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Biomarker innovations in precision psychiatry diagnostics and treatment strategies

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ABSTRACT

Precision psychiatry is an approach designed to improve diagnosis and treatment of mental disorders by leveraging biological insights and developing innovative, mechanism-based treatment strategies unconstrained by current diagnostic boundaries. At its core, precision psychiatry aims to pinpoint the underlying neurobiological mechanisms responsible for the emergence and persistence of symptoms of mental health conditions. This approach strives to create diagnostic tools and therapies targeting these mechanisms, potentially addressing previously resistant aspects of mental health conditions by providing more precise symptom management and possibly altering the disease trajectory. Although still in its nascent stages, the realization of precision psychiatry will result in a more refined and biology-informed diagnostic system for mental disorders, requiring significant adaptations for clinicians, industry, patients and regulators. Identifying, validating and applying both fluid and functional biomarkers are critical steps in the development, testing and application of new precision psychiatry diagnostics and treatments. As part of the 2025 Precision Psychiatry Roadmap initiative meeting in Frankfurt, experts came together to present and discuss the current status of biomarker identification and validation, patient subtyping, and targeted interventions for stratified patient groups. This report features lecture summaries, meeting outcomes, and recommendations from both online and in-person audiences. In general, the recommendations emphasize standardization, collaboration, clinical implementation, digital innovation, long-term planning, and, importantly, patient engagement, as key priorities for advancing precision psychiatry. Despite existing challenges, there is strong optimism for the future of precision psychiatry, with continuous efforts to refine diagnostic tools and treatment strategies.

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1. Introduction

As part of its Precision Psychiatry Roadmap Initiative, The European College of Neuropsychopharmacology (ECNP) organized a two-day meeting regarding the current status on the identification, validation and application of biomarkers in the field of mental disorders with all stakeholders involved, including academic experts, industry leaders, and regulatory representatives. The main goal of this collaborative effort was to emphasize that advancing novel therapeutics in psychiatry requires deep phenotyping and comprehensive biomarker research that incorporates both functional and fluid biomarkers, with large, multimodal datasets gathered through consortia-led transdiagnostic studies expected to yield the most significant benefits. Considering that the meeting mainly focused on the use of biomarkers the following definition is applied: biomarkers are defined as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or interventions (FDA, 2016). The meeting program overview can be found in box 1.

The program started with two opening lectures that highlighted the rationale and background of the ECNP Precision Psychiatry Roadmap initiative, and provided a key example regarding biomarker development in the field of schizophrenia.

2. Martien Kas: the ECNP precision psychiatry roadmap initiative

Measuring biology is considered the cornerstone of diagnosis in medicine. For example, blood tests aid the clinical diagnosis of autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus. Also, cancer patients with, for example, colon cancer, will receive personalized treatments following biomarker diagnostics using biopsies of their tumor. In contrast, current classification methodologies for mental disorders are based entirely on behavioral signs and symptoms whose patterns have been derived from clinical consensus processes, with laboratory serving exclusion diagnosis of medical conditions that may induce similar symptom clusters (e.g., hypothyroidism as a causal factor for a major depressive syndrome). The syndrome-based classification systems supporting DSM-5 and ICD-11 provide a uniform 'language' to assess psychiatric and neurological disorders across the globe. Clinicians use these diagnoses to communicate with their patients, other clinicians, further stakeholders, and to request, when applicable, reimbursement from payors. Also, the current diagnostic systems have a pivotal role when it comes to approval of novel treatments. Unfortunately, currently available psychotherapies and pharmacotherapies are effective only in a proportion of patients within these diagnostic categories (Leichsenring et al., 2022).

This heterogeneity in treatment response within diagnostic categories is likely due, at least in part, to biological variation between patients (Clementz et al., 2016; Fountain et al., 2012; Tozzi et al., 2024) that is not being accounted for in the current classification system for mental disorders. In addition, transdiagnostic overlaps exists for several symptom clusters, such as social dysfunction in Schizophrenia, Major Depressive disorders, and Alzheimer's disease (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013; Saris et al., 2022). This is not unique to mental disorders; fever, e.g., is a common transdiagnostic symptom of many diseases and underlying pathophysiology. This transdiagnostic overlap in symptoms, however, offers the opportunity to develop novel, innovative, and quantitative biological endpoints beyond the current diagnostic framework. Specific pathophysiology (which can be transdiagnostic, for instance, inflammation) is necessary for developing disease-modifying treatments. The ECNP New Frontiers meeting 2024 aimed to address these issues and indicated a high need for a biology-informed framework to establish more precise diagnosis and treatment for mental disorders (Kas et al., 2025a, 2025b).

Furthermore, following the meeting, the steering committee mapped out a Precision Psychiatry Roadmap (PPR) initiative for global alignment and to start implementing such a biology-informed framework for mental disorders. The PPR is comprised of three components: 1) Developing global alignment on principles and procedures, 2) Building consensus on predictive validity of emerging data, and 3) Operationalizing new knowledge into an evolving biology-informed framework (Kas et al., 2025b). An important aspect of the PPR involves reaching

Text box 1. Overview of topics and presenters of the ECNP Precision Psychiatry Roadmap meeting 2025 in Frankfurt, Germany.

Opening lectures

1. Martien J. H. Kas: The ECNP Precision Psychiatry Roadmap Initiative

2. Kim Q. Do: Bridging the gaps towards precision psychiatry: mechanistic biomarkers for early detection and intervention

Session 1: Biomarker development and validation (Chair: Derek Buhl)

3. Michael S. Sand: Biomarker selection and alignment in a global prospective cohort study of clinical high risk for psychosis

4. Rouba Kozak: Precision Medicine and Biomarkers in the Treatment of Depression: Overcoming Challenges in Drug Development and Personalized Care

5. Elizabeth M. Tunbridge: Industry perspective and application of precision psychiatry biomarkers

Session 2: Subtyping patient populations (Chair: Peter Falkai)

6. Maria A. Oquendo: Diagnostic formulations in precisions psychiatry

7. Carol Tamminga: Brain-derived measures for psychosis biotyping

8. Nikolaos Koutsouleris: Neuro-imaging markers for precision psychiatry: depression as an example

9. Gitte Moos Knudsen: Multimodal prognostic and predictive biomarkers in major depressive disorders

Session 3: Targeted interventions in stratified patient groups (Chair: Andreas Reif)

10. Brenda W. J. H. Penninx: Immuno-metabolic depression: strategies and treatment options

11. Frank J. Padberg: Patient stratification and psychotherapy

12. Wayne C. Drevets: The future of precision psychiatry: an industry perspective

consensus on relevant quantitative biological measures for precision diagnostics and treatments for mental health conditions. Therefore, at the Precision Psychiatry meeting in Frankfurt, the following challenges were addressed to inform and provide recommendations to the field: 1) How to select and validate relevant biomarkers for mental health conditions? 2) How to reach consensus on predictive validity from emerging data? 3) How to operationalize new knowledge into an evolving biology-informed framework for mental disorders and to deliver precision diagnostics and treatments?

3. Kim Do: bridging the gaps towards precision psychiatry: mechanistic biomarkers for early detection and intervention

In the opening lecture, Dr. Kim Do addressed the unique challenges faced by precision psychiatry compared to the broader landscape of precision medicine. While precision medicine aims to deliver the right intervention to the right patient at the right time, psychiatry faces additional complexities due to its reliance on symptom-based diagnoses and significant clinical heterogeneity. These factors result in treatments that are effective for only a proportion of patients and variable treatment responses within diagnostic groups. To advance the field, she emphasized the critical need for quantitative biological endpoints enabling precise diagnosis and targeted treatment, coupled with high-accuracy predictive tools for early disease stages.

The presentation outlined a comprehensive translational program focused on early detection and intervention in schizophrenia, emphasizing the development of mechanism-based biomarkers that capture neural circuitry dysfunction. This approach aims to enable improved patient stratification, personalized treatments, and disease progression monitoring.

Dr. Do next illustrated how genetic and environmental risk factors interact during neurodevelopment, converging upon a central hub characterized by neuroinflammation, NMDA receptor hypofunction, mitochondrial dysfunction, dopamine dysregulation, and disrupted redox balance. These factors generate oxidative stress in a detrimental feedforward mechanism, particularly affecting parvalbumin interneurons (PVI) and their associated gamma synchronization, while also impacting myelination. These alterations lead to structural and functional changes in both local microcircuits and long-range connections, crucial for cognitive, affective, and social functioning (Cuenod et al., 2022).

Her research has made significant strides in translating preclinical models into clinical trials, focusing particularly on cognition, an unmet need in transdiagnostic psychiatry. Initial observations revealed decreased glutathione levels in the CSF and prefrontal cortex of schizophrenia patients (Do et al., 2000), with key glutathione genes associated with the disorder (Gysin et al., 2007; Xin et al., 2016). Using transgenic models with impaired glutathione synthesis (gclm-/-), her team demonstrated high vulnerability to oxidative stress and successfully reproduced numerous schizophrenia phenotypes, including NMDAR hypofunction (Hardingham and Do, 2016) and disruptions in PVIs.

A key discovery emerged from Dr. Do's research: the convergence of both genetic and environmental risks on oxidative stress-induced PVI impairment in the prefrontal cortex as a "final pathway" underlying at least some forms of schizophrenia. This finding positioned oxidative stress as a pathological mechanistic hub leading to PVI microcircuitry and associated neurocognitive impairments (Cabungcal et al., 2014; Steullet et al., 2017).

These insights led to successful proof-of-concept clinical studies using N-acetylcysteine (NAC), an antioxidant and glutathione (GSH) precursor. In chronic schizophrenia patients, NAC supplementation improved negative symptoms (Berk et al., 2008) and EEG mismatch negativity, an NMDAR-related component (Lavoie et al., 2008). A subsequent trial in early psychosis patients demonstrated target engagement, with NAC increasing prefrontal glutathione levels and improvements in neurocognition, negative symptoms, and structural and functional connectivity. Notably, the patient subgroup with high blood oxidative markers showed improvement in positive symptoms (Conus et al., 2018). If these findings prove reproducible in independent samples, using such biomarkers a priori to stratify patients for such treatments in clinical trials, they would validate the proposed causal mechanism of the "oxidative stress hub".

Dr. Do also presented a novel molecular mechanism linking mitochondria and oxidative stress-induced PVI impairments, involving dysregulation of miR-137 – the encoding gene being a GWAS locus strongly associated with SZ –, and COX6A2 (a cytochrome C oxidase complex IV marker specific to PVI-dysfunction and impaired mitophagy). These findings translated to the identification of brain-derived exosomal miR-137 and COX6A2 plasma levels as markers of PVI mitochondria alteration 19, suitable for use as objective markers for clinical purpose. They exhibited remarkable accuracy in patient selection for treatments targeting brain mitochondria dysregulation, thus allowing a path toward potential validation of the clinical and functional efficacy of forthcoming clinical trials conducted in the early phase of psychosis.

The lecture concluded by highlighting recent findings on brain-derived exosomal microRNAs associated with the redox hub as blood-based biomarkers for predicting psychosis transition in clinical high-risk individuals and its validation in external cohorts. These advances demonstrate the potential of brain-derived exosomal miRNAs of the redox hub as quantitative mechanism-based biomarkers that capture neural circuitry dysfunction for accurate risk prediction (Khadimallah et al., 2022). These studies pave the way for more precise, personalized approaches in psychosis prevention and early intervention.

Session 1: Biomarker development and validation

4. Michael Sand: biomarker selection and alignment in a global prospective cohort study of clinical high risk for psychosis

The Accelerating Medicines Partnership Schizophrenia (AMP® SCZ), constitutes an unprecedented global initiative dedicated to understanding and addressing clinical high-risk (CHR) states for psychosis (Wannan et al., 2024). Dr. Michael Sand provided further insight into the AMP SCZ study which is a longitudinal observational study that follows approximately 2000 CHR participants and 640 matched healthy controls over two years across 43 clinical sites. The study assesses a wide range of outcomes, including transition to psychosis, remission of CHR symptoms, persistence of attenuated psychotic symptoms, and psychosocial functioning. This ambitious project integrates innovative methodologies and diverse data stream to predict psychosis progression, improve early intervention strategies, and address unmet clinical needs in psychiatry. As the largest global effort of its kind, AMP SCZ represents a paradigm shift in mental health research by combining predictive biomarkers, harmonized global protocols, and open science collaboration.

The CHR state is often defined as a prodromal phase where individuals exhibit attenuated psychotic symptoms, brief psychotic episodes, or genetic and environmental risk factors. Despite the significant risk associated with CHR states—up to 35% convert to full psychosis within ten years—the population exhibits substantial heterogeneity in clinical outcomes. Some individuals recover fully, while others experience persistent symptoms or impaired functioning but neither remit nor convert. Objective markers predicting risk to develop full-blown schizophrenia would therefore be of enormous value, in order to stratify patients into risk-adjusted prevention programs.

Current CHR prediction models, although valuable, lack the precision required for personalized clinical applications. Limited individual-level prognostic accuracy, heterogeneous assessment tools, and challenges in implementing predictive models in real-world settings hinder their utility. Recognizing these gaps, AMP SCZ aims to establish a unified framework for CHR prediction and intervention through large-scale, harmonized data collection and analysis.

The initiative is spearheaded by a public-private consortium that includes the U.S. National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), pharmaceutical companies, and non-profit organizations. As the first AMP project to target a neuropsychiatric disorder, AMP SCZ emphasizes the importance of collaborative, precompetitive research to accelerate breakthroughs in mental health.

