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Beyond seeing only illness in abnormality: Clinical challenges and methodological promises on the road towards precision psychiatry

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ABSTRACT

Mental disorders are highly prevalent and impose substantial burdens on individual well-being, daily functioning, and society; yet early diagnosis, risk identification, subtyping, and effective treatment remain major clinical challenges. Precision psychiatry has emerged to mitigate these challenges and aims to deliver *"the right treatment to the right patient at the right time"*. The translation of precision psychiatry into practice, however, is still limited. Here, we propose that progress towards precision psychiatry depends on addressing four interdependent and interdisciplinary challenges: moving from (i) diagnostic categories to transdiagnostic mechanisms, (ii) homogeneous groups to individual heterogeneity, (iii) only behavioral symptoms to complementary biological markers, and (iv) a cross-sectional to a longitudinal research focus. Importantly, these challenges are not independent, but can rather be organized as a cascading framework of interdependent components that together define the requirements for more personalized mental health care. For each level of this cascade, we review methodological promises and critically evaluate their strengths and limitations in relation to the conceptual framework. In doing so, we delineate why their clinical impact remains limited by identifying key methodological gaps that must be addressed to meet the requirements of the highest level of the cascade and to achieve fully personalized care. Finally, we synthesize all insights into a concrete proposal for moving forward, which calls for a conceptual shift from a diagnosis-centered perspective to a health-centered one, focused on individual mental health trajectories. Ultimately, implementing such individualized, health-centered approaches at the highest level of the cascade might make diagnosis and treatment more globally accessible, thereby improving the well-being of individuals across diverse populations and clinical settings.

1. Introduction

"It is an error to see only illness in abnormality."

[— Lev Vygotsky (Vygotsky, 1993)]

Imagine the situation of a man, John, who has recently been experiencing mental health issues, including persistent low mood and energy, insomnia, and excessive anxiety and worry. His symptoms started subtly but slowly intensified over time until they substantially impacted his well-being, daily life functioning, and social interactions. John sought professional help, and over several sessions, standardized behavioral measures were administered. Using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), the clinician eventually concluded that John met the criteria for Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD). For John, these diagnoses initially brought relief, helping him to better understand and accept his symptoms and experiences.

Proper treatment of these symptoms, however, proved to be more challenging as the next few months were an iterative cycle of trying different treatments, ranging from behavioral therapy to medication, evaluating how well they worked, and making adjustments as needed. While some seemed to diminish his symptoms, others did not seem to help, or even worsened them. Eventually, an effective treatment was found, and John could finally start to move forward again. When asking the clinician why they did not just start with that treatment, the clinician told him that they cannot always explain or predict which treatment works for which patient and why, and that the process is therefore one of trial-and-error. John has since come a long way, but

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is still struggling, as the clinical process is long and intense. Unfortunately, John's story is not an isolated one and is, in fact, just one example of a systematic problem.

Indeed, given the high prevalence (McGrath et al., 2023) and burdens (Coenen et al., 2016; Christensen et al., 2020) of mental disorders, one would expect that our clinical systems are highly effective and efficient with accurate risk identification, early diagnosis, subtyping, and treatment. The reality is, however, that although these topics are an important focus of mental health research (e.g., see Yao et al., 2024; Lee et al., 2019; Leichsenring et al., 2022; Paul and Potter, 2024; Silveira et al., 2016), established risk factors have poor predictive value (Cuijpers et al., 2021), most forms of treatment only reach small to medium effect sizes (Huhn et al., 2014; Leichsenring et al., 2022), mental disorders are often only identified more than one year after onset (Scott et al., 2022; Cheung et al., 2017), and subtyping remains challenging, as identified subtypes can depend strongly on methodological choices (Beijers et al., 2022) and often do not converge across studies (Marquand et al., 2016a; Dinga et al., 2019). These inefficiencies in the clinical process call into question whether the structure of current clinical practices aligns sufficiently with the nature of mental disorders, as well as with the needs of patients in practice.

To understand how such a misalignment might arise, we should consider the structure of current clinical practices for the diagnosis and treatment of mental disorders. Current clinical practices rely on categorical diagnostic systems such as the DSM-5 (American Psychiatric Association, 2013) and International Classification of Diseases (ICD-11) (World Health Organization, 2019), which critically impose discrete boundaries on conditions that are increasingly recognized as continuous (Hyman, 2021; Marquand et al., 2019). This highlights the need to reevaluate current clinical frameworks and identify novel and/or complementary approaches that better match the nature of mental disorders (Kotov et al., 2017; Insel et al., 2010).

These insights have motivated the emergence of *precision psychiatry* (Vieta, 2015), a movement that aims to bring the principles of precision medicine to mental health care (Češková and Šilhán, 2021; Fernandes et al., 2017; Insel and Cuthbert, 2015). Overall, the central aim is to deliver *"the right treatment, to the right patient at the right time"* (Češková and Šilhán, 2021; Trivedi, 2016), thereby shortening long and uncertain trial-and-error-based clinical processes. The promise of precision psychiatry is clear, and it is central to many mental health research programs. Many researchers outlined pathways towards such personalized care, focusing on different approaches and challenges (e.g., Fernandes et al., 2017; Passos et al., 2021; Kas et al., 2025), however, the precision psychiatry framework remains mostly theoretical (Baldwin et al., 2022; Kapur et al., 2012) as a clinical translation of the framework is still limited and work in progress (Salazar de Pablo et al., 2021; Baldwin et al., 2022; Deisenhofer et al., 2024).

In this review, we focus on the requirements to bring precision medicine to psychiatry by synthesizing fragmented insights from the literature into a coherent and accessible structure. Importantly, our aim is not to create a new framework alongside already well-established roadmaps such as Research Domain Criteria (RDoC) (Insel et al., 2010) and the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2017), but merely to integrate different perspectives and points of focus under one conceptual umbrella. Specifically, we propose that progress towards precision psychiatry depends on addressing four interdependent challenges that form a cascading structure: moving (i) from taxonomic categories to transdiagnostic mechanisms, (ii) from homogeneous groups to individual heterogeneity, (iii) from relying only on behavioral symptoms to complementary biological underpinnings, and (iv) from cross-sectional snapshots to longitudinal models. Each of these challenges builds on the previous one, bringing us closer to a comprehensive understanding of mental disorders. We will discuss each of these factors and their theoretical implications for precision psychiatry and patients like John, identify relevant examples from the literature, and use social interaction abilities as a recurring example given its high ecological validity and clinical relevance. We further critically evaluate methodological promises in relation to the conceptual framework, and delineate why their clinical impact remains limited. Finally, we will synthesize all insights into a concrete proposal to advance towards precision psychiatry in practice. We will argue that achieving this demands a conceptual shift from a diagnosis-centered perspective to a health-centered one.

