143]. The near universal adoption of EHR across healthcare systems has enabled the collection and storage of large, population-wide real-world clinical data in a digital format that can be systematically analyzed. Analysis of EHR databases with AI has augmented diagnosis, prognosis, and prediction of disease onset or progression to better inform clinical decision-making [144]. Such models, once trained, could offer a relatively low-cost and scalable alternative to traditional population screening to identify high-risk populations who should be further evaluated with more specific testing [145,146].

In summary, there is a global multidisciplinary effort to implement applied AI techniques across translational/clinical/pharmacological research areas and medical practice. Besides facilitating PM-oriented drug R&D, AI-assisted medicine promises to significantly lower time and resource investment for healthcare infrastructures by streamlining screening, diagnostic, and therapeutic pathways. Although significant progress has been made recently, various challenges, including the need for explainability and trustworthiness [147], hinder the AI-scaled transformation of medicine and neurology. Human-readable physiological insights may facilitate adoption by clinical practitioners. Lastly, ethical aspects of the use of AI in biomedical research and medicine require careful consideration and are being tackled with dedicated approaches [148].

### Potential limitations and challenges for big data approaches in PM

While AI approaches can deliver high performance, a key limitation is that little or no insight may be gleaned into the inner workings of these models (the 'black box' issue). This often limits our understanding of how data have influenced model output [149]. A related point is that AI methods may reveal systems complexity; while recognizing this complexity is an essential step towards understanding the disease state(s) and the compensation to incipient dynamics that prevent systems failure, current AI approaches are limited in elucidating how or why complexity arises, thus making interpretation and clinical decision difficult [149]. Another challenge is the need for an input dataset with consistent curation and harmonization; diverse and rich datasets need to be available to reflect multiple dimensions of health and disease as highlighted for neuroimaging big data analytics [150].

Many of the challenges in applying AI methods arise at the level of systems biology. The challenges become more acute when transitioning from domains such as gene–gene association analyses, protein–protein coexpression networks, or metabolomic pathway analyses, to layering multi-omics analysis. Multimodal, integrative, and systems-scale paradigms hold the potential to map clinical–biological trajectories of brain endophenotypes in cognitively healthy individuals at risk; for instance, in the context of AD, carriers of the apolipoprotein E (APOE)  $\epsilon 4$  allele, individuals with incipient A $\beta$ /tau accumulation, or people reporting subjective memory complaints [5,53,62,151]. However, the need for data standardization and curation in large and automated analyses is particularly relevant when overlaying different big data sets. This complexity likely plays a part in the relatively limited implementation of large-scale, multimodal data collection and monitoring in AD. While in presurgical assessments of epilepsy and neuro-oncology, combined functional imaging (fMRI-EEG coregistration) is routinely used, the use of multimodal neuroimaging in late-onset AD, especially fMRI and molecular brain mapping of amyloid and tau using PET, is still far from widespread clinical implementation, partly due to the cost and complexity of these techniques.

