Candidate biomarkers in psychiatric disorders: state of the field

Anissa Abi-Dargham[1], Scott J. Moeller[1], Farzana Ali[1], Christine DeLorenzo[1], Katharina Domschke[2,3], Guillermo Horga[4,5], Amandeep Jutla[4,5], Roman Kotov[1], Martin P. Paulus[6], Jose M. Rubio[7-9], Gerard Sanacora[10], Jeremy Veenstra-VanderWeele[4,5], John H. Krystal[10]

[1]Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, USA; [2]Department of Psychiatry and Psychotherapy, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [3]Centre for Basics in Neuromodulation, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [4]Department of Psychiatry, Columbia University, New York, NY, USA; [5]New York State Psychiatric Institute, New York, NY, USA; [6]Laureate Institute for Brain Research, Tulsa, OK, USA; [7]Zucker School of Medicine at Hofstra-Northwell, Hempstead, NY, USA; [8]Feinstein Institute for Medical Research - Northwell, Manhasset, NY, USA; [9]Zucker Hillside Hospital - Northwell Health, Glen Oaks, NY, USA; [10]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA

The field of psychiatry is hampered by a lack of robust, reliable and valid biomarkers that can aid in objectively diagnosing patients and providing individualized treatment recommendations. Here we review and critically evaluate the evidence for the most promising biomarkers in the psychiatric neuroscience literature for autism spectrum disorder, schizophrenia, anxiety disorders and post-traumatic stress disorder, major depression and bipolar disorder, and substance use disorders. Candidate biomarkers reviewed include various neuroimaging, genetic, molecular and peripheral assays, for the purposes of determining susceptibility or presence of illness, and predicting treatment response or safety. This review highlights a critical gap in the biomarker validation process. An enormous societal investment over the past 50 years has identified numerous candidate biomarkers. However, to date, the overwhelming majority of these measures have not been proven sufficiently reliable, valid and useful to be adopted clinically. It is time to consider whether strategic investments might break this impasse, focusing on a limited number of promising candidates to advance through a process of definitive testing for a specific indication. Some promising candidates for definitive testing include the N170 signal, an event-related brain potential measured using electroencephalography, for subgroup identification within autism spectrum disorder; striatal resting-state functional magnetic resonance imaging (fMRI) measures, such as the striatal connectivity index (SCI) and the functional striatal abnormalities (FSA) index, for prediction of treatment response in schizophrenia; error-related negativity (ERN), an electrophysiological index, for prediction of first onset of generalized anxiety disorder, and resting-state and structural brain connectomic measures for prediction of treatment response in social anxiety disorder. Alternate forms of classification may be useful for conceptualizing and testing potential biomarkers. Collaborative efforts allowing the inclusion of biosystems beyond genetics and neuroimaging are needed, and online remote acquisition of selected measures in a naturalistic setting using mobile health tools may significantly advance the field. Setting specific benchmarks for well-defined target application, along with development of appropriate funding and partnership mechanisms, would also be crucial. Finally, it should never be forgotten that, for a biomarker to be actionable, it will need to be clinically predictive at the individual level and viable in clinical settings.

Key words: Biomarkers, neuroimaging, GWAS, treatment response, precision medicine, autism spectrum disorder, schizophrenia, depression, bipolar disorder, anxiety disorders, post-traumatic stress disorder, substance use disorder

(World Psychiatry 2023;22:236–262)

The search for biomarkers in psychiatry is motivated by the need for objective measures to inform diagnosis, prognosis, and treatment choices. The ultimate purpose of a biomarker is to improve management of a disease towards better outcomes[1], allowing for preventive and therapeutic interventions that are tailored to a particular person's genes, environment and lifestyle (i.e., a precision medicine approach).

The US Food and Drug Administration (FDA) separates classes of biomarkers based on their applications[2], and several of these are likely to impact the clinical management of mental disorders: a) *susceptibility biomarkers*, aimed at estimating the likelihood of developing an illness, which may inform allocation of preventive interventions; b) *predictive biomarkers*, aimed at estimating the likelihood of experiencing a therapeutic drug effect, which may consequently inform treatment selection; and c) *safety biomarkers*, aimed at predicting side effects, which may further aid in therapeutic decisions by anticipating poor tolerability.

Non-invasive biomarkers, for example those based on magnetic resonance imaging (MRI) and electroencephalography (EEG), are of particular interest for developing personalized approaches. This is not only because they are relevant to the pathophysiology of interest, but also because it is hoped that they may be scalable and adoptable in the clinic – either now or in the near-term future.

The general litmus test for biomarkers in psychiatric disorders is their ability to change clinical practice. To achieve this goal, several steps in their development are required.

The first stage is to identify a target clinical question that a particular biological measure may be appropriate to address. The most valuable target applications for biomarkers are those that can inform "high-risk, high-reward" decisions. For example, targeting decisions to prescribe a medication with potential life-changing benefits but also serious side effects (e.g., clozapine for schizophrenia[3]) may take priority over targeting decisions bearing less potential benefits or risks. Another relevant consideration is the extent to which a biomarker may optimize decision-making above and beyond clinical data. In this respect, diagnostic biomarkers may be less clinically informative in cases where they are unlikely to override decisions based on patients' complaints and clinical presentation. A final consideration is that the value of biomarkers will necessarily evolve with novel therapeutic options. For example, susceptibility biomarkers for conversion to psychosis, or for the emergence of autism spectrum disorder, would become particularly valuable in the case that interventions capable of preventing these outcomes become available.

The second stage is internal validation. In this stage, it must be demonstrated that a relevant biomarker reflects the underlying process of interest, instead of confounds or other epiphenomena. Confounds may include demographic characteristics, illness chronicity or severity, treatment, co-occurring psychiatric and medical conditions, and site characteristics, among

others. There may also be methodological confounds, such as head-motion artifacts that are inextricably tied to the disorder or psychopathological trait itself (e.g., impulsivity[4]), and therefore are not amenable to traditional statistical covariation[5]. Unfortunately, most biomarkers under development fail to move past the internal validation step.