2. Clinical challenges and methodological promises

The path towards precision psychiatry is constrained by four key challenges: accounting for transdiagnosticity, heterogeneity in the clinical population, unknown biological mechanisms, and longitudinal development. Critically, these challenges are not independent but can be organized into a cascading structure of interdependent components that together define the requirements for more personalized mental health care. For each level of this cascade, we review methodological approaches and critically evaluate their strengths and limitations in relation to the conceptual framework. In doing so, we identify methodological gaps that must be addressed to meet the requirements of the highest level and to achieve full personalized care.

2.1. From diagnostic categories to transdiagnostic mechanisms

While comorbidity is a core characteristic of mental disorders (McGrath et al., 2020), current clinical practice and research use a taxonomic approach, treating isolated diagnoses as the primary units of analysis, thereby preventing us from accounting for co-occurring symptoms across diagnoses; that is, the DSM-5 and ICD-11 classify patients into discrete categories with operationalized boundaries between diagnoses. While in practice patients rarely have only one diagnosis and the presence of one mental disorder is associated with an increased risk of developing additional mental disorders over time (Caspi et al., 2020; McGrath et al., 2020). This suggests that multiple disorders might arise from shared underlying mechanisms, often biological in nature, and aligns with research supporting this transdiagnostic nature of mental disorders (e.g., Grisanzio et al., 2018; McQuaid, 2021; Widge et al., 2017; Pelin et al., 2021).

While the DSM-5 acknowledges the existence of comorbidity and the limitations of its categorical design, it retained this structure because at the time of its development, insufficient scientific support was available to create dimensional formulations that would instead characterize clinical manifestations based on quantifying attributes (American Psychiatric Association, 2013). As a result, comorbidity is framed as merely the co-occurrence of distinct disorders rather than the manifestation of shared mechanisms. This perspective constrains clinical decision-making to diagnosis-specific treatment, rather than targeting the underlying mechanisms that give rise to a patient's specific constellation of comorbid symptoms.

The same limitation applies to mental health research, which mostly focuses on predefined clinical endpoints, predicting specific diagnoses or classifying patients with a specific diagnosis against controls (Cuthbert and Insel, 2013). This limits our ability to fully capture the complexity of mental disorders, as it does not provide insights into shared, underlying mechanisms between different disorders. As long as diagnoses in isolation remain the primary units of analysis, the *"right patient"* principle of precision psychiatry is hindered, as the focus is on *right labels* rather than on right mechanisms underlying a specific symptom profile of a patient.

Transdiagnostic approaches, by contrast, move beyond this traditional strict categorization by focusing on mechanisms and dimensions that cut across multiple disorders (Dalgleish et al., 2020). These approaches posit that shared and overlapping underlying mechanisms (e.g., biological underpinnings) give rise to different symptoms across disorders (Paulus and Thompson, 2019), thereby naturally accounting for comorbidity.

One example of such a transdiagnostic dimension relevant for psychiatry is social interaction abilities. Impairments in social interaction are associated with a majority of psychiatric disorders, rather than being a diagnosis-specific symptom, and are thought to be associated with an increased likelihood of developing mental disorders (Schilbach, 2016). Positioning individuals on a functional to dysfunctional social interaction abilities dimension might thus provide valuable clinical information beyond diagnostic categories.

Dimensional approaches. To capture such shared characteristics across disorders, (Hierarchical) dimensional methods have emerged as a promising means. These approaches conceptualize psychopathology as a continuum of symptom severity, ranging from non-pathological to clinical, typically using thresholds to determine clinical status (Farías Venegas et al., 2025). They further assume that lower-order symptoms are organized by higher-order dimensions that span traditional disorders (Dalgleish et al., 2020; Eaton et al., 2023) and that reflect core components of psychopathology that cut across multiple disorders (Eaton et al., 2023). Such approaches underpin well-known frameworks, including the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (Barlow et al., 2017), HiTOP (Kotov et al., 2017), and the related p-factor of psychopathology (Caspi et al., 2014). The fact that such dimension-informed approaches can indeed provide valuable information at the clinical level is illustrated by meta-analytic research suggesting that dysfunctional metacognition is present across different diagnoses, with distinct metacognitive dimensions being more prominent in some disorders such as obsessive-compulsive disorder (OCD), GAD, and eating disorders (Sun et al., 2017).

Despite their popularity and clinical relevance, several limitations should be noted that hinder clinical translation. First, it can be challenging to form a clear interpretation of higher-level dimensions. The p-factor, for example, could be interpreted as a measure of risk, severity, or outcome of psychopathology, all of which carry different implications for clinical use (Eaton et al., 2023). Second, underlying latent variable models impose assumptions that might not hold for psychopathology data; that is, hierarchical dimensional models often assume that observed symptoms are interchangeable indicators sampled from a broader domain (Watts et al., 2024), whereas in practice, resulting factor structures highly depend on the exact way that symptoms are measured, what level of granularity, and with which instrument. Relatedly, higher-order dimensions can be hard to capture with only a limited number of standard measures, thereby limiting their scalability for clinical practice (Lahey et al., 2021; Ruggero et al., 2019). Additional concerns reported by Watts et al. (2024) include that good model fit is often mistaken for evidence of validity, construct validation is often underspecified, general factors show only poor replication over studies, resulting latent variables are often misinterpreted as causal, and underlying latent variable models impose assumptions that might not hold for psychopathology data (Watts et al., 2024).

Taken together, transdiagnostic approaches are a valuable asset on the road towards precision psychiatry, as they shift the unit of analysis from diagnostic categories to relevant underlying mechanisms and dimensions cutting across diagnoses. In doing so, they better reflect the complexity of psychopathology, naturally account for existing comorbidity, and better support the *"right patient"* principle of precision psychiatry. It is therefore essential to overcome the aforementioned methodological limitations with practical transdiagnostic methods.

2.2. From homogeneous groups to individual heterogeneity

A close challenge to transdiagnosticity is the existence of substantial within-diagnosis heterogeneity, another core characteristic of neuropsychiatric conditions (Wu and Yang, 2023; Feczko et al., 2019). Even within a single diagnosis, there is substantial variation in both symptom expression and underlying biological mechanisms that give rise to similar clinical expressions. This critically suggests that there might be a many-to-many mapping between these mechanisms and clinical expressions; that is, one mechanism might give rise to shared symptoms across disorders, contributing to comorbidity, whereas similar symptoms might be driven by multiple distinct mechanisms, causing within-diagnosis heterogeneity (Feczko et al., 2019).