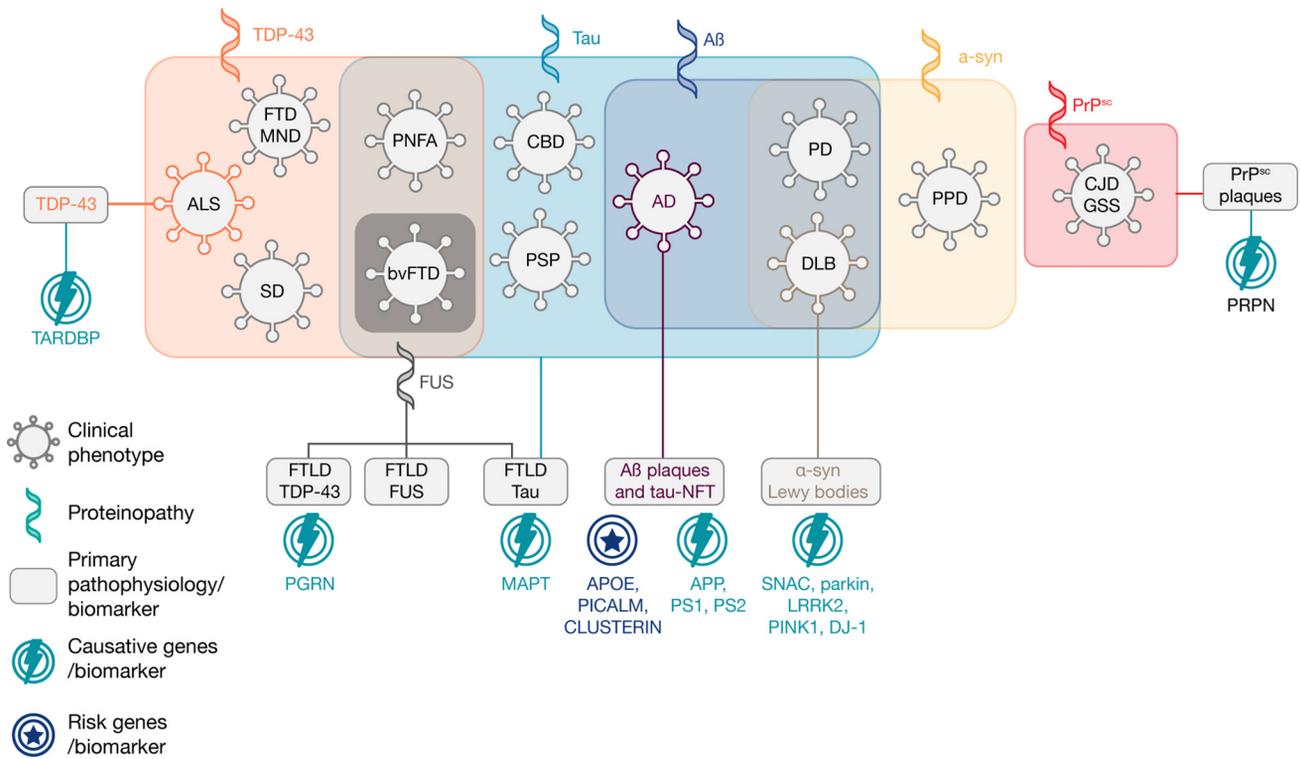
Standardization of AI algorithms in drug R&D and healthcare requires more in-depth analytical and clinical validation. Translating complex systems biology and neurophysiology outputs into reliable, reproducible, and operable data for drug R&D and healthcare decision-making requires user confidence and significant investment to apply the information to patient and physician needs. Another potential issue concerns the capability of AI-based processes in weighting non-clinical factors of individual patients, such as health–economic aspects that play an important role in the P4 framework and healthcare in general. Algorithms that are agnostic to the patient's socio-economic status, access to healthcare, and social determinants of health, may generate infeasible healthcare journeys, thus delaying the diagnosis and management of disease.

### AD: a blueprint towards PM in neurodegenerative diseases

Two decades of large-scale observational and systems-scaled studies, including GWAS, have provided insights into pathophysiological pathways of neurodegenerative diseases. These studies revealed that a given syndromic phenotype may be attributable to multiple (epi)genetic and pathological alterations. However, a particular genetic or pathophysiological pattern could also manifest with divergent syndromic phenotypes (Figure 4).

Frameworks for conceptualizing AD have evolved substantially in the past three decades or so. Traditional frameworks focused mostly on syndromic aspects, particularly cognitive decline and progression of functional impairment. Many current perspectives put greater emphasis on clinical–biological constructs, conceived along a continuum, which importantly includes preclinical stages of underlying pathophysiological alterations without overt clinical symptoms [152]. Clinical evidence also increasingly indicates that AD is highly heterogeneous in its susceptibility, risk factors, biological signatures, disease progression, clinical manifestations, and response to treatments [9,36,152]. In addition, sex differences in AD impact disease risk, biomarker profiles, response to treatments, and overall prognosis (Outstanding questions) [153]. Such heterogeneity has complicated clinical studies and partially explains the considerable failure rates of clinical trials [9].