The third stage is external validation. In this stage, it must be demonstrated that a biomarker has sufficient predictive validity in a sample independent from the one used to develop it. A critical impediment to external validation is overfitting. This refers to a model that excessively reflects the idiosyncratic (noisy) features of the dataset in which it is developed, so that it underperforms when applied to new data[6]. This stage of biomarker development thus focuses on minimizing overfitting and maximizing generalizability. It further focuses on considering and managing issues such as lack of diversity in clinical trials, failure to account for common comorbidities, or a potentially evolving biology over the course of a disorder. Statistical methods such as cross-validation and resampling allow one to measure the generalizability of a model without applying it to an independent sample[7]. However, this does not replace the critical step of confirming generalizability in a fully independent sample not used for model training[6].

At the stage of external validation, the most relevant performance metrics no longer pertain to significant statistical associations; instead, out-of-sample discrimination or predictive performance are most important[8]. Common metrics include the area under the curve (AUC) in receiver-operator curves, and the hazard ratio for time-to-event predictions [9]. The AUC captures a trade-off between true positives and false positives, with higher AUC values indicating improved discriminative ability to identify true positives without excessive false positives. As a general reference, the American Psychiatric Association Work Group on Neuroimaging Markers of Psychiatric Disorders suggested an AUC >0.8 as a minimally useful threshold[10]. Nonetheless, what is considered useful may at least partly depend on contextual factors such as the performance of available predictive models and the consequences of inaccurate prediction[11], or the value of the expected information gain. For example, although available predictive models in suicide prevention have accuracy near zero[12], incorrect predictions are catastrophic, and therefore even a marginal increase in accuracy could be highly valuable from an individual and public-health standpoint. As a final step in external validation, *calibration* of trained models can be used to assess, and fine-tune as necessary, the prediction performance across the entire range of outcome probabilities[8].

The fourth and final stage requires demonstrating clinical utility. At this stage, biomarkers will have to exhibit added value relative to existing tools for clinical decision-making. They must also be scalable and, ultimately, cost-effective. This may involve model comparison against current methods of prediction, such as expert prognostication of relevant outcomes or clinical judgments[13,14], in addition to chance-level prediction. However, once again, the designation of clinical utility may be partly context-dependent. For outcomes with especially high stakes (e.g., suicide, drug overdose, conversion to psychosis), expensive and/or marginally accurate new biomarkers may still provide high clinical value in comparison to the *status quo*, and ultimately may be cost-effective if they can prevent the catastrophic outcome from occurring, particularly if they are proximal predictors of that outcome.

The goal of this paper is to describe and discuss candidate biomarkers – encompassing genetic, molecular, neuroimaging and/or peripheral assays as warranted – for autism spectrum disorder (ASD); schizophrenia spectrum disorders (hereafter referred to as schizophrenia for simplicity); anxiety disorders and post-traumatic stress disorder (PTSD); mood disorders, encompassing major depressive disorder (MDD) and bipolar disorder (BD); and substance use disorders (SUDs). Recognizing that a listing of all potential biomarkers could be overwhelming and lack coherence, we do not provide an exhaustive list of the candidate biomarkers for each disorder that have been proposed or evaluated to date. Rather, we list and critically evaluate the evidence only for selected biomarkers which we view as especially promising for the field.

Biomarker development may be generally viewed as following a stepwise pipeline akin to that in drug development[11]. For some indications, the biomarkers reviewed here are farther along in development and closer to being clinically actionable; for other indications, the focus is on biomarkers which are earlier in development but are seen as having strong potential for breakthrough advancement once validated. We end each section with a brief summary of the reviewed literature, as well as a shortlist of what we consider to be especially promising (if applicable). These especially promising biomarkers could be prioritized for future large-scale, highly powered studies, which in turn can provide the definitive evidence of that particular biomarker's ultimate success or failure.

BIOMARKERS IN AUTISM SPECTRUM DISORDER

Biological markers have been a focus in autism since its initial description in 1943 by L. Kanner, who noted large head size in five of eleven children[15]. Over time, research on biological markers in ASD has ranged from crude measures of head size to longitudinal imaging of the brain to sequencing of the entire genome.

Like all psychiatric diagnoses, ASD describes common behavioral features across individuals, instead of being a "disease" with a unifying pathophysiology. ASD spans a broad range of function and impairment: some patients require lifelong 1:1 care, while others are successful professionals and parents. Yet, unlike in other diagnostic categories reviewed here, ASD is a developmental disorder that presents in early childhood, with less time to identify biomarkers that predict onset, and with longitudinal outcomes typically measured in years rather than in weeks to months. Additionally, treatments are lacking for the core symptoms of autism – behavioral interventions show benefit primarily for IQ or language[16], and medications primarily treat associated symptoms such as agitation or hyperactivity[17].

ASD biomarkers that have been investigated to date primarily correspond to the susceptibility biomarkers discussed elsewhere in this review more than to predictive or safety biomarkers. Some have been

described as stratification or subtyping biomarkers, given that they have sought to parse ASD into subgroups with common features. Truly unifying biology is expected at the level of single genes implicated in ASD, but peripheral or brain-based biomarkers may identify larger subgroups that may predict prognosis or treatment response. Each of these approaches has some emerging data pointing to future utility, but to date only genetic testing is regularly used in the clinic.

Note that, throughout this section, we have endeavored to recognize the strong preference of many in the autistic community for identity-first language ("autistic person") over person-first language ("person with ASD")[18], except when referring to the DSM diagnosis of ASD. This is in contrast to other mental disorders, such as SUDs, where it is suggested to avoid labeling a person by his/her disease[19].

Genetic biomarkers

More genes are implicated in ASD than in any other DSM diagnosis. Most genetic variants are not inherited from either parent but are instead *de novo* mutations. These include single nucleotide variants (SNVs) and small insertions or deletions (indels) that disrupt single gene function, collectively implicating more than 100 genes to date[20-23]. *De novo* copy number variants (CNVs) are also implicated in ASD, most of which either delete or duplicate multiple genes[24]. Emerging data also point to rare inherited SNVs and CNVs that contribute to ASD risk[25-27]. Collectively, rare ASD-associated SNVs and CNVs are found in about 15% of autistic individuals, although no single variant is found in more than 1%.