Importantly, this heterogeneity is not only characteristic of clinical groups, but is also inherent to the typical population. A specific clinical manifestation observed in a patient is therefore not solely the disorder in isolation, but is embedded within normative variation (Feczko et al., 2019). Deviating patterns should thus not be automatically seen as pathological, but should be evaluated against typical variation to distinguish meaningful abnormalities from mere normal variation. Correspondingly, there is growing support for the idea that mental disorders represent a continuum of deviations from typical health, rather than distinct categories (Hyman, 2021; Marquand et al., 2019). Given its importance, multiple studies have focused on the challenges posed by heterogeneity (e.g., Marquand et al., 2016a, 2019; Feczko et al., 2019; Allsopp et al., 2019).

Because of the dominance of categorical frameworks in current diagnostic and treatment processes, most mental health research is dominated by *case-control* designs (Feczko et al., 2019), implicitly assuming within-diagnosis homogeneity. Although the DSM-5 acknowledges heterogeneity among patients with the same diagnosis, its categorical structure does not explicitly capture this variability because DSM-5 relies on overarching symptom profiles by design. Indeed, approaches based on group-level characteristics may describe a general population accurately, but risk failing to capture clinically meaningful individual differences. The ICD-11 and DSM-5, for instance, provide a list of symptoms for each diagnosis, of which a subset must be present to meet the threshold for a positive diagnosis. Consequently, two patients can both reach the specified threshold while having different symptom profiles, distinct underlying biological mechanisms, and different treatment responses. Both patients would, however, receive the same diagnosis and thus often similar treatment, potentially leading to ineffective treatments. This idea that one shared diagnostic label can mask potential clinically relevant heterogeneity is empirically shown by Simmonds-Buckley et al. (2021), for example, who applied latent transition analysis to a large sample of patients with depression that all received cognitive behavioral therapy. While all patients received the same diagnosis and the same treatment, the authors identified five subtypes that were associated with different treatment engagement and responses.

Applied to our example of social interaction abilities, introduced above, clinically meaningful heterogeneity in this transdiagnostic dimension could be captured by individual differences in, e.g., synchrony (Kamp et al., 2025; Kupper et al., 2015), social motivation (Chetcuti et al., 2025), gaze patterns (Keles et al., 2022), interaction style (Scheeren et al., 2012), and interpersonal distance (Givon-Benjio et al., 2024). These examples illustrate the need for methods that are able to identify transdiagnostic dimensions, while simultaneously providing insights at the individual level, depending on specific manifestations.

Dimensional approaches. The dimensional methods discussed above can also provide relevant information at the case level within diagnoses. Recent work on OCD, for example, suggested distinct metacognitive belief profiles across different OCD symptom dimensions (Martiadis et al., 2026). Together with the aforementioned findings of the meta-analytic study on metacognitive dimensions (Sun et al., 2017), this suggests that dimensions such as metacognition might be clinically relevant both as a transdiagnostic dimension as well as for distinguishing meaningful variability within diagnoses.

To further map heterogeneity within and across disorders, a widely used approach is normative modeling (NM) (Marquand et al., 2016a,b, 2019). NM is a statistical method that quantifies variability in a biological measure of interest, while accounting for relevant covariates

such as age, sex, and acquisition site. NM allows modeling typical developmental trajectories and variation in a reference cohort, and quantifying how an individual deviates from this expected pattern, irrespective of diagnosis, thereby acknowledging variability in both patient cohorts and the typical population.

Despite its promise for decoding heterogeneity in clinical populations (e.g., Wolfers et al., 2020; Zabihi et al., 2019; Zamanzadeh et al., 2026; Fraza et al., 2025a; Verdi et al., 2023; Lamsma et al., 2026; Lv et al., 2021; Worker et al., 2023; Wolfers et al., 2018; Segal et al., 2025), NM relies on several strong assumptions that limit its clinical applicability. First, it assumes that the reference cohort adequately captures the full range of typical variability, which can be difficult to achieve in practice due to limited sample sizes and sampling biases (Zamanzadeh et al., 2026; Bozek et al., 2023). Second, deviation scores are inherently relative to the chosen model and covariates, making them sensitive to modeling choices and limiting reproducibility across studies (Bayer et al., 2022; Fraza et al., 2025b). Third, while deviation maps provide individualized information, their clinical interpretation remains unclear, as there are no established thresholds that can distinguish clinically meaningful deviations from benign variation (Genin et al., 2024). NM is a powerful method to understand heterogeneity; nevertheless, these challenges contribute to the current gap between methodological promise and clinical translation and thus need to be addressed.

Categorical approaches. Data-driven segmentation or stratification algorithms are another popular technique to model heterogeneity. These methods use data analytics to partition heterogeneous populations into smaller, more consistent subgroups with similar healthcare profiles (Yan et al., 2018). Marquand et al. (2016b) categorize these methods into two main categories: (i) clustering (Hastie et al., 2009), and (ii) Finite Mixture Models (FMM) (Bishop, 2006; Lazarsfeld and Henry, 1968; Muthén, 2002). Both are unsupervised methods that can be used to stratify diverse clinical populations without any predefined labels. While clustering approaches use similarity metrics to segment data without any underlying statistical model, FMMs are model-based and assume that data are drawn from a mixture of probabilistic distributions. Well-known and commonly used clustering algorithms for clinical stratification include K-means, hierarchical clustering, and community detection. The FMMs include, for example, Gaussian mixture models, Latent Class Analysis (LCA), or growth mixture models (Marquand et al., 2016b). Indeed, these techniques have been used extensively to study heterogeneity across a variety of mental disorders (Green et al., 2020; Alashwal et al., 2019; Krishnagopal et al., 2020; Marquand et al., 2016b).

Although clustering and mixture models are widely used to identify subgroups, they suffer from fundamental limitations. Most notably, these methods will produce clusters even when the underlying data structure is continuous (Loftus et al., 2022; Marquand et al., 2019, 2016b; Liu et al., 2008), raising concerns about over-interpretation. Moreover, clustering solutions are often unstable across datasets (Marquand et al., 2016b) and highly sensitive to preprocessing choices, feature selection, and algorithm parameters (Beijers et al., 2022; Loftus et al., 2022). Critically, identified subtypes rarely replicate across studies (Marquand et al., 2016a; Dinga et al., 2019) and often lack external validation, limiting their clinical utility.