Biomarker profiling offers a key entry point to disentangle disease heterogeneity. In the past two decades, progress has been made in the development of AD fluid and imaging biomarkers. This has led to the conceptualization of a symptom-agnostic, biomarker-based classification system called the Amyloid- $\beta$ /Tau/Neurodegeneration [AT(N)] system, which stratifies individuals upon core pathophysiological changes in AD [154]. In line with the evolving PM-oriented paradigms, the primary objective of the AT(N) system is to circumvent the limitations of the traditional, clinical



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**Figure 4. The evolving spectrum of neurodegenerative diseases: from late-stage syndromic phenotypes to extensive genetic–biological–clinical profiling.** This schematic describes the evolving, evidence-based concept of neurodegenerative diseases spectrum. Biomarker-guided clinical research showed that conditions with divergent clinical phenotypes exhibit genetic and pathophysiological overlap. By contrast, a traditionally defined clinical phenotype (e.g., behavioral variant of frontotemporal dementia) may have different underlying genetic mutations and pathological alterations, including brain proteinopathies. With comprehensive profiling by the integration of genetic, molecular, and multimodal imaging endophenotypes, current understanding of neurodegenerative diseases continues to evolve and future clinical advances are hoped to overcome the limitations of traditional syndrome-oriented approaches. Figure adapted from the concepts in references [5,31,40]. Abbreviation: Aβ, amyloid β; AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; APOE, apolipoprotein E ε4 allele; APP, amyloid protein precursor; bvFTD, behavioral variant FTD; CBD, corticobasal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; FTD-MND, FTD with concurrent motor neuron disease; FTLN, frontotemporal lobar degeneration; FTLN-FUS, FTLN associated with inclusions of protein fused in sarcoma; FTLN-tau, FTLN associated with inclusions of microtubule associated protein tau; FUS, RNA-binding protein FUS; GSS, Gerstmann-Sträussler-Scheinker disease; LRRK2, leucine rich repeat kinase 2; MAPT, microtubule associated protein tau; NFTs, neurofibrillary tangles; PARKIN, parkin RBR E3 ubiquitin-protein ligase; PD, Parkinson’s disease; PGRN, progranulin; PICALM, phosphatidylinositol binding clathrin assembly protein; PINK1, PTEN induced putative kinase 1; PNFA, nonfluent variant primary progressive aphasia; PPD, paranoid personality disorder; PS1, presenilin-1; PS2, presenilin-2; PSP, progressive supranuclear palsy; SD, semantic dementia; SNCA, alpha-synuclein; TDP-43, transactive response DNA-binding protein 43.

phenotype-based approach to AD [152]. As a further step in these developments, the expanding ATX(N) system acts as an extension of the AT(N), where X stands for additional mechanisms (e.g., neuroinflammation and damages to the blood–brain barrier). These biomarker-based classification systems should ultimately inform drug R&D to foster pathway-based, stage-oriented therapeutic strategies in AD. For future clinical practice, the system holds the potential to serve all steps of the evolving AD patient journey from large-scale screening to diagnosis, prognosis, and therapeutic decision-making [62].

Omics sciences studies in AD have already contributed significantly in the quest to decipher the aging–AD continuum, within which upstream genetic polymorphism leads to molecular dynamics accounting for pathomechanistic alterations and downstream biological signatures [9,20,36,53,56,155]. Such an approach has already innovated and boosted AD biomarker/

drug target discovery programs [9,20,36,53,56,155]. For example, activated microglia and astrocytes drive and regulate neuroinflammation, an important contributor to AD pathophysiology. Neuroinflammation impacts several finely modulated molecular pathways interacting with other AD pathophysiological pathways (e.g., A $\beta$  and tau), depending on disease stages and individual susceptibility [156,157]. The temporal-spatial dynamics of the neuroinflammatory process could be dissected through multi-omics profiling along with neuroimaging and could potentially be targeted by specific and stage-guided immune-modulator drugs, such as TREM2 agonists, to modify disease progression [157,158].