The overarching goal of AMP SCZ is to provide tools to enable the selection of enriched patient populations to considerably improve success in developing pharmacologic treatments for patients with CHR for psychosis. The specific objectives include:

- Developing Predictive Tools for CHR Outcomes

The project seeks to develop and validate multimodal biomarkers, including neuroimaging, electrophysiology, fluid biomarkers, and digital phenotyping, to establish early indicators of pharmacologic treatment efficacy.

- Harmonizing Global Research Networks and Creating a Comprehensive Data Repository

By standardizing assessment protocols across 43 international sites, AMP SCZ ensures that findings are generalizable and reproducible across diverse populations. Data from the study will be deposited in the National Institute of Mental Health (NIMH) Data Archive (NDA), making it accessible for secondary research and fostering transparency and collaboration.

The project supports the development of precision therapeutics and clinical trial frameworks to address the diverse needs of CHR individuals.

4.1. Multimodal biomarkers assessed by the AMP-SCZ consortium in the CHR population

The study integrates diverse data streams to capture the complexity of CHR states:

- Neuroimaging: Structural MRI, functional MRI, and diffusion-weighted imaging protocols are standardized across sites to assess brain connectivity and plasticity.
- Electrophysiology: EEG recordings capture neural responses to auditory and visual stimuli, providing insights into neural circuitry associated with psychosis risk.
- Fluid Biomarkers: Blood and saliva samples are analyzed for genetic, immune, and metabolic markers, including polygenic risk scores for schizophrenia.
- Digital Phenotyping: Smartphone-based surveys and passive sensing (e.g., GPS, accelerometer data) provide real-time behavioral and environmental data. Actigraphy devices measure physical activity and rest patterns.
- Speech and Facial Expression Analysis: Natural language processing and facial recognition algorithms analyze verbal and non-verbal communication, offering novel insights into emotional and cognitive states.

Other strengths of the initiative include a large and geographically diverse sample, Real-Time Data Collection via digital tools, the inclusion of feedback from individuals with lived experience of CHR, and an Open Science framework promoting transparency and collaboration.

By leveraging global collaboration, harmonized methodologies, and innovative technologies, the project aims to transform our understanding of CHR states and advance the goal of preventing psychosis onset. As the largest and most comprehensive study of its kind, AMP SCZ has the potential to catalyze a new era of precision psychiatry, improving outcomes for individuals at risk of psychosis and addressing a critical public health need.

5. Rouba Kozak: precision medicine and biomarkers in the treatment of depression: overcoming challenges in drug development and personalized care

Mental health disorders, particularly depression, pose significant global challenges, both economically and in terms of patient outcomes (Friedrich, 2017). Depression is a heterogeneous disorder, characterized by a wide range of symptoms and underlying mechanisms, which leads to substantial unmet medical needs and treatment difficulties (Herrman et al., 2022). The drug development process has been hindered by a limited understanding of the disorder's biology, outdated preclinical models, and the lack of effective, personalized treatments (Carvalho et al., 2016). Despite advancements in neurodegenerative disease research, neuropsychiatric disorders like depression often receive less attention from drug developers due to high costs, long development timelines, and lower success rates in clinical trials.

Given the complexity of depression—encompassing a broad spectrum of symptoms and frequently co-occurring conditions—a one-size-fits-all therapeutic approach is inadequate. There is an urgent need for new paradigms in depression drug development. Traditional treatments, such as selective serotonin reuptake inhibitors (SSRIs), do target some underlying biological mechanism of depression, which is probably not universal across patients (given that not all patients respond to SSRIs) but present only in a subset of patients with depression (Malhi and Mann, 2018; Nestler and Hyman, 2010). These treatments often take time to show effectiveness, have limited efficacy, and are associated with adverse side effects (Herrman et al., 2022). Precision medicine, which commonly integrates biomarker-driven strategies, promises to optimize treatment outcomes by tailoring treatment approaches to individual patients (Arns et al., 2022; Hampel et al., 2023).

Biomarkers play a crucial role in enhancing treatment strategies for depression. Proximal biomarkers are useful for safety and mechanistic validation, while distal biomarkers, although more predictive, are less practical in clinical trials (Hampel et al., 2018; Wagner, 2008). By “proximal,” we mean pharmacodynamic/response and safety biomarkers per BEST—signals that change soon after treatment initiation and are used for mechanistic validation and risk monitoring (e.g., on-treatment changes in autonomic or actigraphy measures, and NfL/GFAP for CNS safety); this is a timing/context-of-use distinction rather than an “upstream/downstream” position in a pathway. By “distal,” we mean predictive and prognostic biomarkers baseline or longer-horizon measures that estimate likelihood of benefit (predictive) or natural disease course (prognostic); while informative for enrichment or long-term outcomes, they are less practical to implement broadly in trials. Drawing lessons from Alzheimer’s disease, where structured biomarker frameworks (e.g., AT(N)) have improved patient selection, diagnostic accuracy, and therapeutic targeting, a similar stratification/monitoring approach can be applied to depression to address diagnostic inaccuracies, heterogeneity, and limited efficacy of current treatments (Jack et al., 2013).

Single-domain biomarker approaches have consistently fallen short in capturing the biological complexity of brain disorders. Advances in omics technologies, combined with AI-driven computational modeling and multimodal integration, are now essential for identifying clinically meaningful biomarkers and enabling precision medicine. Integrating omics, neuroimaging, EEG, and digital health data with machine learning can enable accurate patient stratification, dynamic disease tracking, and prediction of individualized treatment response, accelerating drug development and improving care beyond traditional antidepressants, which are often slow-acting and ineffective for many patients.

The FDA’s Biomarkers, BEST (Biomarkers, EndpointS, and other Tools) guidance provides a framework for incorporating biomarkers into drug development, despite challenges related to validation, standardization, and ethical considerations (FDA-NIH Biomarker Working Group,

2016). A multimodal biomarker strategy—integrating genetic, neuroimaging, molecular markers, and clinical parameters—could revolutionize depression treatment by improving diagnostic accuracy, patient stratification, and therapeutic strategies (Paul and Potter, 2024).

Standardizing and harmonizing data in large clinical datasets is essential for identifying reliable biomarkers for major depressive disorder (MDD) and other serious mental illnesses (Strawbridge et al., 2017; Umbricht et al., 2024). Technologies, such as genomics, transcriptomics, proteomics, and metabolomics, are expected to provide deeper insights into the mechanisms of depression, revealing unique and shared biological pathways. These advances allow for the identification of novel endophenotypes—distinct biological markers that explain variability in depression and treatment responses, enabling personalized treatment strategies (Hu et al., 2022).

In response to the need for a deeper understanding of depression and treatment variability, the Foundation for the National Institutes of Health (FNIH) has launched an initiative to conduct a large-scale naturalistic study to generate a comprehensive, harmonized clinical dataset. This study aims to identify patient characteristics that predict differential treatment responses, focusing on participants with moderate to severe depression. Data collection will include molecular and fluid biomarkers, imaging, digital, and clinical assessments, providing valuable insights into the pathophysiology of depression and the development of more effective, targeted therapies.

5.1. Key recommendations for advancing depression treatment through precision medicine

- Leverage Multi-Biomarker Approaches: Evaluate whether a combination of biomarkers can improve diagnosis, patient stratification, and treatment selection, targeting the underlying biological mechanisms of depression
- Enhance Understanding of Brain Biology: Increase research into the complex brain networks involved in depression, using molecular and fluid biomarkers, imaging, and digital tools to identify modifiable biological targets.
- Advance Drug Development with Technology: Integrate neuroscience, data science, and machine learning to optimize clinical trial designs, accelerate personalized treatment development, and refine patient responses.
- Foster Collaboration Across Sectors: Promote partnerships between academia, industry, and regulatory bodies to incorporate biomarkers early in the drug development process and facilitate the development of reliable biomarkers.
- Personalize Treatment Approaches: Move beyond generalized treatments to develop therapies tailored to individual patients, improving efficacy and reducing adverse effects.
- Integrate Real-World Data for Continuous Improvement: Invest in data-driven approaches, incorporating longitudinal data and digital health technologies, to monitor treatment progress and refine strategies over time.

Through the integration of emerging technologies and biomarker strategies, depression treatment can progress toward more effective and personalized therapies. The FNIH's large-scale study and public-private partnerships illustrate the potential of precision medicine to address the complexities of depression, ultimately improving patient outcomes and accelerating the pace of psychiatric drug discovery.

6. Elizabeth Tunbridge: industry perspective and application of precision psychiatry biomarkers

Dr. Elizabeth Tunbridge, Director of Translational Neuroscience at Boehringer Ingelheim, discussed the current state and future directions of stratification and treatment response biomarkers in neuropsychiatry from a drug discovery perspective.

She highlighted the gap between the current clinical diagnostic criteria and the individual experiences of patients: many symptoms cross diagnostic boundaries and, conversely, there is substantial heterogeneity within a single diagnostic group. As a result, patients receive care on a trial-and-error, rather than tailored, basis. There is a need for more precise, biologically-based approach, grounded in the holistic and changing needs of the individual patient.

A major barrier to achieving this goal is the lack of validated biomarkers, including predictive biomarkers, to enable patient stratification, and monitoring biomarkers, to reliably assess treatment response. Such biomarkers should be objective and quantitative at the level of the individual, and should index some aspect of biological function, even if indirectly.

There is currently a trade-off between the extent to which potential stratification biomarkers directly index brain function vs. their scalability. For example, it is feasible to use neuroimaging measures in early clinical development, but this becomes more challenging in late-stage trails and in routine clinical practice, at least within the current clinical framework. Notably, if sufficiently predictive, stratification biomarkers may ultimately feed into the development of new, biologically-based diagnostic schemes. To maximize utility in clinical practice, tests used to guide diagnosis and treatment pathways should serve the diversity of available therapies and therefore should not be proprietary, emphasizing the need for precompetitive collaboration in this area.

The detailed requirements for treatment response biomarkers changes subtly across clinical development. In early-stage development, there is a need for rapid and sensitive readouts of clinical efficacy, even if these represent a significant operational burden. In later clinical development, treatment response biomarkers need to be suitable for collection at scale and accepted by regulators. It would be beneficial for such biomarkers to be suitable for longitudinal and remote assessment, to capture the true clinical picture and to minimize positive trial effects resulting from increased clinical contact. Ultimately, there is a need for novel biomarkers and endpoints that can be integrated into clinical practice, are accepted by payors and – crucially – index the symptoms that most matter to patients and their advocates.

Current approaches to the identification of both stratification and response biomarkers focus on either mechanism of action-driven approaches (Krystal et al., 2020), which require *a priori* hypotheses about the nature of putative biomarkers, or data-driven approaches (Wu et al., 2020), which require *de novo* data collection and therefore likely increases the size of early clinical studies. It is possible that the collection of large-scale, deeply-phenotyped datasets will ultimately help to bridge the gap between these currently distinct approaches.

In conclusion, Dr. Tunbridge emphasized that, although challenging, realizing the goal of precision psychiatry will be highly beneficial to all stakeholders. She highlighted the importance of centering the patient – by measuring and treating the symptoms that matter – and the need for collaboration with all key stakeholders to achieve these goals.

Session 2: Subtyping patient populations

7. Maria A. Oquendo: diagnostic formulations in precisions psychiatry

Dr. Maria Oquendo, Professor and Chair of the Department of Psychiatry at the University of Pennsylvania, discussed the future strategy for the DSM. She began by listing the critiques of the DSM, including its atheoretical nature, categorical diagnoses, and reliance on expert consensus rather than empirical data. Dr. Oquendo highlighted the realities that underpin these characteristics and emphasized the need to move towards integrating evolving knowledge, including advances in biomarkers, measurements, and classification models.

Dr. Oquendo underscored the importance of harmonizing the DSM with the ICD to facilitate global communication about psychiatric diagnoses. She also noted the need to address comorbidity, which suggests that current diagnoses are imprecise.

She outlined the structure of the DSM committee, which includes experts from various fields and aims to develop a strategic roadmap for future updates. The committee has formed subcommittees focused on structure and dimensions, functioning and quality of life, biomarkers, and social determinants of mental health.

Emphasizing the importance of integrating social determinants of mental health, culture, functioning, and quality of life into psychiatric diagnoses, Dr. Oquendo also stressed the need for the DSM to become a living document that can be updated in real time to reflect new discoveries.

The committee aims to move away from theoretical agnosticism and embrace the biological nature of psychiatric conditions as well as the impact of environmental effects. Dr. Oquendo highlighted the importance of placeholders for biomarkers and tools for assessing quality of life and function. She also mentioned the need to involve people with lived experience and clinicians in the discussion to ensure the DSM meets the needs of all stakeholders.

Dr. Oquendo concluded by expressing the committee's commitment to making the DSM a flexible and plastic system that can integrate new knowledge as it evolves. She invited input from diverse perspectives to improve the DSM so it remains relevant, current and useful.

8. Carol Tamminga: brain-derived measures for psychosis biotyping

Dr. Carol Tamminga, Professor and Chair of Translational Research in Psychosis at UT Southwestern Medical Centre in Dallas, presented on the B-SNIP (Bipolar and Schizophrenia Network for Intermediate Phenotypes) study.