Rare ASD-associated genetic variants are best conceptualized as identifying genetic syndromes within the overall population of autistic individuals. This extends our knowledge beyond syndromes that are typically identified before an ASD diagnosis, such as fragile X syndrome and tuberous sclerosis[28]. None of these rare variants leads to an ASD diagnosis in every individual, and many resulting syndromes also include dysmorphic features or involvement of other organ systems. Rare ASD-associated variants are more often identified in individuals who also have intellectual disability (ID), but are still enriched in those without ID[29,30]. Evidence therefore supports genetic testing, including fragile X testing, chromosomal microarray to detect CNVs, and whole exome sequencing, for *all* autistic individuals[31,32], although clinical uptake remains low[33]. This is unfortunate, as neurodevelopmental CNVs are enriched for congenital disorders and are correlated with multiple psychiatric and medical ailments[34], suggesting that they could potentially be used to assess risk even beyond ASD.

Genetics-based biomarkers could also be used to identify larger subgroups of individuals with unifying biology. As one example, the fragile X mental retardation protein (FMRP) binds to the mRNA of multiple genes implicated in ASD[23,29], and individuals with disruption of any of these genes could potentially respond to a common treatment. A more concrete approach would be to cluster rare genetic variants into larger groupings that have defined impact on a signaling pathway, such as mTor signaling disinhibition in tuberous sclerosis and PTEN hamartoma syndrome[35].

Common genetic variation may be another pathway to identifying biomarkers in ASD. The first five significant genome-wide association studies (GWAS) loci were recently reported in ASD, presenting an opportunity to begin studying common variants that confer risk[36]. Thus far, polygenic risk scores (PRS) predict less than 3% of risk in ASD[36], although this is likely to grow with larger GWAS sample sizes. Approaches to partitioning high and low PRS values already suggest avenues toward clinical utility in schizophrenia risk prediction or treatment response[37,38], and similar opportunities may also open in ASD.

Peripheral biomarkers

Considerable effort has gone toward identifying and understanding potential peripheral biomarkers in ASD, beginning with the first description of elevated blood serotonin levels or hyperserotonemia in 1961[39]. Numerous peripheral findings have been reported in ASD blood, saliva and stool samples, including tests that have been approved for use by the FDA, but none of these has been sufficiently developed to warrant its use in the clinic. In many cases, research on peripheral biomarkers has focused on searching for correspondence to brain or behavioral features of ASD, without necessarily establishing a clear target for the biomarker's clinical utility, such as prediction of diagnosis or response to treatment.

The serotonin system provides an instructive example of the approaches taken to peripheral biomarkers in ASD. The description of hyperserotonemia was an early indicator of a biological origin for ASD[39], in contrast to early attribution of the condition to parenting style[40]. Even while the diagnosis of ASD has climbed from very rare to about 2% of school-aged children[41], rates of hyperserotonemia (>95th percentile) have remained stable at more than 25% in ASD (meta-analysis $p=10^{-12}$)[42]. Various approaches to validation have been applied, including demonstration that hyperserotonemia is specific to ASD[43], heritable[44], primarily seen in boys[45], and more commonly seen in families with multiple affected children[46], but not associated with a particular clinical pattern[47]. Despite investigations spanning six decades, no prospective study has yet assessed whether hyperserotonemia may predict ASD risk in infants or whether it may predict treatment response to medications that target the serotonin system[47].

Numerous other candidate peripheral biomarkers have been identified, although with less consistency across studies or specificity to ASD. Elevated pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and IL-1β, have been described in several studies and are supported by meta-analysis [48]. Increased markers of oxidative stress have also been reported, again supported by meta-analysis[49]. Multiple groups have found differences in components of the stool microbiome in ASD, with some support but also inconsistency noted in meta-analysis[50].

Overall, these peripheral studies have identified broad patterns of difference between groups of autistic children or adults and comparison groups, but have not evaluated their utility as clinical biomarkers. As noted in other sections below, these markers may be largely non-specific, due to overlap with other psychiatric and medical con-

ditions. One group, though, has been systematically evaluating folate receptor-α autoantibody as a potential biomarker in relation to treatment[51]. Initial data are intriguing, indicating that those with the antibody are more likely to show improved verbal communication following folinic acid administration in a placebo-controlled pilot trial[52]. External validation of the biomarker and direct replication of these effects are still needed.

Finally, some groups have focused on composite biomarkers, including transcriptome and metabolome profiles, primarily focused on predicting ASD diagnosis. Initial studies of 100-200 participants provided some hope that lymphocyte transcriptome profiles might separate autistic children from typically developing controls, but lacked a prospective approach[53] and/or were not specific to ASD versus developmental delay [54]. An industry-funded study of 880 participants failed to find any transcriptome or metabolome signature with potential clinical utility in predicting diagnosis in preschoolers recruited prior to ASD evaluation (NCT01810341). In contrast, an industry-funded study of 708 preschoolers with ASD versus non-referred controls reported a cluster of "metabotypes" that predicted ASD diagnosis with a sensitivity of 53% and specificity of 91%[55], with 17% having a branch chain amino acid profile with higher sensitivity. This *NeuroPointDx ASD Test* is currently marketed to consumers without any evidence that it prospectively improves ASD screening or diagnosis, or that it is useful to guide potential treatment. This marketing of a test without requiring FDA approval or prospective evaluation is a cautionary tale for clinician-scientists collaborating with industry to test biomarkers in ASD.

Central nervous system biomarkers

Researchers have sought a brain signature of ASD since the advent of neuroimaging. In the last three decades, many studies have focused on potential brain-based biomarkers quantified by a variety of indicators and techniques. These include head size as a proxy for brain size, structural MRI (sMRI) to delineate the morphology of brain structures, functional MRI (fMRI) and EEG to elucidate brain function, and cerebrospinal fluid (CSF) sampling as a measure of brain neurochemistry.

Kanner's original description of autism noted macrocephaly in some but not all cases. Consistent with this, later systematic examinations of head size in autism found macrocephaly in a subgroup that showed increased head growth after birth through early childhood[15,56]. Subsequent work suggested an initial surge in head growth in infants followed by a regression of growth in late childhood, but methodological problems weaken these results[57]. A recent longitudinal study confirmed the initial observation: a subgroup of ~15% showed persistent macrocephaly, primarily driven by gray matter and cortical surface area, whereas the rest of the ASD sample showed no difference from the control population[58]. Further, those with macrocephaly showed more cognitive impairment and less improvement over time[59].