Moving forward, the assumption of homogeneity should be revisited, and heterogeneity should be acknowledged both in patient cohorts and the general population. Interestingly, since the co-occurrence of comorbidity and heterogeneity follows from the many-to-many mapping between underlying mechanisms and symptom expression, similar methods can be used to study both phenomena by changing the unit of analysis from multiple diagnoses to a specific disorder. Identifying shared and divergent patterns of deviations at multiple levels, both within and across disorders, will facilitate modeling of the inherent heterogeneity and comorbidity of mental disorders, aiding the *"right patient"* principle of precision psychiatry, and improving our understanding and mapping of psychopathologies underlying mental disorders.

2.3. From behavioral symptoms to complementary biological markers

A third clinical challenge is the predominant focus on observable behavioral symptoms and disregard for underlying (neuro)biological mechanisms within current clinical frameworks (Young, 2016; Wakefield, 2013). Indeed, recognizing the importance of comorbidity and heterogeneity in precision psychiatry raises the question of what exactly their underlying causal mechanisms are and how these mechanisms can help distinguish clinically meaningful deviations from normative variation. Critically, symptom-based descriptions alone are inadequate to address these questions, thus motivating additional analysis of biological markers aimed at developing a personalized understanding of mental disorders, and achieving the *"right treatment, right patient"* goal of precision psychiatry.

Biological information might reveal patterns relevant to the aforementioned heterogeneity and transdiagnosticity challenges that purely symptom-based approaches cannot. Segal et al. (2023), for example, showed that although patients with the same clinical diagnosis exhibit substantial heterogeneity in gray matter volume deviations, these often converge to common networks and circuits, potentially explaining both phenotypic differences and similarities within diagnoses. Furthermore, neurological biomarker studies (e.g., Baker et al., 2019; Goodkind et al., 2015; McTeague et al., 2017; Shanmugan et al., 2016) support transdiagnosticity, as neurobiological markers typically pertain to multiple disorders rather than to one isolated condition (Dalgleish et al., 2020). Relatedly, Xie et al. (2023) identified a *transdiagnostic neuropsychological* (NP) factor spanning both internalizing symptoms and externalizing symptoms, suggesting a shared biological basis for comorbidity.

Importantly, biological processes should be studied at multiple levels, as they can reveal biomarkers shared across diagnoses and help explain heterogeneity within diagnoses. Integrating the biological component is therefore essential for achieving the *"right treatment, right patient"* goal, as underlying mechanisms may reveal relevant deviations that symptom profiles alone may obscure. Moreover, because neurobiological changes may precede symptom onset, incorporation of relevant biomarkers may facilitate early detection and more targeted treatment.

Revisiting our example of social interaction abilities, linking differences and similarities in observable aspects of social interaction across individuals with underlying neural mechanisms might help to explain clinically relevant heterogeneity and shared transdiagnostic features (Kamp et al., 2025). For example, Feng et al. (2026) observed differences in neural synchronization mechanisms that varied with different autistic trait levels, illustrating the value of combining interaction-based measures with complementary (neuro)biological markers.

The methods we have discussed thus far enable a better understanding of comorbidity and provide a more comprehensive characterization of individual deviation profiles. Additionally, we identify methods that critically focus on the neurological underpinnings driving these individualized profiles and comorbidity, going beyond information obtained from behavioral symptom profiles.

Neurobiological modeling approaches. Most of the aforementioned approaches are data-driven and thus adaptable to neurobiological data. Clustering methods and Normative Modeling have recently been applied to, for example, functional Magnetic Resonance Imaging (fMRI), Electroencephalography (EEG), and Magnetoencephalography (MEG) data to identify and assess subtypes in a broad range of mental disorders (e.g., Wang et al., 2022; Ren et al., 2023; Tokuda, 2018; Wang et al., 2021; Yassine et al., 2023; Luo et al., 2021; Atluri et al., 2015; Qu et al., 2020; Eroğlu and Arman, 2022; Zamanzadeh et al., 2026; Kia and Marquand, 2019; Itälinna et al., 2023; Wolfers et al., 2018; Zabihi et al., 2019; Berthet et al., 2024; Lv et al., 2021; Villalón-Reina et al., 2026; Rutherford et al., 2023; Verdi et al., 2023; Wolfers et al., 2020). This suggests that applying these methods to neuroimaging data

could be directly informative for clinical practice, as they enable the identification of biologically informed clusters, provide insight into the causal neurobiological mechanisms underlying behavioral symptoms, and allow detection of deviation patterns before behavioral symptoms emerge.

Beyond these more static approaches, Dynamic Functional Connectivity (dFC) analysis aims to capture within-session changes in brain connectivity measures using methods such as sliding window analysis or single-volume co-activation patterns (Hutchison et al., 2013). This method can be especially informative for mental disorder research as differences in static and dynamic functional connectivity have been observed between patients and healthy individuals (Calhoun et al., 2014; Xia and He, 2011; Cohen, 2018). Indeed, dFC has shown promise across disorders and transdiagnostic populations (e.g., Wang et al., 2018; Zhang et al., 2021; Kaiser et al., 2016; Demirtaş et al., 2016; Chen et al., 2024; Li et al., 2021; Pang et al., 2018). While promising, interpreting dFC results remains challenging because it is difficult to disentangle variability arising from physiological noise, fluctuations in arousal, task conditions, and sampling-related factors, all of which influence observed dFC profiles (Laumann et al., 2024).

Moving to more mechanistic models, Dynamic Causal Modeling (DCM) (Friston et al., 2003) is a Bayesian method that aims to extract information about effective connectivity in the brain, using a mathematical model based on differential equations that link latent neural activity to measured functional neuroimaging data, to provide insight into latent dynamical systems that underlie observed data (Heinzle and Stephan, 2018). DCM is a well-established method in neuroimaging (Daunizeau et al., 2011). It is particularly relevant in clinical practice as mental disorders are thought to be linked to deviations in neuromodulatory mechanisms, synaptic communication, and plasticity (Heinzle and Stephan, 2018). It has been widely applied across disorders (Bastos-Leite et al., 2015; Huang et al., 2022; Schlösser et al., 2008; Li et al., 2020; Cai et al., 2023; Shafieizadegan et al., 2024) and may help uncover distinct (dys)connectivity patterns within and across diagnoses. Such insights could inform decisions about which brain circuits or regions to prioritize during treatment.

Their practical applicability, however, is constrained by strong model assumptions, computational complexity, and limited scalability to large datasets or non-task data (Stephan et al., 2010). Moreover, model comparison and resulting inferences are relative to the set of models (Stephan et al., 2010). Given that they are typically applied in highly controlled experimental settings, their robustness in heterogeneous clinical populations is uncertain (Friston et al., 2003).