The time has come for discovering and verifying neural biomarkers as they present across dimensions of psychopathology (e.g., psychosis, depression, aggression) and to attempt to define disease entities by biomarker clusters. This method asks not what biomarkers characterize a diagnosis (e.g., starting with schizophrenia or Major Depression) but, what biological characteristics coalesce within a dimension of psychopathology, across diagnoses. In this fashion, the outcome is not merely the same disease distribution as already known, but a new disease construct based on agnostic neural biological measures, or 'biomarkers' for short. The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium has measured a family of biomarkers, including cognition, electrophysiological markers, and imaging, across five sites in the United States. In the first phase, when the outcomes were not yet known, a large, rational list of biomarkers that were previously demonstrated to be interesting for psychotic disorders was organized, and individuals with psychosis were recruited with the expectation that some biomarkers would fall on each of the diagnoses. However, the outcome was different: no biomarkers fell on any of the conventional diagnoses with enough power to diagnose. Thus, the conventional diagnoses were removed from the probands, and an analysis was performed to assess which biomarkers clustered together. Instead, when the probands were grouped based on biomarker commonality rather than conventional diagnoses, the biomarker-defined groups fell into 3 clusters which we named B-SNIP Biotype-1, −2 and −3 (Clementz et al., 2022; Tamminga et al., 2022). To increase the utility of the B-SNIP Biotypes, the B-SNIP Consortium is conducting several experiments to test hypotheses about clinical outcomes to advantage clinical care. For example, the B-SNIP data showed that clozapine increases intrinsic EEG activity (IEA) in brain in all Biotypes, but clozapine normalized IEA in B-1 only. This led us to hypothesize that clozapine will have antipsychotic action specifically in B-1, but not in B-2 or B-3. In a second study, it was hypothesized that people with Early Psychosis would respond differentially to multi-specialty treatments provided in Early Psychosis programs based on Biotype (B-3>B-2>B-1). This study is now recruiting Early Psychosis individuals, biotyping them and involving them in an early psychosis program near where they live. These young people will be assessed after 1 year to test which Biotype group has progressed most with the treatment. Additionally, Dr. Tamminga is working with a startup pharmaceutical company to bring to market a drug for Cognitive Dysfunction in Schizophrenia; the project is very early and there are no public data yet.

Finally, Dr. Tamminga highlighted the application of stem cell lines derived from individuals with different Biotypes to study psychosis pathophysiology. These cell lines have revealed differences in action potentials between the Biotypes, suggesting potential ion channel defects in certain Biotypes. These research approaches underscore the importance of biological diagnoses in understanding and treating psychosis. Dr. Tamminga concluded by emphasizing the power of molecular diagnoses and the promise of precision psychiatry for patients and their families.

9. Nikolaos Koutsouleris: neuro-imaging markers for precision psychiatry: depression as an example

In his presentation, Dr. Nikolaos Koutsouleris explored the application of neuroimaging biomarkers to refine the classification and management of psychiatric disorders, particularly focusing on depression. Traditionally, psychiatric disorders, including depression, are diagnosed based on a multitude of clinical symptom combinations, which not only leads to clinical heterogeneity but produces the enormous biological variability within this diagnostic group. This heterogeneity manifests in the lack of imaging-based diagnostic separability of patients with depressive disorders (Winter et al., 2024) and may underlie treatment response variability, with current therapies only benefiting a subset of individuals within this diagnostic category.

Using machine learning techniques, Dr. Koutsouleris and colleagues analyzed neuroimaging data from patients with depression and schizophrenia, achieving a 76% balanced accuracy in distinguishing these two conditions. The key factors determining this neuroimaging-based separability were the age of onset and brain age. Patients with early-onset depression exhibited brain patterns more akin to schizophrenia, particularly when associated with accelerated brain aging. This suggests that early-onset depression may not be a homogeneous condition but could represent a distinct neurobiological phenotype, potentially bridging the schizophrenia spectrum. These findings underscore the importance of integrating neurobiological factors into psychiatric diagnosis to account for individual differences in clinical presentation and brain aging.

To further address heterogeneity in depression, Dr. Koutsouleris presented a clustering approach applied to the clinical-behavioral data of a transdiagnostic sample of the PRONIA study, which included patients with first-episode psychosis, first-episode depression and clinical high-risk individuals (Dwyer et al., 2022). Using an oncology-inspired model for subtype analysis, the team identified four primary factors: positive symptoms, negative symptoms, depression severity, and functional impairment. These factors were associated with distinct clinical and brain-based phenotypes, with some depression patients displaying patterns characteristic of schizophrenia, particularly in terms of cortical impoverishment. This highlights the challenge of defining depression solely by symptomatology and suggests that neuroimaging data could offer valuable insights into disease mechanisms.

Furthermore, Dr. Koutsouleris demonstrated how insights from neurodegenerative conditions, such as behavioral variant frontotemporal dementia (bvFTD), could inform the study of psychiatric disorders. By applying a classifier trained on neuroimaging data from bvFTD patients and healthy cohorts, the team observed diagnostic alignment of structural brain patterns in patients with schizophrenia (41% of cases), and major depression (22% of cases). This gradient of increasing neuroanatomical similarity may point to subtle transdiagnostic commonalities in brain system pathology, particularly in regions involved in salience processing, suggesting potential neurodegenerative features in certain depression subtypes. Dr. Koutsouleris showed that increasing "bvFTD-likeness" was associated with worse

clinical outcomes in depression and psychosis, suggesting that this 'in-silico' biomarker holds prognostic value for preventive treatment strategies.

In a further longitudinal analysis, Dr. Koutsouleris and colleagues used neuroimaging data to predict the onset of clinical high-risk (CHR) states in patients with depression. A predictive model that integrated neuro-imaging biomarkers, including B-V-FTD likeness and mixed syndrome classifiers, achieved a 70% balanced accuracy in forecasting the development of CHR symptoms. This model highlighted the importance of using biological data to predict disease progression and outcomes, offering a new avenue for targeted interventions in at-risk populations.

In conclusion, Dr. Koutsouleris emphasized the need for a shift toward precision psychiatry, where diagnoses and treatments are informed by a combination of clinical symptoms and neurobiological markers. By integrating biomarkers such as neuroimaging into clinical practice, psychiatry can overcome limitations of symptom-based taxonomy, improving diagnostic accuracy, treatment efficacy, and patient outcomes. The findings discussed in this presentation advocate for a more refined approach to understanding psychiatric disorders, particularly depression, through the lens of neurobiology and precision medicine.

10. Gitte Moos Knudsen: multimodal prognostic and predictive biomarkers in major depressive disorders

The treatment of Major Depressive Disorder (MDD) is currently based on a "one-size fits all" approach where up to 30% of patients do not respond to first- or second-line antidepressants (Rush et al., 2006). It is now recognized that the lack of prognostic biomarkers is due to a vast heterogeneity within the clinical population diagnosed with MDD. Dr. Gitte Moos Knudsen subsequently pointed out that the goal of precision medicine is to identify biological, psychological, and environmental factors, aka predictive biomarkers, that can be leveraged to personalize treatment for each individual patient, thereby enhancing the quality of care. Previous attempts to identify predictive biomarkers in MDD have typically focused on one or two candidate biomarkers, an approach which has had limited success (Kennis et al., 2020) and have yielded results that have been difficult to replicate with independent data. It was here proposed that if the individual biomarkers truly reflect the same biological pathophysiology, a multi-domain approach where biomarkers are combined should in theory be superior to generate a predictive power. This hypothesis was tested based on nine neuroimaging, biological and psychological biomarkers for recovery after antidepressant treatment in MDD.

The NeuroPharm 1 project is a naturalistic trial (NCT02869035) (Köhler-Forsberg et al., 2020) where non-psychotic and antidepressant-free patients (mean age 27 years, range 18–57) with moderate to severe MDD initiated escitalopram treatment (with the option to switch to duloxetine, if needed) and are followed up at 4, 8, and 12 weeks. Symptom severity was assessed with the Hamilton Depressive Rating Scale 6 (HAMD-6) at baseline ($n = 90$), week 4 ($n = 89$), 8 ($n = 87$) and 12 ($n = 85$). Recovery was defined as $\geq$50% reduction in symptoms compared with baseline and primary clinical endpoint was recovery status at week 8. Before starting antidepressant treatment, patients were phenotyped with a wide range of questionnaires, cognitive testing, blood biochemistry, brain scans, and EEG. Based on baseline deviations from healthy controls and on unimodal predictive power, nine candidate biomarkers that were considered good candidates as a part of multimodal predictive biomarkers were selected. These included 1) brain serotonin 4 receptor (5-HT4R) binding (Köhler-Forsberg et al., 2023); 2) orbitofrontal cortical thickness (Beliveau et al., 2022); 3) EEG-assessed vigilance regulation (Ip et al., 2021); 4) cognition (Dam et al., 2021); 5) cortisol awakening response (Vulpius et al., 2023); 6) high-sensitivity C-reactive protein (hs-CRP); 7) depressive symptom severity; 8) self-reported childhood trauma; 9) and self-reported trait Neuroticism.

Two predictive models were considered: a logistic regression (linear effects on the logit scale) and a Random Forest approach (non-linear effects), with age, sex and the nine biomarkers as predictors. The combined predictiveness of the candidate biomarkers based on the Area Under the Curve (AUC) of the predictive model was assessed in a 25-fold cross-validation framework. The relevance of each biomarker was assessed using Wald regression tests in a logistic model, adjusted for multiple comparisons using a max-test approach.

The logistic regression model showed limited discriminative power at week 8 (AUC=0.62, $p = 0.059$) while the Random Forest model showed poor discriminative power (AUC=0.48, $p = 0.71$). At week 12, both the logistic regression (AUC=0.62, $p = 0.098$) and Random Forest (AUC=0.64, $p = 0.044$) model showed limited discriminative power at week 12. Although a trend was observed for EEG-vigilance, orbitofrontal cortex thickness and cognition to be associated with remission at week 8 in the logistic model (p-values between 0.01–0.097 before adjustment, all above 0.09 after adjustment), combining the unimodal biomarkers did not convincingly outperform single biomarkers. Future analyses should test if machine learning approaches can lend more support for identification of predictive multimodal biomarkers in MDD.

The models employed did not provide much evidence that combining biomarkers generated a consistent picture of underlying pathophysiology in MDD. With machine learning approaches, however, more variables can be taken into account and this strategy is currently being pursued. Keeping in mind that the goal is to predict individual responses to treatment, a single-site sampled cohort of 100 unmedicated patients with MDD where significant co-morbidity has been excluded should be enough for this validation. While some evidence that specific candidate biomarkers may help predict patient recovery was found, reliable or clinically relevant probabilities of recovery for any time point could not be obtained. In addition, the associations between individual biomarkers and treatment response can highly vary across the different timepoints, emphasizing that both follow-up time points and outcome measures should be chosen with great care in future precision medicine studies. Biomarker research is also hampered by differences across trials in how to define responder/non responder groups, and which scales to employ. It is proposed that the field could move faster forward if data from large, completed company-based trials on a pre-competitive basis could be made available to the field. Instruments to provide resources that can make open science a reality would be highly welcome.

Session 3: Targeted interventions in stratified patient groups

11. Brenda Penninx: immuno-metabolic depression: strategies and treatment options

Psychiatric disorders are heterogeneous conditions with diverse symptom and course profiles. This complicates pathophysiological studies as different biological and environmental mechanisms could lead to the same disorders. Unravelling this heterogeneity is important to be able to provide precision medicine. Dr. Brenda Penninx's research illustrates the importance of disease heterogeneity with the example of depressive disorder (depression), a common disorder with large public health impact. Unfortunately, in the last three decades we have not seen a reduction in the impact of depression on our society, as depression continues to be listed as one of the top conditions with the highest disease burden worldwide (Herrman et al., 2022).

The heterogeneity of depression can be seen at various levels. For instance, heterogeneity exists at the level of environmental factors that contribute to depression risk, with certain patients clearly reporting the presence of strong environmental stressors (such as childhood trauma, life events, or socioeconomic situation) whereas others are lacking such stressors. Heterogeneity also exists at the pathophysiological level. The most recent large-scale genome-wide study of depression – involving almost 700 K persons with depression and 2 million controls – yielded almost 700 genome-wide significant hits (Adams et al., 2025). Examining the functional annotation of these genetic variants confirms the

role of brain processes and neuronal dysregulation in depression. However, depression also shares genetic variants and pathways with cardiovascular traits, such as metabolic and inflammatory biomarkers (Bergstedt et al., 2024). These findings are in line with the fact that also at the phenotypic level depression is linked both to dysregulation of brain function as well as to metabolic syndrome, dyslipidemia, inflammation and dysregulated energy metabolism (Marx et al., 2023). In addition, although these pathophysiological dysregulations have been consistently linked to depression, not all persons with depression present all these dysregulations to the same extent. In fact, most depressed individuals do not present with e.g. metabolic syndrome or inflammation. This clearly illustrates that there is extensive heterogeneity in the extent to which different pathophysiological mechanisms are present in individuals.

Another relevant source of heterogeneity in depression stems from symptom presentation. Depression is classified according to nine key symptoms including depressed mood, anhedonia and various cognitive and somatic symptoms. However, there is huge variation in the specific symptoms that individuals with depression have. Certain symptoms – such as sleep and appetite problems – can even have opposite directions in patients, either too much or too little sleep/appetite. Examining which specific symptom profiles link to underlying pathophysiology, could help the identification of specific forms of depression that are less heterogeneous in their presentation and etiology.

Using large-scale cohort data from the Netherlands Study of Depression and Anxiety (NESDA), Penninx et al. have illustrated through a data-driven approach the existence of a subgroup of individuals with 'immuno-metabolic depression'. In this subgroup, comprising 25–30% of all depressed persons in NESDA, a clustering of atypical, energy-related symptoms was found (including gaining weight, hyperphagia, loss of energy, leaden paralysis, hypersomnia) with immune-metabolic dysregulations (including high levels of inflammatory biomarkers (CRP, IL6, glycoprotein acetyls) and metabolic dysregulations (abdominal obesity, dyslipidemia, insulin and leptin resistance) (Milaneschi et al., 2020; Penninx et al., 2025). This supports the hypothesis that immune and metabolic abnormalities cluster with a specific depressive symptom profile. Identification of this form of immunometabolic depression may have relevance for clinical practice. It has been shown that persons with immunometabolic depression characteristics respond more poorly to standard anti-depressants, and may be more responsive to anti-inflammatory or lifestyle interventions. Various studies are currently underway to further test this. When doing so, researchers should put individual trial data together to arrive at the needed scale for testing and validating stratified treatment approaches (Penninx et al., 2025).