Consistent with the systems neurophysiology paradigm, multi-modal imaging studies conducted across aging and the AD continuum have pointed to a spatial-temporal overlap of A $\beta$ /tau accumulation with decreased functional connectivity and structural decay in selectively vulnerable regions in large-scale networks, including the default mode network [5,70,112,159]. Such activity and neuroanatomical changes, described initially at the regional level and more recently also in terms of network modular organization, may ultimately allow prediction of long-term cognitive, behavioral, and functional outcomes even in cognitively healthy individuals at risk for AD [5,112,151].

Rapid development in digital health technologies offers an opportunity to detect early signs of AD in a broadly accessible fashion, including the possibility for at-home assessment and monitoring [118,160]. Automated speech analysis is one promising method to detect mild cognitive impairment [161], although clinical validity in this context remains to be further tested. Real-time assessment of eye movement is possible through smart phones/tablets and is being explored as a potential biomarker of early cognitive impairment [162]. Actigraphy recordings provide robust data about motor activity patterns that can be used to infer sleep–awake cycles and other aspects of behaviors (e.g., apathy) in AD patients [163]. Besides screening and diagnosis, digital tools could help quantify and maintain cognitive reserve, which has been linked to resilience against AD and late-life depression [151].

### Challenges and perspectives in clinical research and drug R&D: shared pathophysiological commonalities across diseases

In oncology and clinical immunology, a single compound can exhibit efficacy on a broad set of conditions, for instance various advanced solid tumors, with therapeutic workup guided by profiling specific pathways such as TRK or microsatellite instability-high/DNA mismatch repair (Box 2).

In neurological and psychiatric diseases, a large body of experimental and human evidence points to pathophysiological commonalities involving shared genetic architecture and failure of multiple biological networks, such as proteostasis (e.g., in A $\beta$  and tau pathways), neuronal adaptation and bioenergy regulation, synaptic homeostasis, immune and inflammatory responses [32,38,53]. Using a tactic that has been effective in tumor- and tissue-agnostic cancer therapies, detailed biological profiling of individuals at risk for neurodegenerative diseases, as well as schizoaffective disorders, mood disorders, and ASD, offers an opportunity to develop a new molecular classification system and a related drug R&D program based on distinct biological features and intermediate endophenotypes instead of focusing on syndromic phenotypes (see Outstanding questions) [32,38,53,164].

As part of this conceptual framework, opportunities offered by the emerging field of systems pharmacology should be considered. When standard pharmacodynamic and pharmacokinetic parameters are combined with *in silico* high resolution analyses, systems pharmacological approaches can provide comprehensive information on (epi)genetic regulatory mechanisms of

target(s) druggability and drug resistance, as well as simulation of biological pathways downstream of efficacy and side effects [165,166].

### Accounting for sex-related vulnerability

Large-scale epidemiological observations and multimodal clinical studies indicate the presence of a sex-biased risk to a broad spectrum of neurological and psychiatric diseases [153,167]. Moreover, physiological sexual dimorphism exists in cortical and subcortical structures of the brain, including the limbic system and in grey and white matter connections throughout normal development and diseases [168,169]. In the neurodegenerative spectrum, AD has been extensively investigated to uncover sexual dimorphism across different biological scales [153,167]. For instance, higher vulnerability to AD of menopausal women relative to age-matched men has been linked by cross-disciplinary studies to higher risk of dysregulation of the A $\beta$  and neuro-inflammatory pathways, disruptions of the cholinergic nuclei of the basal forebrain, and failure of large-scale networks in the brain [153,170–173]. Such an apparent predisposition of females to AD is not influenced by age itself, thus reinforcing the hypothesis that hormonal factors, some of them linked to menopause, may play a critical role [153,174]. The presence of sexual dimorphism in brain health and disease calls for reconsideration of treatment outcome assessments, taking sex-biased biological factors into account rather than treating sex as a simple covariate [153,175].