While the early observation of macrocephaly pointed to the origins of ASD in the brain, structural neuroimaging studies have not consistently found particular brain regions to be implicated in ASD[60,61]. Resting-state functional connectivity studies have found complex patterns of altered connectivity in ASD, with evidence for both over-connectivity and under-connectivity in short- and long-range networks[62,63]. Most promising as potential biomarkers are the findings of longitudinal neuroimaging studies in infants who have an older sibling with autism ("baby siblings") and are therefore at elevated familial risk. In this population, changes in gray matter growth and white matter connectivity across a child's first 6-24 months show robust prediction of later ASD diagnosis[64,65]. These studies have also found increased extra-axial fluid volume in babies and toddlers who are later diagnosed with ASD[66,67], and in toddlers after diagnosis[68].

Only a minority of autistic children can tolerate an MRI scan, and EEG approaches may offer a more feasible alternative. Like MRI measures, EEG results suggest diminished long-range connectivity, but there is inconsistency across studies[69,70]. EEG offers the benefit of low cost and high temporal resolution, despite poor spatial resolution. Investigators use event-related potentials (ERPs) to evaluate processing of sensory stimuli, including social cues. The ERP response to faces is particularly characteristic, with a negative deflection at approximately 170 milliseconds (N170) showing a delay in many autistic children[71,72]. This N170 signal has been well replicated and validated across multiple groups, and is the only ASD biomarker to date to be submitted to the FDA. The initial target of the FDA submission is subgroup identification within ASD, but there may be future potential as a marker of treatment response as well[73,74].

Neurochemical markers have also generated considerable interest in ASD. Magnetic resonance spectroscopy (MRS) studies have suggested possible regional changes in GABA or glutamate levels, though findings are inconclusive[75,76]. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have indicated decreased serotonin receptor 5-HT_{2A} binding[77], which could inform treatment studies using medications that block 5-HT_{2A} in addition to other receptors.

Recently, decreased CSF vasopressin in neonates has been associated with later ASD diagnosis[78]. Parallel findings indicate an association between CSF vasopressin levels and symptom severity in ASD[79]. Following an initial pilot study with promising results for intranasal vasopressin in ASD[80], it would be logical to assess CSF vasopressin as a potential biomarker of treatment response.

Finally, eye-tracking is sometimes described as a biomarker in ASD. However, most eye-tracking studies represent a fine-grained analysis of behavior, rather than a biomarker *per se* – except perhaps for pupillometry, which is occasionally applied. Non-biased approaches to behavioral observation are quite promising in ASD, but are beyond the scope of this review.

Summary of autism biomarkers

Biomarker development in ASD has rarely been systematic, but several potential biomarkers hold promise for future studies.

Genetic testing is now recommended for every child with an ASD diagnosis, with findings identifying genetic syndromes that often explain most of a child's risk, but are not specific to ASD. Some peripheral findings

are well replicated, but most have not been assessed prospectively and none has been adequately tested for clinical utility.

Brain-based markers show promise for subgrouping individuals, and there is some initial evidence in baby sibling studies showing that longitudinal neuroimaging can provide neural signatures that precede ASD diagnosis. After diagnosis, the EEG/ERP N170 signal has been most rigorously tested as a biomarker, with promise for identifying a subgroup within ASD and some potential as an indicator of treatment response. Finally, signals across domains support further study of serotonin- and vasopressin-based biomarkers in relation to subgrouping or response to targeted treatment.

BIOMARKERS IN SCHIZOPHRENIA

The specific relevance of biomarkers for schizophrenia lies in the large burden related to this disease[81] and the costly consequences of trial-and-error approaches to clinical decision-making. Delays in effective treatment involving repeated failed trials unnecessarily prolong social impairment and personal suffering, and can increase danger to self or others. Furthermore, multiple failed trials can undermine treatment engagement, which is generally already tenuous in schizophrenia, especially in the early phases of the illness[82].

Schizophrenia is the psychiatric diagnosis with the most research on personalized biomarker approaches after depression[83]. Recent papers have provided a broad overview of biomarkers for this disorder[84,85], including target biomarkers for drug development[2,86] and diagnostic biomarkers for pathophysiological interrogation[84]. This section will mainly focus on candidate neuroimaging biomarkers that have shown potential for eventual clinical applications by virtue of their ability to allow out-of-sample predictions at the individual-subject level (i.e., beyond in-sample statistical associations at the group level). Discussed topics include prediction of conversion to psychosis, treatment response, treatment discontinuation, and relapse risk, among others. We will, however, make exceptions in the case of relevant potential applications for which predictive performance has not yet been evaluated. In such cases, we will discuss statistical associations as examples of the preliminary stages of biomarker development.

Susceptibility biomarkers of conversion to psychosis

Susceptibility biomarkers to estimate the risk of conversion to psychosis at the individual level could be highly useful in many ways. They could indicate which subjects at clinical high risk (CHR) for psychosis are most likely to develop a full-blown psychotic disorder, which could motivate earlier initiation of available treatments[87,88] to reduce the duration of untreated psychosis and its associated impact. Prognosis associated with these biomarkers would also have inherent value in preparing patients and families for what to expect in terms of chronicity and prognosis. Finally, susceptibility biomarkers could facilitate personalized treatment selection of novel disease-modifying agents as they become available[89-91].

Prognostic models based solely on clinical data are reasonably developed. For example, the North American Prodrome Longitudinal Study (NAPLS2) individualized risk calculator[92] predicted conversion to psychosis with an AUC of 0.71 in the development cohort, and subsequently was externally validated in two large independent cohorts with an AUC ranging between 0.63 and 0.79[93,94]. A machine-learning model from the Personalized Prognostic Tools for Early Psychosis Management (PRONIA) consortium achieved substantial prognostic accuracy using only clinical data, showing a balanced accuracy of 76.9%[14]. Similar predictive accuracy was achieved with the Columbia risk calculator (i.e., 73%), based on data from the Structured Interview for Prodromal Syndromes[95]. A major challenge for clinical predictive models is that they are unlikely to modify clinical practice, as high-scoring individuals will have greater symptom burden and may already be allocated additional resources.