In conclusion, what this line of research clearly indicate is the large-scale cohort studies could help identify clustering of specific pathophysiological mechanisms with relevant symptom dimensions within a specific patient group. Next, cross-disorder studies are necessary to illustrate to what extent such a symptom-pathophysiology clustering crosses diagnostic boundaries. Immuno-metabolic dysfunction as well as atypical, energy-related mood symptoms are also present in other psychiatric conditions, including e.g. bipolar disorder and psychosis. This illustrates the need for future research to focus on harmonizing cohort and trial data to arrive at validated and data-driven precision medicine approaches in psychiatry.

12. Frank Padberg: patient stratification and psychotherapy

Dr. Frank Padberg discussed the role of patient stratification in the field of psychotherapy. He highlighted the individualized nature of psychotherapy and the importance of validity for psychological models and interventions.

He began by outlining the current state of stratification in psychotherapy, noting that while digital interventions, standardized methods and manuals guide practice, psychotherapy is naturally highly individualized. It comprises a large variety of mostly psychological interventions, which vary in terms of time per session, frequency of sessions and length of overall treatment with at its maximum over 200 individual of sessions applied over years. Thus, a term 'precision psychotherapy' (Martinez-Aran and Vieta, 2022) (analogous to 'precision psychiatry') has not yet been coined, and the field would be reluctant to do so. Lastly, differential efficacy of psychological interventions in some fields (e.g. in depression) is not easily demonstrated, leading to the notion that psychotherapies are equally effective (known as the 'Dodo Bird Verdict'). This phenomenon is also represented in some clinical guidelines. Looking with this background at the topics of potential theragnostic markers and stratification, one can readily say that there is a long list of criteria that could be used for stratification: disease severity scores, risk predictors (e.g. Leeds Risk Index), complexity of the condition (co-morbidities), demographic information, socio-economic characteristics, disease subtypes, additional clinical information, and biomarkers. Among these, mostly severity measures and risk indices have been applied for stratification in clinical studies. In contrast, numerous biological parameters have been investigated in psychotherapy research as well (e.g. fMRI activation markers in critical brain regions), and many small studies with significant findings have been published; however, validated biomarkers are still missing.

Dr. Padberg presented two examples of stratification studies based on clinical information. Delgadillo et al. (2022) conducted a pragmatic, multisite, single-blind RCT (randomization clustered by clinicians) involving four Improving Access to Psychological Therapies (IAPT) services in northern England. Clinicians involved were psychological well-being practitioners who conducted initial assessments in the participating services and were qualified in low intensity psychological interventions. Patients seeking treatment for common mental disorders (MDD, PTSD, OCD, body dysmorphic disorder, phobias, and other anxiety disorders) were randomized to either a stepped-care or a stratified approach both providing a low or a high intensity intervention. The latter was based on the recommendation of a machine learning algorithm with participant-reported input measures of depression, anxiety, functional impairment, personality traits, employment status, and race and ethnicity. The low intensity intervention included cognitive behavioral therapy (CBT)-based, coping skills, of up to 8 sessions (30 min) that were administered under various settings, whereas the high intensity interventions included up to 20 sessions (50 min) and evidence-based psychotherapy (PT)(CBT, person-centered experiential counseling for depression, or Eye Movement Desensitization and Reprocessing (EMDR)). The authors found that stratified treatment performed better than stepped care.

Another study investigated migrants and refugees from Syria and Afghanistan living with depressive symptoms. Dr. Padberg described a study involving refugees from Syria and Afghanistan, which used a stratified care model based on the Patient Health Questionnaire-9 (PHQ-9) to determine the level of intervention needed (Böge et al., 2022). The Mental health in Refugees and Asylum Seekers (MEHIRA) trial was a multicenter randomized controlled trial in Germany that evaluated a stepped and collaborative care model (SSCM) that included culturally adapted digital applications, group interventions, and individual psychotherapy. In the SSCM model, participants were stratified to these interventions according to symptom severity as measured with the PHQ-9. The study showed that the stratification SSCM model was cost-effective and superior to treatment as usual (TAU) in reducing depressive symptoms with several key predictors of symptom improvement. Thus, both trials represent examples of successfully introducing stratified treatment based on clinical information in mental health care.

Next, Dr. Padberg introduced the concept of using childhood maltreatment as a further source of information for stratifying psychological interventions. Generally, a developmental model (Draper et al., 2024) could provide a heuristic framework for the discovery of theragnostic markers covering essential domains of development (e.g.

nutrition and health, education and cognition) during childhood and adolescence. Adverse Childhood Experiences (ACE) and more interpersonally expressed child maltreatment (i.e. the WHO term) may hamper of even disrupt healthy development. Thus, impaired somatic and mental health have been associated with ACEs. A recent transdiagnostic study by Dr. Padberg's group that included individuals with borderline personality disorders and chronic depression, showed that a novel hierarchical clustering approach of Childhood Trauma Questionnaire (CTQ) subscale information predicted depressive symptoms and loneliness (Goerigk et al., 2024, 2023). This CTQ clustering approach was then applied to the large data set of a multicenter randomized controlled trial (RCT) where individuals with an early onset chronic depression were randomized to two types of psychotherapy: 1) a therapy model that included ACE information and provided an array of methods to target dysfunctional interpersonal patterns and their associated self-concepts (i.e. Cognitive Behavioral Analysis System of Psychotherapy; CBASP); and 2) a supportive psychotherapy (SYSP) model, which was provided as active comparator (Schramm et al. 2017). In this study, the CTQ clusters were qualitatively replicated and clearly predicted the differential treatment outcome between CBASP and SYSP during the acute study phase and a 2-year follow-up. Thus, for people with higher CTQ scores in several domains, CBASP was more effective than SYSP, whereas in clusters with lower CTQ scores, both treatments were equally effective. Taken together, CM and ACE information could be clearly valuable for clinically informing psychological interventions. In addition, this perspective may theoretically open new avenues for discovering theragnostic markers guiding stratification in psychotherapy (Berens et al., 2017).

Dr. Padberg further highlighted the stratification potential of modular psychotherapy, which combines elements from various therapeutic models to address the specific needs of patients. He presented a study by Schramm et al. (2024) that compared modular psychotherapy to conventional CBT in patients with depression and early trauma. Individuals with depression, but also relevant comorbidities (e.g. anxiety disorders, personality disorders and posttraumatic stress disorder) and a history of ACEs were treated with CBT or with modular psychotherapy where CBT can be combined with CBASP, mentalizing and mindfulness elements according to their individual profiles of interpersonal and emotional problems. This pilot RCT clearly demonstrated the feasibility of modular psychotherapy and observed superiority in single clinical domains, though there was no difference between treatment arms at the limited sample size. Thus, a next generation of studies could for example compare stepped- and stratified care approaches based on modular psychotherapy interventions.

Finally, Dr. Padberg pointed out that psychotherapy research should create synergies with the fields of precision psychiatry as psychotherapy includes a continuous diagnostic process, e.g. providing context information about patients' real-life interactions with others or their emotional responses to stress. Beside clinical information, validated rating scales, tests, and interviews including patient reported outcome measures (PROMs), dynamic measures as ecological momentary assessments (EMA), as well as biological markers could be obtained during this process. Thus, psychotherapy could be a unique 'discovery model" for developing valid theragnostic markers that inform the differential application of psychological interventions in mental health care.

13. Wayne Drevets: the future of precision psychiatry: an industry perspective

Dr. Wayne Drevets provided a forward-looking industry perspective on precision psychiatry and discussed examples from recent J&J clinical trials in MDD.

Psychiatric nosology has struggled to advance beyond the extant syndromic classification, in which diverse clinical symptoms and behavioral signs are compiled to define a disorder, toward a classification based on pathophysiology. This limitation hinders the discovery of new treatments for psychiatric disorders on multiple levels. Firstly, the lack of certain knowledge regarding the pathophysiology of psychiatric disorders obscures paths to novel mechanistic targets that may prove therapeutic for some patients. Secondly, the absence of clinical approaches for identifying the patients most likely to benefit from a novel treatment mechanism interferes with the ability to show superiority in efficacy relative to currently available treatments that are generically available, because the biological heterogeneity encompassed within the syndromic diagnostic constructs contributes to variability in the clinical response to new treatments. Without differentiation in efficacy, however, many payor systems have been reluctant to value novel treatments over the current standard of care—which is priced too low to support the research and development costs that companies incur while bringing a new drug through development and regulatory approval. Precision approaches for identifying biologically based subgroups of psychiatric disorders for stratification in clinical trials thus have become essential to the development of new treatments.

To develop such approaches, companies have tested a variety of precision approaches for identifying the patients most likely to benefit from a novel therapeutic mechanism. At the simplest level, several companies are using the pharmacodynamic biomarker of being non-responsive to conventional monoamine reuptake inhibiting antidepressants to demonstrate the superior efficacy of a new treatment versus standard of care treatments. For example, in randomized, controlled trials patients with treatment-resistant MDD randomized to receive esketamine nasal spray demonstrated greater improvement in MADRS scores than placebo when both treatments were administered either in conjunction with a newly added SSRI/SNRI antidepressant or as a monotherapy (Kim et al., 2019; Reif et al., 2023), and greater improvement versus quetiapine XR when each drug was administered in conjunction to an continued treatment with an SSRI or SNRI antidepressant (Reif et al., 2023). In these studies, treatment resistance was defined as having not responded to two different antidepressant pharmacotherapies within the current major depressive episode, each administered at an approved therapeutic dose for an adequate treatment duration.

Other studies in MDD that tested compounds with novel, highly selective mechanisms hypothesized to act synergistically with monoamine reuptake inhibiting antidepressants instead selected patients who had *partially* (but inadequately) responded to an antidepressant, comparing the efficacy of adding the new treatment versus placebo for augmenting the antidepressant effect. Such study designs held the advantage of eliminating the need to prove a novel treatment's efficacy was superior to that of a standard of care antidepressant treatment in a head-to-head randomized controlled trial (a feat which has been an extremely high bar for new antidepressant therapies to hurdle). Based on the selectivity of some of these new treatments for mechanisms that regulate circuits with known behavioral or symptom outputs, nascent precision approaches were tested for the ability to enrich the study participants for the likelihood of responding to the new treatment. While many companies are endeavoring to develop circuit-based biomarkers and precision approaches to refine subject selection, as well as to develop more objective outcome measures, two studies sponsored by Johnson & Johnson merit comment.

One set of studies evaluated the antidepressant efficacy and safety of the selective orexin-2 receptor antagonist, Seltorexant, as both a monotherapy and as an adjunctive therapy in MDD. Because this mechanism had soporific effects and the excessive signaling of orexin-2 receptors was hypothesized to contribute to insomnia and other hyperarousal symptoms in MDD, the study participants were stratified a priori based on insomnia symptoms. In Phase 2 proof of concept (POC) trials the patient subgroups with higher levels of insomnia showed greater improvement in MADRS scores relative to placebo, whether administered as monotherapies or as adjunctive therapies to the current SSRI/SNRI antidepressant to which the patient had shown inadequately responsive (Mesens et al., 2025; Savitz et al., 2021). This nascent

precision approach currently is being tested in Phase 3 studies.

Another program assessed the antidepressant efficacy and safety of the selective κ-opioid receptor antagonist, aticaprant, in participants with MDD who had inadequately responded to current antidepressant treatment. In preclinical and clinical studies this mechanism reduced anhedonia symptoms and behaviors in experimental animals subjected to repeated stress and in humans with mood or anxiety disorders (Carlezon et al., 2009; Krystal et al., 2020; Pizzagalli et al., 2020). The neurobiological mechanisms underlying the symptom of anhedonia putatively involve altered function of the mesocorticolimbic dopaminergic circuits during the processing of associations between sensory and social stimuli, motivated behavior, and experiences of reward and pleasure. One mechanism that interferes with reward processing through this circuit and produces anhedonia like behaviors in preclinical models is mediated by κ-opioid receptor activation by increased dynorphin signaling (Muschamp and Carlezon, 2013). Therefore, in the randomized, controlled Phase 2 study evaluating the efficacy and safety of aticaprant versus placebo, each added to the ongoing SSRI or SNRI antidepressant treatment to which the participants had been inadequately responsive, a precision hypothesis was tested comparing the antidepressant treatment effect in participants with higher versus lower baseline levels of anhedonia (Schmidt et al., 2024). Anhedonia symptoms were assessed using the Snaith-Hamilton Pleasure Scale (SHAPS) scores. While the primary endpoint (mean change in MADRS at week 6) for aticaprant was significant versus placebo the between-group difference was larger among participants with $\geq$ to versus $<$ baseline median SHAPS scores. This nascent precision approach of using a threshold SHAPS score at baseline for patient stratification was tested in Phase 3 studies, however, and proved insufficient to predict a positive outcome in response to aticaprant (ClinicalTrials.gov ID NCT05455684 and NCT05550532).

Even if such development programs succeed at identifying precision approaches capable of matching the right patient with the right circuit-based therapeutic, additional obstacles remain before such paradigms can be implemented in clinical practice. First, health authorities require validation of the stratification approaches used to identify the target subpopulation as well as any novel endpoints used to index a therapeutic benefit. Additional regulatory requirements will apply if the stratification approach is intended as a companion diagnostic test, or if a biomarker used for this purpose has not already been qualified or validated according to current regulatory standards. Furthermore, any diagnostic tool or biomarker used in the clinic must be both scalable and relatively convenient for both the patient and the clinician to use. Finally, the stratification approach should ideally be cost-effective; otherwise, payors may erect additional barriers to use before they are willing to reimburse the diagnostic and its associated new treatment.