Neurobiological mapping and prediction approaches. Researchers not only aim to understand heterogeneous and overlapping neural patterns, but also try to map these neurological markers to clinical symptoms. Among those mapping approaches, neurobiological dimensional methods aim to understand heterogeneity and comorbidity based on biological components (Lynch et al., 2020; Buch and Liston, 2021; Parkes et al., 2020), by using multivariate statistical models, such as canonical correlation analysis (CCA) (Hotelling, 1936), to relate neuroimaging measures to variations in clinical manifestations and study underlying neurological dimensions of psychopathology (e.g., Xia et al., 2018).

Taking this approach one step further, neurobiological predictome methods use neurobiological information to predict the presence, progression, or outcomes of mental disorders, typically by employing (semi-)supervised methods, such as Support Vector Machines, linear discriminant analysis, Gaussian processes, neural networks, or logistic regression (Rashid and Calhoun, 2020). Insights from these models could be especially informative for disease progression prediction or risk identification.

Despite extensive research on predictive modeling (as summarized by Rashid and Calhoun, 2020), clinical translation remains limited due to important remaining challenges (Rashid and Calhoun, 2020). First, many models are trained and validated on small, homogeneous datasets, leading to poor generalization to real-world clinical populations. Second, predictive performance is often evaluated using metrics that do not directly translate to clinical decision-making, such as accuracy or Area Under the Curve (AUC), without considering clinical utility or cost-benefit trade-offs (Varoquaux and Colliot, 2023). Finally, the lack of straightforward interpretability of many machine learning models further hinders their adoption in clinical settings (Rudin, 2019). Addressing these limitations is essential to exploit the full potential of predictome models for the clinical translation of precision psychiatry.

Note that, while this review places particular emphasis on neurobiological markers and methods, especially neuroimaging, precision psychiatry encompasses a broader range of data modalities (including genetics, omics, biofluid-based markers, and physiological signals; Kas et al., 2025). Providing a comprehensive overview for each of these domains is outside the scope of this review, but we aimed to illustrate the relevance of biological information for precision psychiatry by focusing on the well-established field of neuroimaging. Undoubtedly, biological markers beyond neuroimaging components and methods should be considered, as they can provide complementary information and are likely to play a crucial role in developing comprehensive models of mental health.

2.4. From a cross-sectional towards a longitudinal research focus

Lastly, mental disorders are not stable; they evolve, and so do symptom expression and biological markers (Caspi et al., 2020). Extant models, however, are often cross-sectional, focusing on temporal snapshots, thereby not accounting for developments over time. This state of affairs is suboptimal, as longitudinal changes may in fact be informative for early diagnosis, risk identification, and treatment; therefore, a final challenge lies in the use of cross-sectional over longitudinal models, especially in mental health research (Etkin, 2019). While a cross-sectional approach focuses on symptoms and features of individuals at a single point in time, longitudinal approaches follow individuals over multiple time points, enabling the tracking of changes and temporal developments. In clinical practice, diagnosis is largely cross-sectional as the DSM-5 relies on cross-sectional criteria, forming a snapshot of symptoms at a given time without considering the developmental trajectory of disorders until the point of diagnosis. While the DSM-5 often specifies how long a symptom is present before diagnosis, it does not systematically consider how symptoms evolve. Following diagnosis, however, clinicians routinely monitor patients and track symptom trajectories to adapt treatments in response to observed changes.

"The right time" principle of precision neuropsychiatry cannot be achieved without considering the longitudinal dimension of biological markers. This temporal dimension of data can inform optimal intervention points at which certain treatments can be most beneficial for a specific patient, leading to more effective treatment. Moreover, including longitudinal information might eventually facilitate early diagnosis, as certain developments in neural patterns might provide information about emerging mental disorders, even before behavioral symptoms are fully established and clearly observable (Insel, 2014). To this end, more longitudinal biomarker research is needed before meaningful patterns of neurological change can be reliably identified and interpreted.

The social interaction abilities discussed so far are particularly well suited to be studied in a longitudinal manner. Lahnakoski et al. (2022), for example, proposed a framework for multi-scale assessment of psychopathology. This framework consists out of deep behavioral phenotyping, such as digital phenotyping, that can measure the amount of social interaction in a naturalistic environment daily. In turn, this can then provide information on neurobiological underpinnings associated with symptom dimensions, and inform clinical practice (Lahnakoski et al., 2022). Other useful methods exist to track social interaction abilities in a longitudinal, real-world manner, including ecological momentary assessment (EMA), passive sensing, and structured dyadic tasks. While a detailed discussion of those is outside the scope of this review, they do illustrate the value and feasibility of using and longitudinal information for clinical practice.

Towards dynamic methods. Targeting *"right time"* requires methods that can model the dynamic nature of biological components, behavioral symptoms, and mental disorders. In the literature, these methods are underrepresented because longitudinal datasets are sparse; nevertheless, new longitudinal initiatives have emerged recently (Bayer et al., 2026, preprint; Rehak Buckova et al., 2025).

Critically, none of the aforementioned methods are inherently longitudinal, but some have the potential of being extended to incorporate this longitudinal component. Bayer et al., 2026 (preprint), for instance, introduce velocity models and thrive lines as methodological extensions of normative modeling, which allow for tracking changes over time and can provide insights into, for example, centile shifting (Rehak Buckova et al., 2025; Fraza et al., 2025b; Bayer et al., 2026, preprint). Conceptually, velocity models represent the rate of change between time points for an individual, expressed as a slope in original units or a standardized change score. Thrive lines, on the other hand, represent population velocity centiles at a specific age, overlaid on a standard cross-sectional normative model chart (Fraza et al., 2025b). Indeed, initial studies show the value of longitudinal normative models, but they are limited to structural data and use only two or three time points (e.g., Rehak Buckova et al., 2025; Fraza et al., 2025a; Berthet et al., 2024).

Longitudinal approaches can provide additional value for precision psychiatry. Rehak Buckova et al. (2025), for example, adapted a model pretrained on cross-sectional data to evaluate longitudinal measures, enabling the characterization of individual temporal changes relative to population norms. A second promising example is the Precision Predictive Priors (P^3) framework, which explicitly aims to operationalize longitudinal modeling in real-world settings by conceptualizing individual differences in how the brain deals with prediction errors across four domains: interoceptive, exteroceptive, action-outcome, and social. Interestingly, by using a smartphone-based design, they make it both accessible and scalable, and allow for continuous updating (Lyndon, 2026).