Neural susceptibility biomarkers could be clinically useful if they improve predictions above and beyond what is possible using clinical data. Investigators from the PRONIA consortium trained machine-learning algorithms using clinical and gray matter volume maps to predict impaired function in a CHR cohort of 116 individuals, of whom 66 met impairment criteria at one-year follow-up[14]. The model using clinical data predicted social function at outcome with a balanced accuracy of 76.9%, which improved to 82.7% when adding volumetric MRI data.

In another study, the same group optimized a predictive algorithm for conversion risk in CHR states by sequentially integrating clinical-neurocognitive-based, expert-based, PRS-based, and sMRI-based risk estimates for individual subjects, which resulted in a combined balanced accuracy of 85.9% (84.6% sensitivity, 87.3% specificity) using leave-one-site-out cross-validation[96]. The accuracy for the algorithm combining risk estimates across modalities surpassed that based solely on clinical and neurocognitive data or other individual modalities. Notably, this stepwise algorithm only required additional modalities that were deemed necessary (i.e., MRI data would be required only if clinical data were insufficient), a feature that could improve the feasibility of its clinical implementation by reducing costs and diagnostic burden.

In a smaller study, striatal glutamate measured by MRS showed promise in 19 individuals, including 7 converters. The accuracy of a predictive model based on clinical information alone was 82.1%, and this increased to 86.9% when adding a striatal glutamate measure into the model[97].

Other biological measures that could be integrated in predictive algorithms show some promise. One example is a neuroanatomical-maturity marker developed by the NAPLS2 consortium: in secondary analyses of 275 CHR adolescents (39 converters), a "brain-age-gap" marker showed an AUC of 0.63 in predicting conversion in the development sample using 10-fold cross-validation[98]. Another promising candidate is the EEG-based mismatch negativity (MMN): in a study of 62 research participants who were categorized into high or low risk based on MMN, the respective hazard rate for conversion was 85% versus 13%[99].

These and other encouraging results showing in-sample associations[100,101] call for additional studies directly testing the

predictive ability and generalizability of MMN as a susceptibility biomarker for conversion. Similarly, while resting-state fMRI measures, including indices of cerebello-thalamo-cortical connectivity[102], have shown robust results in association studies, their ability to improve upon the predictive capabilities of structural, neurochemical or MMN-based measures – alone or in combination – remains to be studied. Overall, though, most susceptibility neural biomarkers for conversion have not yet been tested against models using clinical information.

It is important to note that the candidate markers reviewed here have undergone varying levels of validation. For instance, the volumetric MRI model from PRONIA[14] showed internal validity in several analyses, ruling out scanner/site effects by using nested leave-one-site-out cross-validation and assessing various effects of site, image quality, follow-up interval, and baseline social function. Similar internal-validation steps were taken for the NAPLS2 brain-age-gap marker[98], but not for the striatal glutamate biomarker[97]. With respect to external validation, the initial gray-matter-volume PRONIA biomarker[14] used rigorous cross-validation but so far lacks validation in independent samples. In contrast, the subsequent multimodal algorithm for conversion risk from PRONIA was externally validated in independent samples, yielding a balanced accuracy of 65.3-70.4%. This exception withstanding, lack of independent validation remains a caveat that applies to most candidate biomarkers.

Finally, striatal dopamine excess has been measured with PET in CHR subjects[103,104]. Elevated striatal [^{18}F]DOPA uptake precedes the onset of psychosis[105], correlates with greater severity of prodromal symptoms and neuropsychological impairment, predicts conversion, and, in both the prodrome and schizophrenia, relates negatively to prefrontal cortical activation during cognitive tasks[106,107], although findings are not consistent[108,109]. Uptake is also predominant in the associative striatum[110,111]. Thus, striatal [^{18}F]DOPA uptake could advance to validation in multisite studies as a predictive diagnostic biomarker, but the cost and limited availability of PET facilities may limit its practicality. Neuromelanin-sensitive MRI[112], a non-invasive and reliable measure of nigrostriatal dopamine function relevant to psychosis[113], could provide an alternative. However, more work is needed to show its potential and justify the investment in broader testing and validation.

Susceptibility biomarkers of complications in psychosis

Susceptibility biomarkers could be clinically useful if they predict the development of complications over the course of schizophrenia. One example is the prediction of violent and/or self-injurious behavior, for which individuals with schizophrenia are at risk[114,115]. Some models using clinical information have shown fair in-sample associations[116,117], but their generalizability needs to be evaluated. Neuroimaging studies have similarly shown associations of certain structural and functional features with dangerous behaviors[118], and in some cases these neuroimaging measures have been studied alongside clinical variables[119]. Further biomarker development is needed in this area.

Predictive biomarkers of treatment response

Acute psychosis

Around 20-30% of individuals may have treatment-resistant schizophrenia[120], and for these patients clozapine is the only approved drug[39,40,120,121]. Despite its clear superiority over other antipsychotics, clozapine has response rates neighboring 40% and carries potentially life-threatening side effects[3]. Thus, expediting clozapine treatment for those likely to exhibit treatment resistance and who may benefit most from clozapine represents a relevant target for predictive biomarkers. More broadly, biomarkers of treatment response could further aid in personalized treatment selection, as more treatments with distinct mechanisms of action, such as cholinergic agents [122], become available.

Perhaps the most advanced treatment-response biomarkers along the development pipeline focus on striatal resting-state fMRI measures, including the functional striatal abnormalities (FSA) index[123] and the striatal connectivity index (SCI)[124].

The FSA index has been conceptualized as a diagnostic classifier. It was developed using data from 1,100 participants across seven sites, incorporating measurements that included fractional amplitude of resting-state derived low-frequency fluctuations[125] of striatal voxels as well as intra- and extra-striatal functional connectivity of those voxels. A support vector machine (SVM) classifier was first trained to predict the diagnostic status of each individual using these features, and the FSA for any given individual was defined as the distance in the SVM feature space to the hyperplane separating cases and controls. Using leave-one-site-out cross-validation, the FSA discriminated cases from controls with 80% accuracy[123].