14. A path forward

The meeting brought into sharp focus the pivotal role of collaboration and networking between various stakeholders in advancing precision psychiatry. Strengthening cooperation networks has not only facilitated more effective data sharing and joint analyses but also created fertile ground for future interdisciplinary projects. These networks have enabled researchers to connect with peers investigating similar questions, fostering a sense of community and shared purpose. Importantly, discussions extended beyond academia, engaging stakeholders from industry, regulatory bodies, and patient advocacy groups, all of whom have acknowledged the challenges - and opportunities - ahead. Conversations about integrating precision medicine into existing diagnostic frameworks were particularly promising, laying the groundwork for projects that align more closely with the biological complexity of psychiatric disorders.

A key theme throughout the meeting was the recognition that progress in psychiatry hinges on deep phenotyping and robust biomarker research that incorporates both functional and fluid biomarkers. Large, multi-modal datasets, obtained through consortialed studies, taking a transdiagnostic approach, will likely provide the most value. There was a broad consensus that psychiatric phenotypes often transcend traditional diagnostic categories, pointing to the need for a supplementary classification system that is grounded in biological markers. While enthusiasm for biomarkers in neuropsychiatry continues to grow, participants emphasized the importance of defining and standardizing these tools, as well as ensuring their pragmatic relevance in clinical settings (e.g., scalability, costs, movement of the biomarker with treatment). Recent research updates - such as the AMP Schizophrenia initiative and findings in immuno-metabolic depression - illustrate the strides being made. However, translation into routine clinical practice remains limited, highlighting the need for methodologically sound trials and long-term commitment to international open data initiatives and large-scale validation of biological markers across sufficiently diverse, and thus representative patient cohorts. Forward and backward translational research approaches were discussed as complementary avenues, with acknowledgment that significant impact may take more than a decade to materialize.

Delivering precision psychiatry will require multimodal, quantitative data and multi-factor models to enable, first, a stratified medicine approach, and then fully personalized precision psychiatry. Validated functional and mechanistic biomarkers that operationalize patient subtypes should be used to develop treatments based on the given pathophysiological signatures and then tested together in stratified clinical trials (Joyce et al., 2017). Furthermore, real world evidence will be crucial in establishing a better understanding of patient biology, behavior, and symptomatology. Indeed, combining datasets will provide the most value; care must be taken to include data from people of all diversities. While digital health tools are an exciting and rapidly developing space in mental health, more research is needed to understand interpretation of the metrics and issues around adherence and data collection. The field needs to be more coordinated in its efforts, and standardization of terminology across organizations is needed to progress together. This will be a long and difficult journey in which all stakeholders, especially patients, need to work together to make meaningful progress.

Despite persistent challenges there was a shared sense of optimism about the direction in which the field is heading. Educational sessions enriched participants' understanding of multimodal biomarker strategies, treatment innovations, and the practicalities of implementation. Theoretical discussions were grounded in real-world clinical experiences, reinforcing the importance of bridging diagnosis, research, and clinical practice. Looking ahead, early identification of trends, increased emphasis on prevention, and sustained cross-disciplinary collaboration will be essential. While reforming diagnostic frameworks poses challenges, maintaining structured communication among clinicians remains crucial. Overall, the meeting served as a catalyst for renewed momentum, inspiring a collective effort to refine diagnostic tools, personalize treatment strategies, and ultimately improve patient outcomes in psychiatric care.

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Martien J.H. Kas: Writing – original draft, Writing – review & editing. **Kim Q. Do:** Writing – review & editing. **Michael S. Sand:** Writing – review & editing. **Rouba Kozak:** Writing – review & editing. **Elizabeth M. Tunbridge:** Writing – review & editing. **Maria A. Oquendo:** Writing – review & editing. **Carol Tamminga:** Writing – review & editing. **Nikolaos Koutsouleris:** Writing – review & editing. **Gitte Moos Knudsen:** Writing – review & editing. **Brenda W.J.H. Penninx:** Writing – review & editing. **Frank J. Padberg:** Writing –

review & editing. **Wayne C. Drevets:** Writing – review & editing. **Peter Falkai:** Writing – review & editing. **Derek L. Buhl:** Writing – review & editing. **Andreas Reif:** Writing – review & editing.

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References

Adams, M.J., Streit, F., Meng, X., Awasthi, S., Adey, B.N., Choi, K.W., Chundru, V.K., Coleman, J.R.I., Ferwerda, B., Foo, J.C., Gerring, Z.F., Giannakopoulou, O., Gupta, P., Hall, A.S.M., Harder, A., Howard, D.M., Hübel, C., Kwong, A.S.F., Levey, D.F., Mitchell, B.L., Ni, G., Ota, V.K., Pain, O., Pathak, G.A., Schulte, E.C., Shen, X., Thorp, J.G., Walker, A., Yao, S., Zeng, J., Zvrskovec, J., Aarsland, D., Actkins, K.V., Adli, M., Agerbo, E., Aichholzer, M., Aiello, A., Air, T.M., Als, T.D., Andersson, E., Andlauer, T.F.M., Arolt, V., Ask, H., Bäckman, J., Badola, S., Ballard, C., Banasik, K., Bass, N.J., Beekman, A.T.F., Belangero, S., Bigdeli, T.B., Binder, E.B., Bjerkeset, O., Bjornsdottir, G., Børte, S., Bränn, E., Braun, A., Brodersen, T., Brückl, T.M., Brunak, S., Bruun, M.T., Burmeister, M., Buspavanich, P., Bybjerg-Grauholm, J., Byrne, E.M., Cai, J., Campbell, A., Campbell, M.L., Campos, A.I., Castelao, E., Cervilla, J., Chaumette, B., Chen, C.Y., Chen, H.C., Chen, Z., Cichon, S., Colodro-Conde, L., Corbett, A., Corfield, E.C., Couvy-Duchesne, B., Craddock, N., Dannlowski, U., Davies, G., de Geus, E.J.C., Deary, I.J., Degenhardt, F., Dehghan, A., DePaulo, J.R., Deuschle, M., Didriksen, M., Dinh, K.M., Direk, N., Djurovic, S., Docherty, A.R., Domschke, K., Dowsett, J., Drange, O.K., Dunn, E.C., Eaton, W., Einarsson, G., Eley, T.C., Elsheikh, S.S.M., Engelmann, J., Benros, M.E., Erikstrup, C., Escott-Price, V., Fabbri, C., Fang, Y., Finer, S., Frank, J., Free, R.C., Gallo, L., Gao, H., Gill, M., Gilles, M., Goes, F.S., Gordon, S.D., Grove, J., Gudbjartsson, D.F., Gutierrez, B., Hahn, T., Hall, L.S., Hansen, T.F., Haraldsson, M., Hartman, C.A., Havdahl, A., Hayward, C., Heilmann-Heimbach, S., Herms, S., Hickie, I.B., Hjalgrim, H., Hjerling-Leffler, J., Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.J., Hougaard, D.M., Hovatta, I., Huang, Q.Q., Hucks, D., Huider, F., Hunt, K.A., Ialongo, N.S., Ising, M., Isometsä, E., Jansen, R., Jiang, Y., Jones, I., Jones, L.A., Jonsson, L., Kanai, M., Karlsson, R., Kasper, S., Kendler, K.S., Kessler, R.C., Kloiber, S., Knowles, J.A., Koen, N., Kraft, J., Kranzler, H.R., Krebs, K., Kallak, T.K., Kutalik, Z., Lahtela, E., Lake, M., Larsen, M.H., Lenze, E.J., Lewins, M., Lewis, G., Li, L., Lin, B.D., Lin, K., Lind, P.A., Liu, Y.L., MacIntyre, D.J., MacKinnon, D.F., Maher, B.S., Maier, W., Marshe, V.S., Martinez-Levy, G.A., Matsuda, K., Mbarek, H., McGuffin, P., Medland, S.E., Meinert, S., Mikkelsen, C., Mikkelsen, S., Milaneschi, Y., Millwood, I.Y., Molina, E., Mondimore, F.M., Mortensen, P.B., Mulsant, B.H., Naamanka, J., Najman, J.M., Nauck, M., Nenadić, I., Nielsen, K.R., Nolt, I.M., Nordentoft, M., Nöthen, M.M., Nyegaard, M., O'Donovan, M.C., Oddsson, A., Oliveira, A.M., Olsen, C.M., Oskarsson, H., Ostrowski, S.R., Owen, M.J., Packer, R., Palviainen, T., Pan, P.M., Pato, C.N., Pato, M.T., Pedersen, N.L., Pedersen, O.B., Peyrot, W.J., Potash, J.B., Preisig, M., Preuss, M.H., Quiroz, J.A., Renteria, M.E., Reynolds III, C.F., Rice, J.P., Sakaue, S., Santoro, M.L., Schoevers, R.A., Schork, A., Schulze, T.G., Send, T.S., Shi, J., Sigurdsson, E., Singh, K., Sinnamon, G.C.B., Sirignano, L., Smeland, O.B., Smith, D.J., Sofer, T., Sørensen, E., Srinivasan, S., Stefansson, H., Stefansson, K., Straub, P., Su, M.H., Tadic, A., Teismann, H., Teumer, A., Thapar, A., Thomson, P.A., Thørner, L.W., Topaloudi, A., Tsai, S.J., Tzoulaki, I., Uhl, G., Uitterlinden, A.G., Ullum, H., Umbricht, D., Ursano, R.J., Van der Auwera, S., van Hemert, A.M., Veluchamy, A., Viktorin, A., Völzke, H., Walters, G.B., Wang, X., Wani, A., Weissman, M.M., Wellmann, J., Whiteman, D.C., Wildman, D., Willemsen, G., Williams, A.T., Winsvold, B.S., Witt, S.H., Xiong, Y., Zillich, L., Zwart, J.A., , Twenty-Three and Me Research Team, China Kadoorie Biobank Collaborative Group, Estonian Biobank Research Team, Genes & Health Research Team, HUNT All-In Psychiatry, The BioBank Japan Project, VA Million Veteran Program, Andreassen, O. A., Baune, B.T., Berger, K., Boomsma, D.I., Børglum, A.D., Breen, G., Cai, N., Coon, H., Copeland, W.E., Creese, B., Cruz-Fuentes, C.S., Czamara, D., Davis, L.K., Derks, E.M., Domenici, E., Elliott, P., Forstner, A.J., Gawlik, M., Gelernter, J., Grabe, H.J., Hamilton, S.P., Hveem, K., John, C., Kaprio, J., Kircher, T., Krebs, M.O., Kuo, P.H., Landén, M., Lehto, K., Levinson, D.F., Li, Q.S., Lieb, K., Loos, R.J.F., Lu, Y., Lucae, S., Luykx, J.J., Maes, H.H.M., Magnusson, P.K., Martin, H.C., Martin, N.G., McQuillin, A., Middeldorp, C.M., Milani, L., Mors, O., Müller, D.J., Müller-Myhsok, B., Okada, Y., Oldehinkel, A.J., Paciga, S.A., Palmer, C.N.A., Paschou, P., Penninx, B.W.J.H., Perlis, R.H., Peterson, R.E., Pistis, G., Polimanti, R., Porteous, D. J., Posthuma, D., Rabinowitz, J.A., Reichborn-Kjennerud, T., Reif, A., Rice, F., Ricken, R., Rietschel, M., Rivera, M., Rück, C., Salum, G.A., Schaefer, C., Sen, S., Serretti, A., Skalkidou, A., Smoller, J.W., Stein, D.J., Stein, F., Stein, M.B., Sullivan, P.F., Tesli, M., Thorgeirsson, T.E., Tiemeier, H., Timpson, N.J., Uddin, M., Uher, R., van Heel, D.A., Verweij, K.J.H., Walters, R.G., Wassertheil-Smoller, S., Wendland, J.R., Werge, T., Zwinderman, A.H., Kuchenbaecker, K., Wray, N.R., Ripke, S., Lewis, C.M., McIntosh, A.M., 2025. Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies. In: Cell, 188, pp. 640–652. https://doi.org/10.1016/j.cell.2024.12.002 e9.

Arns, M., van Dijk, H., Luykx, J.J., van Wingen, G., Olbrich, S., 2022. Stratified psychiatry: tomorrow's precision psychiatry? Eur. Neuropsychopharmacol. 55, 14–19. https://doi.org/10.1016/j.euroneuro.2021.10.863.

Beliveau, V., Hedeboe, E., Fisher, P.M., Dam, V.H., Jørgensen, M.B., Frokjaer, V.G., Knudsen, G.M., Ganz, M., 2022. Generalizability of treatment outcome prediction in major depressive disorder using structural MRI: a NeuroPharm study. Neuroimage Clin. 36, 103224. https://doi.org/10.1016/j.nicl.2022.103224.

Berens, A.E., Jensen, S.K.G., Nelson, C.A., 2017. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. BMC Med. 15, 135. https://doi.org/10.1186/s12916-017-0895-4.

Bergstedt, J., Pasman, J.A., Ma, Z., Harder, A., Yao, S., Parker, N., Treur, J.L., Smit, D.J. A., Frei, O., Shadrin, A.A., Meijsen, J.J., Shen, Q., Hägg, S., Tornvall, P., Buil, A., Werge, T., Hjerling-Leffler, J., Als, T.D., Børglum, A.D., Lewis, C.M., McIntosh, A.M., Valdimarsdóttir, U.A., Andreassen, O.A., Sullivan, P.F., Lu, Y., Fang, F., 2024. Distinct biological signature and modifiable risk factors underlie the comorbidity between major depressive disorder and cardiovascular disease. Nat. Cardiovasc. Res. 3, 754–769. https://doi.org/10.1038/s44161-024-00488-y.