Despite the promise of these initial studies and the adaptability of existing methods to repeated-measures data, robust longitudinal investigations in psychopathology remain scarce. To further extend these initiatives, inspiration could be drawn from, for instance, Time Series Analysis (TSA) approaches, a longstanding, broad collection of techniques to analyze data recorded at regular intervals over a period of time, including functional neuroimaging data, which can be particularly relevant for psychological research (Jebb et al., 2015). Similarly, statistical methods that are specifically designed for the analysis of repeated measures, including Repeated Measures Analysis of Variance (ANOVA) and multivariate ANOVA (Girden, 1992), generalized estimating equations (GEE) (Liang and Zeger, 1986), generalized linear mixed models (GLMM) (Breslow and Clayton, 1993), or Latent Growth or Trajectory Modeling (McArdle and Epstein, 1987) could provide good starting points.

3. Discussion

3.1. A cascade of challenges and methodological promises

The four challenges outlined above do not exist in isolation. They can be organized into a cascading structure, where each layer builds on the previous layer and brings us closer to a more comprehensive understanding of the underlying psychopathologies of mental disorders. This cascading structure, as shown in Fig. 1, is not a sequence of independent improvements but rather a chain of necessities, where addressing one challenge automatically advances to the next. A transdiagnostic approach enables the identification of clinically relevant patterns of deviations that are not restricted to diagnostic labels and cut across different disorders. Identification of shared transdiagnostic patterns, however, does not yet inform us about how these can be expressed differently across individuals, relative to the healthy population or other patients. The next level, therefore, requires methods that can capture individual-level variability or subgroup structure, rather than relying solely on group averages. This then brings us to the question of which underlying biological mechanisms drive these transdiagnostic patterns and variability in patient-specific profiles. The next step is to address methods that incorporate biological measurements and relate them to clinical or behavioral features. Lastly, given that these mechanisms and expressions can change over time, we require longitudinal methods that model these temporal dynamics using repeated measurements, enabling the study of trajectories rather than static snapshots. With this cascade we aim to provide a structured roadmap towards precision psychiatry, with the highest level facilitating us to potentially reach *"the right treatment, to the right patient, at the right time"*. Importantly, while we believe that methods situated at this last tier would give us the most comprehensive understanding of psychopathology, this does not mean that other methods that are not in complete agreement with one of the tiers are not valuable for psychiatric research.

The cascading nature of this framework reflects the relationship between the challenges. For instance, modeling heterogeneity (Tier II) supposes that variation is represented in a transdiagnostic space (Tier I), while identifying biologically meaningful mechanisms (Tier III) can help us to understand both transdiagnostic representation and individual-level characterization. Similarly, longitudinal modeling (Tier IV) builds on all preceding levels, as temporal trajectories must be defined over meaningful dimensions, individual profiles, and underlying mechanisms. This dependency structure distinguishes the cascade from frameworks that treat these components as independent dimensions.

A variety of methods to study mental disorders are available at every tier of the cascading structure, as shown in Fig. 2. However, there is no holy grail that fully meets all requirements of Tier IV. Methods addressing comorbidity and heterogeneity are extensively represented in the literature, whereas specific gaps remain, especially at Tiers III and IV. Across tiers and methods, several other recurring limitations emerge that further limit clinical implementation. First, many approaches rely on assumptions that are difficult to satisfy in heterogeneous, real-world clinical populations. Second, reproducibility across datasets remains a major challenge, particularly for data-driven methods such as clustering. Third, most approaches are developed and validated on relatively small and homogeneous samples, limiting their generalizability. Studies reporting a transdiagnostic sample often include only a subset of clinical populations that are rather similar. While it is reasonable to expect that similar disorders are more likely to share underlying neural mechanisms, this limits the ability to capture the broader transdiagnostic patterns. Finally, a critical gap remains between methodological outputs and actionable clinical decisions, as few methods provide interpretable and clinically validated metrics. These shared limitations, both methodological and in data availability, help explain why, despite substantial methodological advances, translation of precision psychiatry into practice remains limited.

Besides these shared methodological limitations, a central challenge, however, is the limited availability and quality of suitable data. First, many datasets are characterized by sampling biases, often overrepresenting Western, Educated, Industrialized, Rich, and Democratic (WEIRD) populations (Henrich, 2024, 2022), thereby limiting the equity, inclusiveness, and global generalizability of findings. Second, multi-site neuroimaging data are subject to substantial variability due to differences in acquisition protocols, scanner types, and preprocessing pipelines (Bhagwat et al., 2021; Warrington et al., 2025), complicating integration of datasets and potentially confounding model outputs. Third, most studies operate in a high-dimensional, low-sample-size regime, increasing the risk of overfitting and limiting reproducibility (Szucs and Ioannidis, 2020; Scheinost et al., 2019; Marek et al., 2022). Fourth, clinical labels themselves are often noisy and heterogeneous, reflecting limitations of current diagnostic systems rather than true underlying mechanisms (Insel et al., 2010; Feczko et al., 2019).