In a second step, the investigators measured the association between FSA scores and symptom change over six weeks of antipsychotic treatment in a subset of 91 individuals from two of the sites. At both sites, more control-like FSA scores showed moderate-to-strong correlations with improvements in total symptom severity ($r=0.62$, $p<0.001$ and $r=0.42$, $p<0.001$, respectively). Substantial efforts were made to rule out confounding factors associated with antipsychotic treatment, head motion, baseline symptom severity, and site effects, and to show specificity of the FSA relative to other psychiatric diagnoses and markers based on non-striatal fMRI features[123]. However, a caveat is that the FSA's predictive ability was not externally validated, as the demonstration of treatment-response prediction relied on data trained to classify diagnosis (although in orthogonal tests).

The SCI was first developed on a cohort of 41 individuals undergoing initial treatment with aripiprazole or risperidone, 24 of whom responded to treatment over 12 weeks. Functional connectivity maps for six bilateral subregions within the striatum[126] were used to identify pairwise connectivity features associated with time to response in univariate tests. Ninety-one features were identified and weighted according to their association with time to response, and this information was used to estimate a scalar value summarizing the connectivity profiles for each individual, albeit using uni-

variate methods without cross-validation. Nonetheless, external validation was demonstrated in an independent cohort of 40 individuals with multi-episode schizophrenia, where individual SCI scores, calculated with the same methodology as the discovery cohort, discriminated between responders and non-responders with an AUC of 0.78[126]. Further studies have linked the SCI to processes implicated in treatment responsiveness, such as duration of untreated psychosis[127], relapse[128], and interactions with cannabis use[129], providing some support for its internal validity.

Non-striatal functional biomarkers have also been examined. Resting-state functional connectivity between bilateral superior temporal cortex and other cortical regions was used in an SVM classifier model to predict 10-week risperidone response in 38 medication-naïve individuals[130]. This classifier showed a leave-one-subject-out cross-validation accuracy of 82.5%, although checks of internal validity were limited. Other studies have tested measures of hippocampal functional connectivity[131,132], or anterior cingulate cortex glutamate levels measured with spectroscopy[133-136], as potential biomarkers of treatment response, but so far these studies have only provided support for in-sample statistical associations and are awaiting further validation. This is also the case for neuromelanin-sensitive MRI[112], which is currently being tested[137] as a potential biomarker of treatment response, building on previous dopamine PET work[138].

While elevated dopamine levels in the striatum are linked to antipsychotic treatment responsiveness[139,140], no prospective studies have assessed their potential utility as a biomarker for treatment response. This relates to the difficulty in implementing PET biomarkers at large scale and the limited therapeutic choices from which to select, in the case that patients were found to be non-responsive to currently used antipsychotics, which are all acting on D2 receptors.

Psychosis relapse

Another major problem in schizophrenia is the frequency and burden of relapse, underscoring the need for predictive biomarkers of this important clinical outcome. About 80% of patients with schizophrenia will relapse at least once over the course of their illness, and many of these patients will relapse numerous times[141,142]. Relapse correlates to increased potential danger to self or others, and to cumulative decrements in treatment responsiveness[142,143].

Antipsychotic drugs, in addition to mitigating acute psychotic symptoms, are efficacious in preventing relapse[144]. So, relapse usually occurs after interruption of maintenance antipsychotic treatment[145], although many patients relapse while on maintenance treatment[146]. Because pathophysiological differences may exist between relapse that occurs while patients are on or off antipsychotics, these two scenarios warrant separate lines of investigation[147]. Biomarkers could allow identification of low-relapse-risk individuals as candidates for monitored interruption of maintenance treatment, and for high-relapse-risk individuals as requiring more intensive and consistent intervention[148]. To date, the literature on this topic is fairly limited, and no validated biomarkers have shown predictive value as yet. Nonetheless, exploratory analyses suggest that the SCI may be distinctly sensitive to relapse associated with treatment interruption[128], which encourages its study in the future as a potential biomarker of relapse risk, in addition to its utility in diagnostic prediction.

Cognitive dysfunction

Although most biomarkers to date have aimed to predict and intervene on positive symptoms of schizophrenia, interest has recently emerged in developing predictive biomarkers for interventions addressing cognitive dysfunction. MMN has been studied for this purpose, based on its favorable test-retest reliability[149,150] and the relationship between its deficits and cognitive dysfunction in schizophrenia[149-151].

To date, no investigations have reported cross-validated performance of MMN in predicting treatment response to cognitive training, but several studies are suggestive in this respect. For example, one trial found that the change in MMN after 1 hour of auditory cognitive training was associated with the final improvements seen with a full course of treatment[152]. Two other studies found that baseline MMN deficits predicted greater gains across various cognitive domains in response to a similar type of training[153,154]. Thus, converging data suggest the potential for developing MMN as a predictive biomarker for treatments addressing cognition. However, internal validity remains to be established, particularly as MMN may reflect illness duration and nicotine smoking[155]. Moreover, utility for this class of biomarkers will ultimately depend on the availability of effective interventions for cognitive dysfunction in schizophrenia.

Other pragmatic outcomes

A critical aspect of successful biomarker development is real-world implementation. For example, the SCI was related to length of hospital stay[123], speaking to its potential impact in real-world clinical settings. Other early examples include a study predicting treatment discontinuation on the basis of subfield hippocampal volumes[156], which reported that dentate gyrus volume predicted treatment disengagement with an AUC of 0.75.

However, as real-world implementation must follow other necessary steps in the biomarker development pipeline, most candidate biomarkers are not ready for testing in real-world clinical settings.

Predictive biomarkers of medication side effects

The prediction of treatment side effects, while highly important, is likely among the most challenging goals for neurophysiological biomarkers in schizophrenia. This is because some side effects may be partly due to non-neural mechanisms (e.g., atypical antipsychotics modulating insulin effects on adipocytes[157]), and some of the most serious side effects, such as neuroleptic malignant syndrome[158], are relatively rare.