### Concluding remarks

Following decades of progress in brain research, and powered by convergent and foundational conceptual-technological breakthroughs, we are now advancing towards the detection of pathophysiological signatures underlying neurological and psychiatric disease at much earlier stages. These advances also allow deconstruction of large, complex, and heterogeneous disease conglomerates into smaller and biologically defined subclusters along the nonlinear dynamic temporal disease continuum. A novel PM approach will rely on biomarker-guided workflows and allow early screening, accurate detection of differentiated pathophysiological signatures, preventative strategies, and time-sensitive, biomarker-guided, pathway-based, targeted therapies tailored to the individual's specific multidimensional characteristics.

While ambitious in its ultimate aspirations, PM has now arrived at a critical juncture. Neurology has finally entered the intermediate PM development stage, with biomarker-guided pathway-based targeted therapies. The promise of PM for generating mechanistically guided treatments for the suitable patient population, beyond cancer and genetic disorders, has yet to be achieved [8] and examples of ML-powered PM solutions that have significantly impacted clinical practice remain scarce across the spectrum of neuroscience therapeutic areas [144,176]. The PM strategy that has guided recent successes in oncology can inform application and adaptation to neurology and psychiatry. That said, direct accessibility of the affected tissues (and tumors) in living persons for screening and molecular profiling in oncology are not fully transferrable to neurological and psychiatric diseases given the difficulties in direct access to the CNS. In addition, the unique complexity of the anatomical, biological, and genetic architectures of CNS disorders when combined with interindividual heterogeneity can hinder the development of cost-effective biomarkers as a proxy to pathology. For neurological and psychiatric diseases, such strategies need a more sophisticated and differentiated approach to address the underlying systems complexity of brain conditions [177]. Advanced approaches should include integration of rapidly progressing technological areas, such as multi-omics, neuroimaging, neurophysiology, along with clinical and digital phenotype data to accurately subtype CNS diseases and identify druggable targets. As knowledge of human biology and disease pathophysiology advances, it would be possible to perform disease subtyping with increasing granularity. Even so, a balance must be achieved

### Outstanding questions

Mapping clinical–biological trajectories in asymptomatic persons at risk, and in individuals with incipient pathophysiology, is currently challenging. The hurdles stem in part from the complexity of CNS physiology and the simultaneous functional disruption of processes across various hierarchical biological system levels. What could be the ways to validate and standardize systems-level integration approaches in clinical research, based on the PM pillars, to better characterize the underlying genetic–biological nature of CNS diseases?

Integration of multimodal neuroimaging with omics and machine learning-based analysis methods represents a holistic approach to identify groups of individuals with shared genetic architecture and pathophysiology, from molecular pathways up to large-scale networks. Which PM-oriented approaches would be the most effective in drug R&D to create pathway-based, symptoms-agnostic therapies across neurology and psychiatry?

In anticipation to a stage when PM preventive and diagnostic-therapeutic approaches are available for application in neurology and psychiatry, which would be the most relevant implementation strategies to attain healthcare system preparedness?

between convergence and divergence of knowledge to ensure that PM can deliver on its inherent potential and help fulfill the promise of improved early patient identification and individualized treatment.

Considering the transformative nature of PM, cross-disciplinary collaboration is essential. To resolve the complex unknowns across CNS disorders, healthcare systems, which are currently clinically operationalized through medical specialties, will require systematic integration of the partially fragmented scientific and medical domains of expertise. Overcoming this barrier also needs enhanced collaboration among stakeholders such as care partners, healthcare providers, regulators, and policy-makers [178]. As a next step, big data science approaches could facilitate the development of these multimodal biomarker variables [50] to support PM-oriented, individualized, stage-dependent treatments for older individuals who suffer from age-related diseases. Ultimately, PM is hoped to offer health span-prolonging solutions throughout different phases of life, such as aging and senescence.