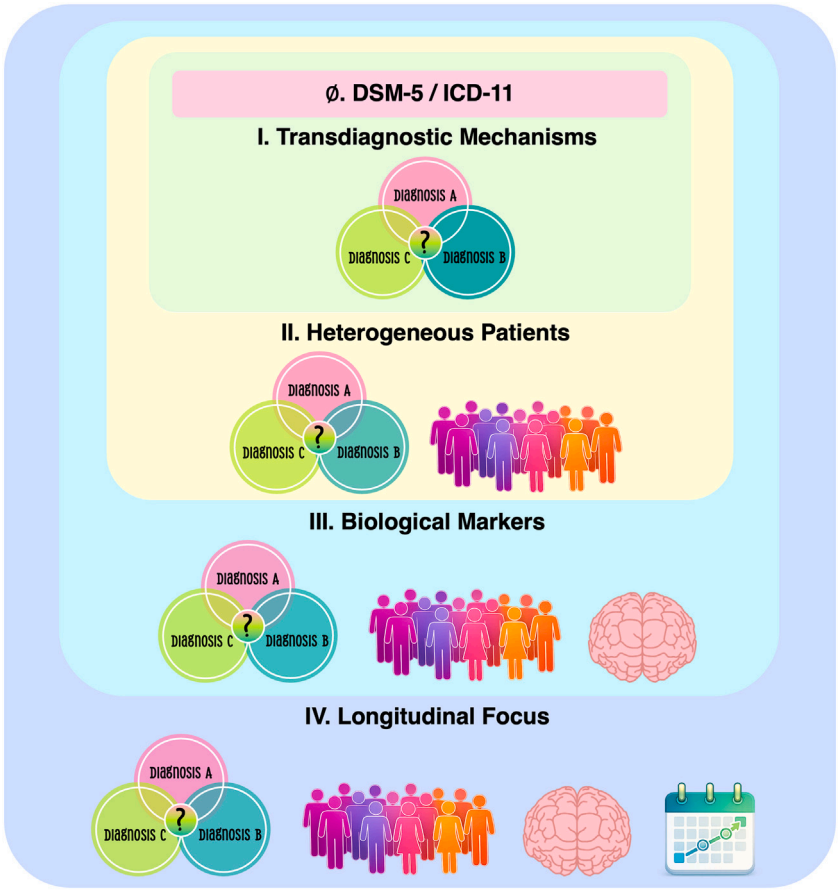

Fig. 1. Schematic visualization of four key challenges that should be prioritized in developing solutions for precision neuropsychiatry. These factors build on one another, with each tier bringing the field closer to a comprehensive, personalized understanding of mental disorders, in line with *"the right treatment, to the right patient at the right time"* principle of precision psychiatry (Cešková and Šilhán, 2021; Trivedi, 2016). Tier I transitions away from traditional approaches such as the ICD-11 and DSM-5 that operationalize strict boundaries between homogeneous diagnoses, towards a transdiagnostic approach that accounts for comorbidity. Tier II builds on that by explicitly acknowledging heterogeneity instead of focusing on mean-level patterns in a case-control design. Subsequently, Tier III advocates integrating (neuro)biological components alongside behavioral measures, and lastly, Tier IV calls for a focus on longitudinal models, as these might provide valuable information about the development and variation of mechanisms across time. By focusing on methods on this highest tier, a deeper understanding of the underlying psychopathologies of mental disorders can be achieved, allowing for a more personalized focus of psychiatry.

Finally, longitudinal and multimodal datasets that combine behavioral, biological, and environmental measures remain scarce, hindering the development of models that satisfy the full requirements of the highest tier (Mandal et al., 2025, preprint).

These data-related challenges directly constrain progress across cascading tiers. For instance, limited transdiagnostic datasets restrict the ability to model shared mechanisms (Tier I), while insufficient sample sizes and measurement noise hinder reliable estimation of individual-level deviations (Tier II). The scarcity of large-scale multimodal datasets limits integration of biological markers (Tier III). Furthermore, the lack of dense longitudinal measurements prevents robust modeling of temporal dynamics (Tier IV). As such, addressing data limitations is a prerequisite for advancing towards precision psychiatry.

Addressing these challenges requires coordinated efforts towards large-scale, standardized, and open data collection initiatives. Consortia such as ENIGMA (Thompson et al., 2014) and platforms like OpenNeuro (Markiewicz et al., 2021) represent important steps in this direction, enabling aggregation of data across sites and modalities. In addition, advances in data harmonization techniques and federated learning approaches may facilitate integration of distributed datasets while preserving privacy. Expanding longitudinal and multimodal data collection, including through digital phenotyping and wearable technologies, will be critical for developing models that capture the full complexity of mental disorders.

3.2. A path towards precision psychiatry in practice

Precision psychiatry is advancing rapidly, with promising methods emerging across all tiers of the cascading framework. The next step is to deploy these methods optimally in routine clinical workflows, enabling translation of theoretical principles of precision psychiatry into real-world clinical decision-making, informing whom to treat, how, and when.

To facilitate translation, the proposed framework can be mapped onto a potential clinical workflow. At intake, a patient like John would undergo a multi-modal assessment including behavioral measures and, where available, biological data (e.g., neuroimaging or physiological measures). These data would be projected onto transdiagnostic dimensions (Tier I), allowing characterization of John's symptom profile beyond his diagnostic labels. Next, individual-level deviation profiles would be estimated relative to normative models (Tier II), providing insight into how John differs from typical variation and from other patients. These profiles could then be linked to underlying biological

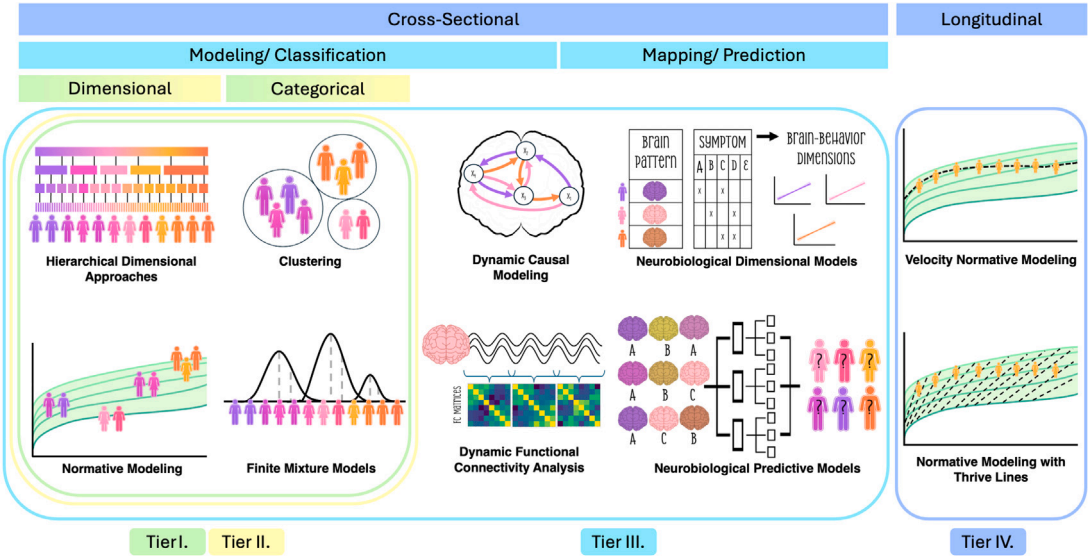

Fig. 2. Schematic visualization of the methods discussed at every tier of the cascading structure. Methods at Tier I and II are divided into categorical and dimensional transdiagnostic approaches and include Hierarchical dimensional approaches, Normative Modeling, Clustering, and Finite Mixture Models. Depending on the unit of analysis (i.e., focusing on subjects within a particular diagnosis versus subjects with different diagnoses), these methods can be used to discover patterns within a specific diagnosis to disentangle heterogeneity, or across diagnoses to discover shared mechanisms across disorders. In Tier III, methods are distinguished that either (i) model neurobiological measurements with the goal of classification (Tier II methods, along with Dynamic Causal Modeling and Dynamic Functional Connectivity Analysis) or (ii) map the (neuro)biological measurements to clinical symptoms or even use the neurobiological measurements to predict clinical outcomes (neurobiological dimensional and predictive models). Lastly, at Tier IV, methods are identified that can model longitudinal neurobiological measures.

mechanisms (Tier III), enabling identification of relevant neural systems or pathways associated with John's symptoms. This could allow treatment selection to be more directed towards relevant biological underpinnings driving his symptoms and potentially help predict treatment response. Finally, longitudinal monitoring of these profiles (Tier IV) might help identify clinically meaningful turning points, thereby informing optimal moments for intervention and possible time windows of increased risks of developing other mental health symptoms, as well as enabling tracking of treatment response and adaptation of interventions over time.