Bearing in mind these limitations, neural markers for weight gain have been studied based on observations that atypical antipsychotics can enhance anticipatory reward activations to food in the striatum[159] and

affect the hypothalamic histaminergic system[160]. Some initial data suggest that striatal function may predict antipsychotic-induced weight gain. For example, in a trial with amisulpride in 69 early-phase patients, weight gain was associated with low reward-related activation of the right putamen[161]. In another clinical trial in 81 early-phase patients treated with atypical antipsychotics, baseline left putamen volume and lower sensory-motor connectivity at rest correlated with weight gain[162].

This area of biomarker development is thus at a preliminary stage and requires more work. Similarly, other side effects for which neural measures may be appropriate, such as tardive dyskinesia[163], represent a potential target for future development.

Summary of schizophrenia biomarkers

Recent efforts are advancing biomarker development for schizophrenia, particularly in clinically relevant areas of prediction of conversion to psychosis in at-risk individuals and prediction of treatment response in acute psychosis.

In the area of conversion prediction, we have discussed examples of well-validated multimodal algorithms incorporating sMRI and clinical information (and in some cases genetic and other data), which have reached the third stage of external validation in the biomarker development pipeline. In the area of treatment-response prediction, we have also discussed reasonably well-developed candidate biomarkers, mostly those based on striatal resting-state fMRI (FSA[123] and SCI[124]), which show different levels of generalizability in external samples.

While none of the reviewed candidate biomarkers have established clinical utility – the fourth and final stage of biomarker development required for incorporation into clinical practice – the highlighted candidates are cause for optimism. For these most promising candidates, definitive demonstrations of external validity by independent groups or via large-scale international studies are recommended, followed by demonstrations of clinical utility. Investing in these studies, particularly those using relatively accessible measures (e.g., sMRI, PRS, resting-state fMRI) for clinically actionable indications (e.g., conversion and treatment-response prediction) seems well justified, given supportive evidence and high potential impact on clinical practice. Further development of multimodal sequential algorithmic workflows with the ability to decrease costs and diagnostic burden[96] also seems a fruitful area for future work. Finally, since there is no guarantee that these highlighted candidate biomarkers will show clinical utility, development of other reliable, broadly accessible, and well-motivated measures (e.g., EEG MMN and neuromelanin-sensitive MRI[112]) currently at the early stages is still warranted.

A potential genetic biomarker is the PRS derived from the latest GWAS in schizophrenia, which can index substantial differences in liability between individuals. Compared with the lowest centile of PRS, the highest centile of PRS has an odds ratio for schizophrenia of 39 (95% CI: 29-53). However, the clinical utility of the PRS as a diagnostic biomarker is limited, since the median area under the receiver operating characteristic curve (AUROC) is only 0.72, meaning that the liability explained is insufficient for predicting diagnosis in the general population[164].

BIOMARKERS IN ANXIETY DISORDERS

Anxiety disorders – encompassing specific phobias, social anxiety disorder, agoraphobia, panic disorder, generalized anxiety disorder (GAD), separation anxiety disorder, and selective mutism – are the most frequent mental disorders, with a 12-month prevalence of 10-14%[165-167]. These disorders generate a substantial socioeconomic burden [168], as well as significant direct and indirect health care costs[169]. They are also highly comorbid with each other, and carry an increased risk of sequential comorbidity with depression[170] and SUDs[171].

Cognitive-behavioral psychotherapy (CBT) and various psychotropic medications have proven efficacy in anxiety disorders, but treatment response is achieved in only half to two thirds of cases[172-174]. Accordingly, these disorders often follow a chronic course, with a high rate of recurrence (32.1%), and may even show stable treatment resistance (8.6%) at nine-year follow-up[175].

Given this high burden and limited treatment efficacy, the identification of valid biomarkers for anxiety disorders is critical. Multiple biological mechanisms that may potentially serve as biomarkers of pathogenesis or treatment response to psychotherapy or pharmacotherapy have been identified[176-181]. Selected findings based on genetic, neuroimaging, neurochemical, neurophysiological and/or neurocognitive assays, which could potentially lead to biomarkers with additional validation, are presented below.

Susceptibility biomarkers

Genetics

Candidate gene studies have found that *COMT* (rs4680, G [val] allele), *NPSR1* (rs324981, T allele), *TPH1* (rs1800532, AA genotype), *HTR2A* (rs6313, T allele), and *MAOA* (uVNTR, long alleles) gene variants are most consistently involved in the pathogenesis of panic disorder. *OXTR* (e.g., rs2254298 GG genotype), *SLC6A4* (5-HTTLPR, short [s] allele), *MAOA* (uVNTR, long alleles), and *HTR1A* (rs6295, G allele) gene variation is most consistently involved in other anxiety phenotypes[182-185]. However, since replication has largely been elusive, candidate gene studies have mostly given way to GWAS, a more powerful and unbiased approach.

GWAS conducted in cooperative efforts – such as the ANGST (Anxiety NeuroGenetics Study) consortium, the UK Biobank, and the Danish iPSYCH study – have suggested that several single nucleotide polymorphisms (SNPs) in genes such as *ESR1, GLRB*, *MYH15*, *NTRK2*, *PDE4B*, *RBFOX1*, *SATB1, TMEM132D*, *TMEM106B*, and a non-coding RNA locus associated with the *CAMKMT* gene, are linked to anxiety-related traits, current anxiety symptoms, or lifetime anxiety disorders[186]. The largest GWAS of anxiety traits to date, using the Million Veteran Program dataset, identified genome-wide significant associations with the Generalized Anxiety Disorder 2-item (GAD-2) score near genes involved in global regulation of gene expression (SATB1) and the

estrogen receptor alpha (ESR1)[187]. These are promising leads, but the effects require confirmation as more data are acquired.

Given the close interaction of genetic factors with environmental influences in the pathogenesis of anxiety disorders, studies are increasingly testing gene-environment (GxE) interaction effects using both candidate gene (e.g., *RGS2*[188]) and genome-wide[e.g.,189] approaches. These, too, have produced initial, but as-yet unreplicated results. The GxE concept has recently been expanded to include a dimension of "coping", yielding a three-dimensional model (GxExC). For instance, replicated evidence has been reported for an interactive effect on trait anxiety of a neuropeptide S receptor (*NPSR1*) gene variant, early adversity, and coping factors, such that adaptive coping compensates for the otherwise deleterious effects of a GxE risk constellation[190].