Finally, a PM-oriented approach requires characterization of each individual in the broader context of population-related factors such as sex, ethnicity, geographic location, and socioeconomic status. Just as genetics is influenced by evolutionary dimensions, such as ancestry, environmental and lifestyle factors are impacted by geographic location and socioeconomic status, among other determinants.

One could envision PM-implementation in neurology and psychiatry progress through two major phases. The first phase requires large-scale populations, large enough to include all relevant classifying variables, such as specific genetic and genomic makeup, different ethnicities and sexes, with all the related complex genetic-biological differences, that can then be segmented into subgroups with relatively consistent molecular characteristics and sufficient pathophysiological commonalities, so that each subgroup can be targeted with effective therapeutic and preventive interventions. When harmonized AI-assisted medicine blueprints are increasingly consolidated into clinical research and healthcare practice, PM can transition to its second phase of truly individualized treatments. Achieving these ambitious goals requires first recognizing and embracing human diversity and ensuring inclusion during the different stages of PM development. Hopefully, this path will lead to prolonged health span and better treatments for a wide range of disease conditions, implemented within a broader framework aiming for brain health equity.

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### Author contributions

H.H. and A.V. generated the foundation of this work, created the theoretical framework, and together with P.G. and M.C., developed the differentiated concept for this article. All authors contributed to researching the literature and data, discussing the content, writing, reviewing, and/or editing of the article.

### Declaration of interests

H.H. is an employee of Eisai and serves as senior associate editor for the Journal Alzheimer's & Dementia and has not received any fees or honoraria since May 2019. H.H. is inventor of 11 patents and has received no royalties for: In Vitro Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders patent no.

8916388; In Vitro Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases patent no. 8298784; Neurodegenerative Markers for Psychiatric Conditions publication no. 20120196300; In Vitro Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders publication no. 20100062463; In Vitro Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders publication no. 20100035286; In Vitro Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases publication no. 20090263822; In Vitro Method for The Diagnosis of Neurodegenerative Diseases patent no. 7547553; CSF Diagnostic In Vitro Method for Diagnosis of Dementias and Neuroinflammatory Diseases publication no. 20080206797; In Vitro Method for The Diagnosis of Neurodegenerative Diseases publication no. 20080199966; Neurodegenerative Markers for Psychiatric Conditions publication no. 20080131921; Method for diagnosis of dementias and neuroinflammatory diseases based on an increased level of procalcitonin in cerebrospinal fluid: US patent no. 10921330. P.G. is an employee of Eisai Inc. J.C. has provided consultation to AB Science, Acadia, Alkahest, AlphaCognition, ALZPathFinder, Annovis, AriBio, Artery, Avanis, Biogen, Biosplice, Cassava, Cerevel, Clinilabs, Cortexyme, Diadem, EIP Pharma, Eisai, GatehouseBio, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Lexeo, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Otsuka, Pharmacotrophix, PRODEO, Prothena, ReMYND, Renew, Resverlogix, Roche, Signant Health, Suven, Unlearn AI, Vaxxinity, VigilNeuro pharmaceutical, assessment, and investment companies. N.T. has provided consultation to Eisai. P.M.T. has received a research grant from Biogen, Inc., for work unrelated to this manuscript, and has provided consultation to Kairos Venture Capital, Inc. Y.H. is an employee of Eisai Inc. M.C. is an employee of Eisai Inc. A.V. declares no competing financial interests related to the present article, and his contribution to this article reflects entirely and only his own academic expertise on the matter. A.V. was an employee of Eisai Inc. (Nov 2019–June 2021). A.V. does not receive any fees or honoraria since November 2019. Before November 2019 he had received lecture honoraria from Roche, MagQu LLC, and Servier.

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