Taken together, arriving at a full implementation of Tier IV in clinical practice yields personalized, dynamic profiles that quantify how much an individual deviates from the norm, how these deviations are linked to biological mechanisms, and how they evolve. This goes beyond what diagnostic categories can capture and calls for a conceptual shift in how mental disorders are framed; that is, the question should no longer be "which disorder does John have?" but rather "does John deviate from a healthy trajectory, and is this deviation clinically meaningful?" In other words, we should transition from a diagnosis-centered label-based perspective towards a health-centered perspective that estimates the degree to which an individual is healthy.

This perspective is inspired by well-accepted practices in modern medicine, where clinical decisions often rely on individual, standardized health scores that summarize complex physiological states into one informative and actionable score, such as Body Mass Index (BMI) or blood pressure. These scores do not provide a diagnosis or strictly define a course of action on their own, but offer an initial point of information that can facilitate informed assessment, risk stratification, and treatment planning. They give an indication of how much a certain person deviates from the norm, taking into account variability in the population. Slight deviations are therefore not necessarily an indication of an illness, as a broader range of values can be considered 'normal' given the typical variation in the population. The value of such composites thus lies in helping to identify patterns of deviations that are less expected compared to the norm, and that need further attention, rather than providing a definitive assessment.

Critically, these scores meet all requirements of the cascading challenges that we presented. They are inherently transdiagnostic as they can be administered to anyone and provide informative measures independent of the presence or type of illness. They also capture meaningful heterogeneity: two individuals with the same BMI may both receive a diagnosis of obesity, yet their condition may arise from different underlying mechanisms, such as metabolic dysfunction versus lifestyle-related factors. Third, some of these scores can provide information about underlying biological processes that go beyond symptom expression, for example, high blood pressure can indicate risk, even when behavioral symptoms are absent. Finally, these scores support longitudinal modeling, as they can easily be collected repeatedly over time and are straightforward to compare across measurements. Change in scores between measurements may indicate disease progression or treatment response and inform the following steps in the intervention plan. Indeed, defining an analogous score for mental health appears to be a particularly promising way forward.

One possible example of this is an index that estimates the probability of healthy brain functioning. This index could summarize a broad range of multivariate deviation patterns from normative brain functioning into one probabilistic score of healthy brain functioning. In this way, the complex brain state is summarized by a measure that indicates for each individual how much they deviate from the norm. Quantifying brain health as a continuum might enable us to distinguish meaningful deviations, which can indicate the presence of mental health pathologies, from mere normal variation, echoing the premise *"it is an error to see only illness in abnormality"* (Vygotsky, 1993). Such an index should not be intended for diagnostic purposes, or to replace clinical assessment, but rather to inform the assessment of brain health and support active monitoring and proactive intervention. In doing so, it could help orient neuropsychiatry from reactive intervention towards proactive stewardship and prevention of mental disorders. A low score, for example, could flag potential meaningful deviations in

the underlying profile that might need further attention onward. Such a composite score potentially allows the identification of multivariate patterns of deviation that univariate analysis of isolated underlying mechanisms might miss. Such a score is thus not meant to replace the underlying profile, but rather sit atop and provide complementary information about brain health at a glance.

While such a brain health probability index would be promising, research is needed on how to combine multivariate patterns into one scalar without risking reductionism, algorithmic bias, and false pathologization or patient reassurance. The index could, for example, be estimated by employing uncertainty-aware statistical methods that explicitly quantify confidence in individual risk estimates, enabling low-confidence predictions to be identified and interpreted with appropriate caution, thereby reducing the risk of overinterpretation and supporting more responsible clinical use. Moreover, such an index should be clinically validated, for example, by showing meaningful correlation with other clinical outcomes.

It is important to note, however, that such a composite index fully aligns with the requirements of the cascading challenges, and that, as such, it has the potential to inform multiple levels of the clinical process and improve risk identification, early diagnosis, subtyping, and effective treatment. A decreasing value, for example, could indicate emerging pathologies, even before observable symptoms are present (early diagnosis), whereas an increasing probability after treatment could suggest an effective treatment response. Importantly, rather than replacing current symptom-based practices, such an index would be intended to supplement them by informing on biologically meaningful mechanisms at the level of the individual patient, ultimately aligning with the goal of *"the right treatment, to the right patient, at the right time"* and lessening the burdens for patients like John.

4. Conclusion

Precision psychiatry strives for *"the right treatment, to the right patient, at the right time"*, such that the substantial burdens associated with mental disorders can be lessened by improving early diagnosis, risk identification, subtyping, and effective treatment. To come to the full realization of this idea in practice, we discussed four challenges that should be prioritized, both in research and in clinical practices: (i) a transdiagnostic approach, (ii) accounting for heterogeneity, (iii) including biological markers, and (iv) a longitudinal focus. Critically, we argued that these challenges do not exist in isolation, but should be addressed as a cascading set of chained requirements. Unlike existing frameworks that conceptualize psychopathology along dimensions or domains, the proposed cascade provides a process-oriented roadmap that specifies necessary conditions for achieving precision psychiatry in practice. Substantial methodological progress has been made, particularly in addressing transdiagnosticity and heterogeneity. However, important gaps remain, especially regarding the availability and quality of suitable data and the development of longitudinal neurobiological models. Finally, we argued that achieving a full implementation of Tier IV in practice calls for a conceptual shift from a diagnostis-centered towards a health-centered perspective on precision psychiatry. Such health-centered, individualized approaches may also facilitate more equitable and globally accessible mental health care across diverse populations and clinical settings.

CRediT authorship contribution statement

Ymke Verduyn: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Seyed Mostafa Kia:** Writing – review & editing, Supervision, Conceptualization. **Harm Brouwer:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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