Berk, M., Copolov, D., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., Anderson-Hunt, M., Judd, F., Katz, F., Katz, P., Ording-Jespersen, S., Little, J., Conus, P., Cuenod, M., Do, K.Q., Bush, A.I., 2008. N-acetyl cysteine as a glutathione precursor for schizophrenia—A double-blind, randomized, placebo-controlled trial. Biol. Psychiatry 64, 361–368. https://doi.org/10.1016/j.biopsych.2008.03.004.

Böge, K., Karnouk, C., Hoell, A., Tschorn, M., Kamp-Becker, I., Padberg, F., Übleis, A., Hasan, A., Falkai, P., Salize, H.J., Meyer-Lindenberg, A., Banaschewski, T., Schneider, F., Habel, U., Plener, P., Hahn, E., Wiechers, M., Strupf, M., Jobst, A., Millenet, S., Hoehne, E., Sukale, T., Dinauer, R., Schuster, M., Mehran, N., Kaiser, F., Bröcheler, S., Lieb, K., Heinz, A., Rapp, M., Bajbouj, M., 2022. Effectiveness and cost-effectiveness for the treatment of depressive symptoms in refugees and asylum seekers: a multi-centred randomized controlled trial. Lancet Reg. Health Eur. 19, 100413. 10.1016/j.lanepe.2022.100413.

Cabungcal, J.H., Counotte, D.S., Lewis, E.M., Tejeda, H.A., Piantadosi, P., Pollock, C., Calhoon, G.G., Sullivan, E.M., Presgraves, E., Kil, J., Hong, L.E., Cuenod, M., Do, K. Q., O'Donnell, P., 2014. Juvenile antioxidant treatment prevents adult deficits in a developmental model of schizophrenia. Neuron 83, 1073–1084. https://doi.org/10.1016/j.neuron.2014.07.028.

Carlezon, W.A., Béguin, C., Knoll, A.T., Cohen, B.M., 2009. Kappa-opioid ligands in the study and treatment of mood disorders. Pharmacol. Ther. 123, 334–343. https://doi.org/10.1016/j.pharmthera.2009.05.008.

Carvalho, A.F., Köhler, C.A., Fernandes, B.S., Quevedo, J., Miskowiak, K.W., Brunoni, A. R., Machado-Vieira, R., Maes, M., Vieta, E., Berk, M., 2016. Bias in emerging biomarkers for bipolar disorder. Psychol. Med. 46, 2287–2297. https://doi.org/10.1017/S0033291716000957.

Clementz, B.A., Parker, D.A., Trotti, R.L., McDowell, J.E., Keedy, S.K., Keshavan, M.S., Pearlson, G.D., Gershon, E.S., Ivleva, E.I., Huang, L.Y., Hill, S.K., Sweeney, J.A., Thomas, O., Hudgens-Haney, M., Gibbons, R.D., Tamminga, C.A., 2022. Psychosis biotypes: replication and validation from the B-SNIP consortium. Schizophr. Bull. 48, 56–68. https://doi.org/10.1093/schbul/sbab090.

Clementz, B.A., Sweeney, J.A., Hamm, J.P., Ivleva, E.I., Ethridge, L.E., Pearlson, G.D., Keshavan, M.S., Tamminga, C.A., 2016. Identification of distinct psychosis biotypes using brain-based biomarkers. Am. J. Psychiatry 173, 373–384. https://doi.org/10.1176/appi.ajp.2015.14091200.

Conus, P., Seidman, L.J., Fournier, M., Xin, L., Cleusix, M., Baumann, P.S., Ferrari, C., Cousins, A., Alameda, L., Gholam-Rezaee, M., Golay, P., Jenni, R., Woo, T.U.W.,

Keshavan, M.S., Eap, C.B., Wojcik, J., Cuenod, M., Buclin, T., Gruetter, R., Do, K.Q., 2018. N-acetylcysteine in a double-blind randomized placebo-controlled trial: toward biomarker-guided treatment in early psychosis. Schizophr. Bull. 44, 317–327. https://doi.org/10.1093/schbul/sbx093.

Cuenod, M., Steullet, P., Cabungcal, J.H., Dwir, D., Khadimallah, I., Klauser, P., Conus, P., Do, K.Q., 2022. Caught in vicious circles: a perspective on dynamic feed-forward loops driving oxidative stress in schizophrenia. Mol. Psychiatry 27, 1886–1897. https://doi.org/10.1038/s41380-021-01374-w.

Dam, V.H., Stenbæk, D.S., Köhler-Forsberg, K., Ip, C., Ozenne, B., Sahakian, B.J., Knudsen, G.M., Jørgensen, M.B., Frokjaer, V.G., 2021. Hot and cold cognitive disturbances in antidepressant-free patients with major depressive disorder: a NeuroPharm study. Psychol. Med. 51, 2347–2356. https://doi.org/10.1017/S0033291720000938.

Delgadillo, J., Ali, S., Fleck, K., Agnew, C., Southgate, A., Parkhouse, L., Cohen, Z.D., DeRubeis, R.J., Barkham, M., 2022. Stratified care vs stepped care for depression. JAMA Psychiatry 79 (101). https://doi.org/10.1001/jamapsychiatry.2021.3539.

Do, K.Q., Trabesinger, A.H., Kirsten-Krüger, M., Lauer, C.J., Dydak, U., Hell, D., Holsboer, F., Boesiger, P., Cuénod, M., 2000. Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex *in vivo*. Eur. J. Neurosci. 12, 3721–3728. https://doi.org/10.1046/j.1460-9568.2000.00229.x.

Draper, C.E., Yousafzai, A.K., McCoy, D.C., Cuartas, J., Obradović, J., Bhopal, S., Fisher, J., Jeong, J., Klingberg, S., Milner, K., Pisani, L., Roy, A., Seiden, J., Sudfeld, C.R., Wrottesley, S.V., Fink, G., Nores, M., Tremblay, M.S., Okely, A.D., 2024. The next 1000 days: building on early investments for the health and development of young children. Lancet 404, 2094–2116. https://doi.org/10.1016/S0140-6736(24)01389-8.

Dwyer, D.B., Buciuman, M.O., Ruef, A., Kambeitz, J., Sen Dong, M., Stinson, C., Kambeitz-Ilankovic, L., Degenhardt, F., Sanfelici, R., Antonucci, L.A., Lalousis, P.A., Wenzel, J., Urquijo-Castro, M.F., Popovic, D., Oeztuerk, O.F., Haas, S.S., Weiske, J., Hauke, D., Neufang, S., Schmidt-Kraepelin, C., Ruhrmann, S., Penzel, N., Lichtenstein, Theresa, Rosen, M., Chisholm, Katharine, Riecher-Rössler, A., Egloff, L., Schmidt, A., Andreou, C., Hietala, J., Schirmer, T., Romer, G., Michel, C., Rössler, W., Maj, C., Borisov, O., Krawitz, P.M., Falkai, P., Pantelis, C., Lencer, R., Bertolino, A., Borgwardt, S., Noethen, M., Brambilla, P., Schultze-Lutter, F., Meisenzahl, E., Wood, S.J., Davatzikos, C., Upthegrove, R., Salokangas, R.K.R., Koutsouleris, N., Mackintosh, A., Kaiser, N., Lichtenstein, T., Seves, M., Chisholm, Katie, Reniers, R., Stainton, A., From, T., Heinimaa, M., Ilonen, T., Jalo, P., Laurikainen, H., Tuominen, L., Luutonen, S., Paju, J., Tikka, M., Armio (Säilä), R.L., Toivonen, A., Walta, M., Fabbro, F., Balestrieri, M., Bonivento, C., Garzitto, M., Cabras, G., Piccin, S., Castellani, U., Bellani, M., Maieron, M., Girometti, R., Zuiani, C., Skafidas, S., Velakoulis, D., Everall, I., Merritt, A., Jovicevic, M., Plicht, M., Bequé, D., Solana Sánchez, A.B., Hehn, N., Herrmann, K., Burke, M.X., Fernandez, B., Altamura, C., Rango, M., Ferro, A., Belleri, M., Maggioni, E., Squarcina, L., Re, M., Delvecchio, G., Meneghelli, A., Monzani, E., Sassi, R., Sberna, M., Gennari, L., Torremante, P., Surmann, M., Dannlowski, U., Bienek, O., Blasi, G., Pergola, G., Quarto, T., Andriola, I., Romano, R., Gelao, B., Fazio, L., Korda, A., Rohner, H., Mann, M., Geyer, P., Treit, P., Müller, J., Frackowiak, R., Wasserman, D., Maier, W., Binder, E., Woopen, C., Spranger, T.M., Möhrmann, K.H., 2022. Clinical, brain, and multilevel clustering in early psychosis and affective stages. JAMA Psychiatry 79, 677. https://doi.org/10.1001/jamapsychiatry.2022.1163.

FDA-NIH Biomarker Working Group, 2016. BEST (Biomarkers, EndpointS, and other Tools) Resource. Food and Drug Administration (US), Silver Spring, MD.

Fountain, C., Winter, A.S., Bearman, P.S., 2012. Six developmental trajectories characterize children with autism. Pediatrics 129, e1112–e1120. https://doi.org/10.1542/peds.2011-1601.

Friedrich, M.J., 2017. Depression is the leading cause of disability around the world. JAMA 317, 1517. https://doi.org/10.1001/jama.2017.3826.

Goerigk, S., Elsaesser, M., Reinhard, M.A., Kriston, L., Härter, M., Hautzinger, M., Klein, J.P., McCullough, J.P., Schramm, E., Padberg, F., 2024. Childhood trauma questionnaire-based child maltreatment profiles to predict efficacy of the Cognitive Behavioral Analysis System of Psychotherapy versus non-specific psychotherapy in adults with early-onset chronic depression: cluster analysis of data from a randomised controlled trial. Lancet Psychiatry 11, 709–719. https://doi.org/10.1016/S2215-0366(24)00209-8.

Goerigk, S., Reinhard, M.A., Barton, B.B., Burkhardt, G., Ehring, T., Bertsch, K., Amann, B.L., Sarubin, N., Seidl, E., Falkai, P., Musil, R., Jobst, A., Padberg, F., 2023. Transdiagnostic analysis of adverse childhood experiences and their association with psychopathology–A TRANS-D conform study. Psychiatry Res. 329, 115545. https://doi.org/10.1016/j.psychres.2023.115545.

Gysin, R., Kraftsik, R., Sandell, J., Bovet, P., Chappuis, C., Conus, P., Deppen, P., Preisig, M., Ruiz, V., Steullet, P., Tosic, M., Werge, T., Cuénod, M., Do, K.Q., 2007. Impaired glutathione synthesis in schizophrenia: convergent genetic and functional evidence. Proc. Natl. Acad. Sci. 104, 16621–16626. https://doi.org/10.1073/pnas.0706778104.

Hampel, H., Gao, P., Cummings, J., Toschi, N., Thompson, P.M., Hu, Y., Cho, M., Vergallo, A., 2023. The foundation and architecture of precision medicine in neurology and psychiatry. Trends Neurosci. 46, 176–198. https://doi.org/10.1016/j.tins.2022.12.004.

Hampel, H., O'Bryant, S.E., Molinuevo, J.L., Zetterberg, H., Masters, C.L., Lista, S., Kiddle, S.J., Batrla, R., Blennow, K., 2018. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. Nat. Rev. Neurol. 14, 639–652. https://doi.org/10.1038/s41582-018-0079-7.

Hardingham, G.E., Do, K.Q., 2016. Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. Nat. Rev. Neurosci. 17, 125–134. https://doi.org/10.1038/nrn.2015.19.

Herrman, H., Patel, V., Kieling, C., Berk, M., Buchweitz, C., Cuijpers, P., Furukawa, T.A., Kessler, R.C., Kohrt, B.A., Maj, M., McGorry, P., Reynolds, C.F., Weissman, M.M., Chibanda, D., Dowrick, C., Howard, L.M., Hoven, C.W., Knapp, M., Mayberg, H.S., Penninx, B.W.J.H., Xiao, S., Trivedi, M., Uher, R., Vijayakumar, L., Wolpert, M., 2022. Time for united action on depression: a Lancet–World Psychiatric Association Commission. Lancet 399, 957–1022. 10.1016/S0140-6736(21)02141-3.

Hu, B., Cha, J., Fullerton, J.M., Hesam-Shariati, S., Nakamura, K., Nurnberger, J.I., Anand, A., 2022. Genetic and environment effects on structural neuroimaging endophenotype for bipolar disorder: a novel molecular approach. Transl. Psychiatry 12 (137). https://doi.org/10.1038/s41398-022-01892-3.

Ip, C.T., Ganz, M., Dam, V.H., Ozenne, B., Rüesch, A., Köhler-Forsberg, K., Jørgensen, M. B., Frokjaer, V.G., Søgaard, B., Christensen, S.R., Knudsen, G.M., Olbrich, S., 2021. NeuroPharm study: EEG wakefulness regulation as a biomarker in MDD. J. Psychiatr. Res. 141, 57–65. https://doi.org/10.1016/j.jpsychires.2021.06.021.

Jack, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12, 207–216. https://doi.org/10.1016/S1474-4422(12)70291-0.

Joyce, D.W., Kehagia, A.A., Tracy, D.K., Proctor, J., Shergill, S.S., 2017. Realising stratified psychiatry using multidimensional signatures and trajectories. J. Transl. Med. 15 (15). https://doi.org/10.1186/s12967-016-1116-1.

Kas, M.J.H., Hyman, S., Williams, L.M., Hidalgo-Mazzei, D., Huys, Q.J.M., Hotopf, M., Cuthbert, B., Lewis, C.M., De Picker, L.J., Lalousis, P.A., Etkin, A., Modinos, G., Marston, H.M., 2025a. Towards a consensus roadmap for a new diagnostic framework for mental disorders. Eur. Neuropsychopharmacol. 90, 16–27. https://doi.org/10.1016/j.euroneuro.2024.08.515.

Kas, M.J.H., Penninx, B.W.J.H., Knudsen, G.M., Cuthbert, B., Falkai, P., Sachs, G.S., Ressler, K.J., Bałkowiec-Iskra, E., Butlen-Ducuing, F., Leboyer, M., Marston, H., Luthman, J., Mantua, V., 2025b. Precision psychiatry roadmap: towards a biology-informed framework for mental disorders. Mol. Psychiatry. https://doi.org/10.1038/s41380-025-03070-5.

Kennis, M., Gerritsen, L., van Dalen, M., Williams, A., Cuijpers, P., Bockting, C., 2020. Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis. Mol. Psychiatry 25, 321–338. https://doi.org/10.1038/s41380-019-0585-z.

Khadimallah, I., Jenni, R., Cabungcal, J.H., Cleusix, M., Fournier, M., Beard, E., Klauser, P., Knebel, J.F., Murray, M.M., Retsa, C., Siciliano, M., Spencer, K.M., Steullet, P., Cuenod, M., Conus, P., Do, K.Q., 2022. Mitochondrial, exosomal miR137-COX6A2 and gamma synchrony as biomarkers of parvalbumin interneurons, psychopathology, and neurocognition in schizophrenia. Mol. Psychiatry 27, 1192–1204. https://doi.org/10.1038/s41380-021-01313-9.

Kim, J., Farchione, T., Potter, A., Chen, Q., Temple, R., 2019. Esketamine for treatment-resistant depression–first FDA-approved antidepressant in a new class. N. Engl. J. Med. 381, 1–4. https://doi.org/10.1056/NEJMp1903305.

Köhler-Forsberg, K., Dam, V.H., Ozenne, B., Sankar, A., Beliveau, V., Landman, E.B., Larsen, S.V., Poulsen, A.S., Ip, C.T., Jørgensen, A., Meyer, M., Stenbæk, D.S., Eiberg, H.R.L., Madsen, J., Svarer, C., Jørgensen, M.B., Frokjaer, V.G., Knudsen, G. M., 2023. Serotonin 4 receptor brain binding in major depressive disorder and association with memory dysfunction. JAMA Psychiatry 80, 296. https://doi.org/10.1001/jamapsychiatry.2022.4539.

Köhler-Forsberg, K., Jorgensen, A., Dam, V.H., Stenbæk, D.S., Fisher, P.M., Ip, C.T., Ganz, M., Poulsen, H.E., Giraldi, A., Ozenne, B., Jørgensen, M.B., Knudsen, G.M., Frokjaer, V.G., 2020. Predicting treatment outcome in major depressive disorder using serotonin 4 receptor PET brain imaging, functional MRI, cognitive-, EEG-based, and peripheral biomarkers: a NeuroPharm open label clinical trial protocol. Front. Psychiatry 11. https://doi.org/10.3389/fpsyt.2020.00641.

Krystal, A.D., Pizzagalli, D.A., Smoski, M., Mathew, S.J., Nurnberger, J., Lisanby, S.H., Iosifescu, D., Murrough, J.W., Yang, H., Weiner, R.D., Calabrese, J.R., Sanacora, G., Hermes, G., Keefe, R.S.E., Song, A., Goodman, W., Szabo, S.T., Whitton, A.E., Gao, K., Potter, W.Z., 2020. A randomized proof-of-mechanism trial applying the 'fast-fail' approach to evaluating κ-opioid antagonism as a treatment for anhedonia. Nat. Med. 26, 760–768. https://doi.org/10.1038/s41591-020-0806-7.

Lavoie, S., Murray, M.M., Deppen, P., Knyazeva, M.G., Berk, M., Boulat, O., Bovet, P., Bush, A.I., Conus, P., Copolov, D., Fornari, E., Meuli, R., Solida, A., Vianin, P., Cuénod, M., Buclin, T., Do, K.Q., 2008. Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology 33, 2187–2199. https://doi.org/10.1038/sj.npp.1301624.

Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee, S.H., Ripke, S., Neale, B.M., Faraone, S.V., Purcell, S.M., Perlis, R.H., Mowry, B.J., Thapar, A., Goddard, M.E., Witte, J.S., Absher, D., Agartz, I., Akil, H., Amin, F., Andreassen, O. A., Anjorin, A., Anney, R., Anttila, V., Arking, D.E., Asherson, P., Azevedo, M.H., Backlund, L., Badner, J.A., Bailey, A.J., Banaschewski, T., Barchas, J.D., Barnes, M. R., Barrett, T.B., Bass, N., Battaglia, A., Bauer, M., Bayés, M., Bellivier, F., Bergen, S. E., Berrettini, W., Betancur, C., Bettecken, T., Biederman, J., Binder, E.B., Black, D. W., Blackwood, D.H.R., Bloss, C.S., Boehnke, M., Boomsma, D.I., Breen, G., Breuer, R., Bruggeman, R., Cormican, P., Buccola, N.G., Buitelaar, J.K., Bunney, W. E., Buxbaum, J.D., Byerley, W.F., Byrne, E.M., Caesar, S., Cahn, W., Cantor, R.M., Casas, M., Chakravarti, A., Chambert, K., Choudhury, K., Cichon, S., Cloninger, C.R., Collier, D.A., Cook, E.H., Coon, H., Cormand, B., Corvin, A., Coryell, W.H., Craig, D. W., Craig, I.W., Crosbie, J., Cuccaro, M.L., Curtis, D., Czamara, D., Datta, S., Dawson, G., Day, R., De Geus, E.J., Degenhardt, F., Djurovic, S., Donohoe, G.J., Doyle, A.E., Duan, J., Dudbridge, F., Duketis, E., Ebstein, R.P., Edenberg, H.J., Elia, J., Ennis, S., Etain, B., Fanous, A., Farmer, A.E., Ferrier, I.N., Flickinger, M., Fombonne, E., Foroud, T., Frank, J., Franke, B., Fraser, C., Freedman, R., Freimer, N. B., Freitag, C.M., Friedl, M., Frisén, L., Gallagher, L., Gejman, P.V., Georgieva, L.,

Gershon, E.S., Geschwind, D.H., Giegling, I., Gill, M., Gordon, S.D., Gordon-Smith, K., Green, E.K., Greenwood, T.A., Grice, D.E., Gross, M., Grozeva, D., Guan, W., Gurling, H., De Haan, L., Haines, J.L., Hakonarson, H., Hallmayer, J., Hamilton, S.P., Hamshere, M.L., Hansen, T.F., Hartmann, A.M., Hautzinger, M., Heath, A.C., Henders, A.K., Herms, S., Hickie, I.B., Hipolito, M., Hoefels, S., Holmans, P.A., Holsboer, F., Hoogendijk, W.J., Hottenga, J.J., Hultman, C.M., Hus, V., Ingason, A., Ising, M., Jamain, S., Jones, E.G., Jones, I., Jones, L., Tzeng, J. Y., Kähler, A.K., Kahn, R.S., Kandaswamy, R., Keller, M.C., Kennedy, J.L., Kenny, E., Kent, L., Kim, Y., Kirov, G.K., Klauck, S.M., Klei, L., Knowles, J.A., Kohli, M.A., Koller, D.L., Konte, B., Korszun, A., Krabbendam, L., Krasucki, R., Kuntsi, J., Kwan, P., Landén, M., Långström, N., Lathrop, M., Lawrence, J., Lawson, W.B., Leboyer, M., Ledbetter, D.H., Lee, P.H., Lencz, T., Lesch, K.P., Levinson, D.F., Lewis, C.M., Li, J., Lichtenstein, P., Lieberman, J.A., Lin, D.Y., Linszen, D.H., Liu, C., Lohoff, F.W., Loo, S.K., Lord, C., Lowe, J.K., Lucae, S., MacIntyre, D.J., Madden, P.A. F., Maestrini, E., Magnusson, P.K.E., Mahon, P.B., Maier, W., Malhotra, A.K., Mane, S.M., Martin, C.L., Martin, N.G., Mattheisen, M., Matthews, K., Mattingsdal, M., McCarroll, S.A., McGhee, K.A., McGough, J.J., McGrath, P.J., McGuffin, P., McInnis, M.G., McIntosh, A., McKinney, R., McLean, A.W., McMahon, F.J., McMahon, W.M., McQuillin, A., Medeiros, H., Medland, S.E., Meier, S., Melle, I., Meng, F., Meyer, J., Middeldorp, C.M., Middleton, L., Milanova, V., Miranda, A., Monaco, A.P., Montgomery, G.W., Moran, J.L., Moreno-De-Luca, D., Morken, G., Morris, D.W., Morrow, E.M., Moskvina, V., Muglia, P., Mühleisen, T.W., Muir, W.J., Müller-Myhsok, B., Murtha, M., Myers, R.M., Myin-Germeys, I., Neale, M.C., Nelson, S.F., Nievergelt, C.M., Nikolov, I., Nimgaonkar, V., Nolen, W.A., Nöthen, M.M., Nurnberger, J.I., Nwulia, E.A., Nyholt, D.R., O'Dushlaine, C., Oades, R.D., Olincy, A., Oliveira, G., Olsen, L., Ophoff, R.A., Osby, U., Owen, M.J., Palotie, A., Parr, J.R., Paterson, A.D., Pato, C.N., Pato, M.T., Penninx, B.W., Pergadia, M.L., Pericak-Vance, M.A., Pickard, B.S., Pimm, J., Piven, J., Posthuma, D., Potash, J.B., Poustka, F., Propping, P., Puri, V., Quested, D. J., Quinn, E.M., Ramos-Quiroga, J.A., Rasmussen, H.B., Raychaudhuri, S., Rehnström, K., Reif, A., Ribasés, M., Rice, J.P., Rietschel, M., Roeder, K., Roeyers, H., Rossin, L., Rothenberger, A., Rouleau, G., Ruderfer, D., Rujescu, D., Sanders, A.R., Sanders, S.J., Santangelo, S.L., Sergeant, J.A., Schachar, R., Schalling, M., Schatzberg, A.F., Scheftner, W.A., Schellenberg, G.D., Scherer, S.W., Schork, N.J., Schulze, T.G., Schumacher, J., Schwarz, M., Scolnick, E., Scott, L.J., Shi, J., Shilling, P.D., Shyn, S.I., Silverman, J.M., Slager, S.L., Smalley, S.L., Smit, J.H., Smith, E.N., Sonuga-Barke, E.J.S., St Clair, D., State, M., Steffens, M., Steinhausen, H. C., Strauss, J.S., Strohmaier, J., Stroup, T.S., Sutcliffe, J.S., Szatmari, P., Szelinger, S., Thirumalai, S., Thompson, R.C., Todorov, A.A., Tozzi, F., Treutlein, J., Uhr, M., van den Oord, E.J.C.G., Van Grootheest, G., Van Os, J., Vicente, A.M., Vieland, V.J., Vincent, J.B., Visscher, P.M., Walsh, C.A., Wassink, T.H., Watson, S.J., Weissman, M. M., Werge, T., Wienker, T.F., Wijsman, E.M., Willemsen, G., Williams, N., Willsey, A. J., Witt, S.H., Xu, W., Young, A.H., Yu, T.W., Zammit, S., Zandi, P.P., Zhang, P., Zitman, F.G., Zöllner, S., Devlin, B., Kelsoe, J.R., Sklar, P., Daly, M.J., O'Donovan, M. C., Craddock, N., Sullivan, P.F., Smoller, J.W., Kendler, K.S., Wray, N.R., International Inflammatory Bowel Disease Genetics Consortium (IIBDGC), 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat. Genet. 45, 984–994. https://doi.org/10.1038/ng.2711.

Leichsenring, F., Steinert, C., Rabung, S., Ioannidis, J.P.A., 2022. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry 21, 133–145. https://doi.org/10.1002/wps.20941.

Malhi, G.S., Mann, J.J., 2018. Depression. Lancet 392, 2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2.

Martinez-Aran, A., Vieta, E., 2022. Precision psychotherapy. Eur. Neuropsychopharmacol. 55, 20–21. https://doi.org/10.1016/j.euroneuro.2021.10.771.

Marx, W., Penninx, B.W.J.H., Solmi, M., Furukawa, T.A., Firth, J., Carvalho, A.F., Berk, M., 2023. Major depressive disorder. Nat. Rev. Dis. Primers 9, 44. https://doi.org/10.1038/s41572-023-00454-1.

Mesens, S., Kezic, I., Van Der Ark, P., Etropolski, M., Pandina, G., Benes, H., Savitz, A., Drevets, W.C., 2025. Treatment effect and safety of seltorexant as monotherapy for patients with major depressive disorder: a randomized, placebo-controlled clinical trial. Mol. Psychiatry 30, 2427–2435. https://doi.org/10.1038/s41380-024-02846-5.

Milaneschi, Y., Lamers, F., Berk, M., Penninx, B.W.J.H., 2020. Depression heterogeneity and its biological underpinnings: toward immunometabolic depression. Biol. Psychiatry 88, 369–380. https://doi.org/10.1016/j.biopsych.2020.01.014.

Muschamp, J.W., Carlezon, W.A., 2013. Roles of nucleus accumbens CREB and dynorphin in dysregulation of motivation. Cold Spring Harb. Perspect. Med. 3, a012005. https://doi.org/10.1101/cshperspect.a012005. –a012005.

Nestler, E.J., Hyman, S.E., 2010. Animal models of neuropsychiatric disorders. Nat. Neurosci. 13, 1161–1169. https://doi.org/10.1038/nn.2647.

Paul, S.M., Potter, W.Z., 2024. Finding new and better treatments for psychiatric disorders. Neuropsychopharmacology 49, 3–9. https://doi.org/10.1038/s41386-023-01690-5.

Penninx, B.W.J.H., Lamers, F., Jansen, R., Berk, M., Khandaker, G.M., De Picker, L., Milaneschi, Y., 2025. Immuno-metabolic depression: from concept to implementation. Lancet Reg. Health Eur. 48, 101166. https://doi.org/10.1016/j.lanepe.2024.101166.

Pizzagalli, D.A., Smoski, M., Ang, Y.S., Whitton, A.E., Sanacora, G., Mathew, S.J., Nurnberger, J., Lisanby, S.H., Iosifescu, D.V., Murrough, J.W., Yang, H., Weiner, R. D., Calabrese, J.R., Goodman, W., Potter, W.Z., Krystal, A.D., 2020. Selective kappa-opioid antagonism ameliorates anhedonic behavior: evidence from the Fast-fail Trial in Mood and Anxiety Spectrum Disorders (FAST-MAS). Neuropsychopharmacology 45, 1656–1663. https://doi.org/10.1038/s41386-020-0738-4.

Reif, A., Bitter, I., Buyze, J., Cebulla, K., Frey, R., Fu, D.J., Ito, T., Kambarov, Y., Llorca, P. M., Oliveira-Maia, A.J., Messer, T., Mulhern-Haughey, S., Rive, B., von Holt, C., Young, A.H., Godinov, Y., 2023. Esketamine nasal spray versus quetiapine for treatment-resistant depression. N. Engl. J. Med. 389, 1298–1309. https://doi.org/10.1056/NEJMoa2304145.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am. J. Psychiatry 163, 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905.

Saris, I.M.J., Aghajani, M., Reus, L.M., Visser, P.J., Pijnenburg, Y., van der Wee, N.J.A., Bilderbeck, A.C., Raslescu, A., Malik, A., Mennes, M., Koops, S., Arrango, C., Ayuso-Mateos, J.L., Dawson, G.R., Marston, H., Kas, M.J., Penninx, B.W.J.H., 2022. Social dysfunction is transdiagnostically associated with default mode network dysconnectivity in schizophrenia and Alzheimer's disease. World J. Biol. Psychiatry 23, 264–277. https://doi.org/10.1080/15622975.2021.1966714.

Savitz, A., Wajs, E., Zhang, Y., Xu, H., Etropolski, M., Thase, M.E., Drevets, W.C., 2021. Efficacy and safety of Seltorexant as adjunctive therapy in major depressive disorder: a phase 2b, randomized, placebo-controlled, adaptive dose-finding study. Int. J. Neuropsychopharmacol. 24, 965–976. https://doi.org/10.1093/ijnp/pyab050.

Schmidt, M.E., Kezic, I., Popova, V., Melkote, R., Van Der Ark, P., Pemberton, D.J., Mareels, G., Canuso, C.M., Fava, M., Drevets, W.C., 2024. Efficacy and safety of aticaprant, a kappa receptor antagonist, adjunctive to oral SSRI/SNRI antidepressant in major depressive disorder: results of a phase 2 randomized, double-blind, placebo-controlled study. Neuropsychopharmacology 49, 1437–1447. https://doi.org/10.1038/s41386-024-01862-x.

Schramm, E., Elsaesser, M., Jenkner, C., Hautzinger, M., Herpertz, S.C., 2024. Algorithm-based modular psychotherapy vs. cognitive-behavioral therapy for patients with depression, psychiatric comorbidities and early trauma: a proof-of-concept randomized controlled trial. World Psychiatry 23, 257–266. https://doi.org/10.1002/wps.21204.

Steullet, P., Cabungcal, J.H., Coyle, J., Didriksen, M., Gill, K., Grace, A.A., Hensch, T.K., LaMantia, A.S., Lindemann, L., Maynard, T.M., Meyer, U., Morishita, H., O'Donnell, P., Puhl, M., Cuenod, M., Do, K.Q., 2017. Oxidative stress-driven parvalbumin interneuron impairment as a common mechanism in models of schizophrenia. Mol. Psychiatry 22, 936–943. https://doi.org/10.1038/mp.2017.47.

Strawbridge, R., Young, A.H., Cleare, A.J., 2017. Biomarkers for depression: recent insights, current challenges and future prospects. Neuropsychiatr. Dis. Treat. 13, 1245–1262. https://doi.org/10.2147/NDT.S114542. Volume.

Tamminga, C.A., Pearlson, G., Gershon, E., Keedy, S., Hudgens-Haney, M.E., Ivleva, E.I., Parker, D.A., McDowell, J.E., Clementz, B., 2022. Using psychosis biotypes and the Framingham model for parsing psychosis biology. Schizophr. Res. 242, 132–134. https://doi.org/10.1016/j.schres.2022.01.018.

Tozzi, L., Zhang, X., Pines, A., Olmsted, A.M., Zhai, E.S., Anene, E.T., Chesnut, M., Holt-Gosselin, B., Chang, S., Stetz, P.C., Ramirez, C.A., Hack, L.M., Korgaonkar, M.S., Wintermark, M., Gotlib, I.H., Ma, J., Williams, L.M., 2024. Personalized brain circuit scores identify clinically distinct biotypes in depression and anxiety. Nat. Med. https://doi.org/10.1038/s41591-024-03057-9.

Umbricht, D., Kas, M.J.H., Dawson, G.R., 2024. The role of biomarkers in clinical development of drugs for neuropsychiatric disorders–a pragmatic guide. Eur. Neuropsychopharmacol. 88, 66–77. https://doi.org/10.1016/j.euroneuro.2024.08.511.

Vulpius, G.M., Köhler-Forsberg, K., Ozenne, B., Larsen, S.V., Nasser, A., Svarer, C., Gillings, N., Keller, S.H., Jørgensen, M.B., Knudsen, G.M., Frokjaer, V.G., 2023. Stress hormone dynamics are coupled to brain serotonin 4 receptor availability in unmedicated patients with major depressive disorder: a NeuroPharm study. Int. J. Neuropsychopharmacol. 26, 639–648. https://doi.org/10.1093/ijnp/pyad041.

Wagner, J.A., 2008. Strategic approach to fit-for-purpose biomarkers in drug development. Annu. Rev. Pharmacol. Toxicol. 48, 631–651. https://doi.org/10.1146/annurev.pharmtox.48.113006.094611.

Wannan, C.M.J., Nelson, B., Addington, J., Allott, K., Anticevic, A., Arango, C., Baker, J. T., Bearden, C.E., Billah, T., Bouix, S., Broome, M.R., Buccilli, K., Cadenhead, K.S., Calkins, M.E., Cannon, T.D., Cecci, G., Chen, E.Y.H., Cho, K.I.K., Choi, J., Clark, S.R., Coleman, M.J., Conus, P., Corcoran, C.M., Cornblatt, B.A., Diaz-Caneja, C.M., Dwyer, D., Ebdrup, B.H., Ellman, L.M., Fusar-Poli, P., Galindo, L., Gaspar, P.A., Gerber, C., Glenthøj, L.B., Glynn, R., Harms, M.P., Horton, L.E., Kahn, R.S., Kambeitz, J., Kambeitz-Ilankovic, L., Kane, J.M., Kapur, T., Keshavan, M.S., Kim, S. W., Koutsouleris, N., Kubicki, M., Kwon, J.S., Langbein, K., Lewandowski, K.E., Light, G.A., Mamah, D., Marcy, P.J., Mathalon, D.H., McGorry, P.D., Mittal, V.A., Nordentoft, M., Nunez, A., Pasternak, O., Pearlson, G.D., Perez, J., Perkins, D.O., Powers, A.R., Roalf, D.R., Sabb, F.W., Schiffman, J., Shah, J.L., Smesny, S., Spark, J., Stone, W.S., Strauss, G.P., Tamayo, Z., Torous, J., Upthegrove, R., Vangel, M., Verma, S., Wang, J., Rossum, I.W., Wolf, D.H., Wolff, P., Wood, S.J., Yung, A.R., Agurto, C., Alvarez-Jimenez, M., Amminger, P., Armando, M., Asgari-Targhi, A., Cahill, J., Carrión, R.E., Castro, E., Cetin-Karayumak, S., Mallar Chakravarty, M., Cho, Y.T., Cotter, D., D'Alfonso, S., Ennis, M., Fadnavis, S., Fonteneau, C., Gao, C., Gupta, T., Gur, R.E., Gur, R.C., Hamilton, H.K., Hoftman, G.D., Jacobs, G.R., Jarcho, J., Ji, J.L., Kohler, C.G., Lalousis, P.A., Lavoie, S., Lepage, M., Liebenthal, E., Mervis, J., Murty, V., Nicholas, S.C., Ning, L., Penzel, N., Poldrack, R., Polosecki, P., Pratt, D.N., Rabin, R., Rahimi Eichi, H., Rathi, Y., Reichenberg, A., Reinen, J., Rogers, J., Ruiz-Yu, B., Scott, I., Seitz-Holland, J., Srihari, V.H., Srivastava, A., Thompson, A., Turetsky, B.I., Walsh, B.C., Whitford, T., Wigman, J.T.W., Yao, B., Yuen, H.P., Ahmed, U., Byun, A., Jin, S., Chung, Y., Do, K., Hendricks, L., Huynh, K., Jeffries, C., Lane, E., Langholm, C., Lin, E., Mantua, V., Santorelli, G., Ruparel, K., Zoupou, E., Adasme, T., Addamo, L., Adery, L., Ali, M., Auther, A., Aversa, S.,

Baek, S.H., Bates, K., Bathery, A., Bayer, J.M.M., Beedham, R., Bilgrami, Z., Birch, S., Bonoldi, I., Borders, O., Borgatti, R., Brown, L., Bruna, A., Carrington, H., Castillo-Passi, R.I., Chen, J., Cheng, N., Ching, A.E., Clifford, C., Colton, B.L., Contreras, P., Corral, S., Damiani, S., Done, M., Estradé, A., Etuka, B.A., Formica, M., Furlan, R., Geljic, M., Germano, C., Getachew, R., Goncalves, M., Haidar, A., Hartmann, J., Jo, A., John, O., Kerins, S., Kerr, M., Kesselring, I., Kim, H., Kim, N., Kinney, K., Krcmar, M., Kotler, E., Lafanechere, M., Lee, C., Llerena, J., Markiewicz, C., Matnejl, P., Maturana, A., Mavambu, A., Mayol-Troncoso, R., McDonnell, A., McGowan, A., McLaughlin, D., McIlhenny, R., McQueen, B., Mebrahtu, Y., Mensi, M., Hui, C.L.M., Suen, Y.N., Wong, S.M.Y., Morrell, N., Omar, M., Partridge, A., Phassouliotis, C., Pichiecchio, A., Politi, P., Porter, C., Provenzani, U., Prunier, N., Raj, J., Ray, S., Rayner, V., Reyes, M., Reynolds, K., Rush, S., Salinas, C., Shetty, J., Snowball, C., Tod, S., Turra-Fariña, G., Valle, D., Veale, S., Whitson, S., Wickham, A., Youn, S., Zamorano, F., Zavaglia, E., Zinberg, J., Woods, S.W., Shenton, M.E., 2024. Accelerating medicines partnership® schizophrenia (AMP® SCZ): rationale and study design of the largest global prospective cohort study of clinical high risk for psychosis. Schizophr. Bull. 50, 496–512. https://doi.org/10.1093/schbul/sbae011.

Winter, N.R., Blanke, J., Leenings, R., Ernsting, J., Fisch, L., Sarink, K., Barkhau, C., Emden, D., Thiel, K., Flinkenflügel, K., Winter, A., Goltermann, J., Meinert, S., Dohm, K., Repple, J., Gruber, M., Leehr, E.J., Opel, N., Grotegerd, D., Redlich, R., Nitsch, R., Bauer, J., Heindel, W., Gross, J., Risse, B., Andlauer, T.F.M., Forstner, A. J., Nöthen, M.M., Rietschel, M., Hofmann, S.G., Pfarr, J.K., Teutenberg, L., Usemann, P., Thomas-Odenthal, F., Wroblewski, A., Brosch, K., Stein, F., Jansen, A., Jamalabadi, H., Alexander, N., Straube, B., Nenadić, I., Kircher, T., Dannlowski, U., Hahn, T., 2024. A systematic evaluation of machine learning–based biomarkers for major depressive disorder. JAMA Psychiatry 81, 386. https://doi.org/10.1001/jamapsychiatry.2023.5083.

Wu, W., Zhang, Y., Jiang, J., Lucas, M.V., Fonzo, G.A., Rolle, C.E., Cooper, C., Chin-Fatt, C., Krepel, N., Cornelssen, C.A., Wright, R., Toll, R.T., Trivedi, H.M., Monuszko, K., Caudle, T.L., Sarhadi, K., Jha, M.K., Trombello, J.M., Deckersbach, T., Adams, P., McGrath, P.J., Weissman, M.M., Fava, M., Pizzagalli, D.A., Arns, M., Trivedi, M.H., Etkin, A., 2020. An electroencephalographic signature predicts antidepressant response in major depression. Nat. Biotechnol. 38, 439–447. https://doi.org/10.1038/s41587-019-0397-3.

Xin, L., Mekle, R., Fournier, M., Baumann, P.S., Ferrari, C., Alameda, L., Jenni, R., Lu, H., Schaller, B., Cuenod, M., Conus, P., Gruetter, R., Do, K.Q., 2016. Genetic polymorphism associated prefrontal glutathione and its coupling with brain glutamate and peripheral redox status in early psychosis. Schizophr. Bull. 42, 1185–1196. https://doi.org/10.1093/schbul/sbw038.