Finally, growing evidence is emerging for epigenetic mechanisms that can bridge between genetic and environmental levels[191]. For instance, altered DNA methylation patterns in the *MAOA*, *OXTR*, *BDNF*, *NET*, *GAD1*, *CRHR1* and *NR3C1* genes have been associated with panic disorder or social anxiety disorder[192,193]. In addition, still-underpowered epigenome-wide association studies (EWAS) in panic disorder and social anxiety disorder suggestively point to altered DNA methylation in previously unidentified risk genes[194-197].

Given the small effect sizes of individual genetic variants, a combination of genetic, epigenetic and further molecular markers might be more informative than genetic or epigenetic data alone. For example, as the field matures, PRS such as those used to predict illness course in schizophrenia[198] could be developed for anxiety disorders. An important caveat in epigenetic studies is that they have largely relied on peripheral tissues (with the exception of investigations in post-mortem samples), and epigenetic changes in peripheral tissues do not provide direct evidence of changes in the central nervous system[199]. Providing some optimism, though, studies that compared peripheral and central tissue have often reported considerable functional overlap[192].

Neuroimaging

Numerous structural and task-related fMRI, PET, SPECT and MRS studies have been conducted in anxiety disorders. Structural studies have not provided consistent results, in terms of regions or directionality. In functional studies, altered brain activation elicited in response to words or pictures with anxiety- or fear-related content has been observed in the "fear network". This includes both increased and decreased inhibitory control-relevant activity in the orbitofrontal and in the dorsolateral, dorsomedial and ventrolateral prefrontal cortex, as well as mostly increased activity in limbic structures such as the amygdala, insula, anterior cingulate cortex, bed nucleus of the stria terminalis (BNST), and striatum. The BNST may be involved in sustained rather than phasic anxiety[180,200].

Particularly consistent evidence has emerged for increased amygdala reactivity towards negative emotional stimuli in combination with insufficient prefrontal control[201]. One interpretative constraint, though, is that this activation phenotype tends to be seen across anxiety, stress-related and mood disorders, limiting its value as a biomarker able to distinguish between clinical presentations.

Psychophysiological assays and challenges

In general, "fear"-based disorders are often characterized by heightened physiological reactivity to salient threat stimuli, as measured by skin conductance response, fear-potentiated startle, pupillometry, cortisol, alpha amylase, or heart rate variability. In contrast, "anxiety"-related disorders are often characterized by a more blunted pattern of physiological reactivity using these same assays[202]. This is a potentially noteworthy dissociation providing some support to the notion that these biological measurements may be at least partly disorder-specific and developed as potential biomarkers.

An exemplary longitudinal study demonstrated the utility of the error-related negativity (ERN) as a specific, albeit not highly sensitive, electrophysiological biomarker predicting the first onset of GAD over 1.5 years in adolescent girls: ΔERN increased the odds of GAD onset to 1.64 even after controlling for clinical risk factors[203]. There is also evidence for altered interoceptive sensitivity as a marker or mechanism of anxiety disorders[204]: for example, hypersensitivity to carbon dioxide (CO_2) introduced during a laboratory challenge has been proposed as a relatively specific and heritable predictive marker for subsequent panic attacks, but not necessarily panic disorder, during long-term follow-up[205,206].

There are also pharmacological challenges that have the potential to serve as risk or diagnostic biomarkers, particularly in panic disorder. In one study, a yohimbine challenge increased panic symptoms in patients with panic disorder more than healthy controls, and the extent of the yohimbine-induced symptoms in patients (but not controls) correlated with a trait measure assessing fear of publicly observable anxiety[207]. Similarly, another study showed that m-chlorophenyl-piperazine (mCPP) provoked panic symptoms in patients with panic disorder but not in those with generalized social anxiety disorder[208], showing some diagnostic specificity. Finally, cholecystokinin tetrapeptide (CCK-4) induces panic symptoms in individuals with panic disorder at a greater frequency than in healthy controls[209], and the extent of symptom expression seems to be dose-dependent[210].

Predictive biomarkers of therapeutic response

Genetics

The 5-HTTLPR/rs25531 variant in the *SLC6A4* gene has been extensively explored in the context of psychotherapy-genetic studies of anxiety disorders, which however have produced mixed results. A recent meta-analysis incorporating 10 independent samples totaling 2,195 patients could not confirm a role of this genetic variant in moderating the effect of CBT on anxiety disorder outcomes[211]. Similarly, limited studies investigating other serotonin-related

(e.g., *HTR1A*, *HTR2A*, *MAOA*, *TPH*, *TPH2*), dopamine/noradrenaline-related (e.g., *COMT*, *DRD2*, *DAT1*), or neurotrophic factor-related (*BDNF*, *NGF*) genes did not report consistently replicable results[212]. The largest therapygenetic GWAS meta-analysis of CBT treatment response in adults with anxiety disorders or major depressive disorder and in children with anxiety disorders (total N=2,724) failed to detect any sufficiently robust association of genetic variation with treatment outcome[213]. Finally, some recent studies have focused on potential epigenetic predictors of psychotherapy response in anxiety disorders, mostly pointing to a potential role of predictive DNA methylation patterns in the *MAOA*, *SLC6A4*, and *FKBP5* genes[192].

Pharmacogenetic studies in anxiety disorders have investigated candidate genes involved in pharmacokinetics (i.e., drug availability, metabolism and degradation) such as *CYP2D6* and *CYP2C19*, or candidate genes involved in pharmacodynamics (i.e., receptors, transporters) of the serotonin, dopamine and noradrenaline systems; hypothalamic-pituitary-adrenal axis (HPA); stress pathways; and neurotrophic factors. Thus far, the results have been inconclusive[186,214]. One study used a commercially available test (*NeuroIDgenetix*®) in GAD[215], but industry-sponsored pharmacogenetic tests have yet to be implemented in daily clinical practice. To the best of our knowledge, only one GWAS to date has investigated genetic markers of treatment response to venlafaxine in GAD, but there was no genome-wide significant association[216]. Pharmacoepigenetic research in anxiety is still in its infancy and has yet to yield any consistently promising findings[193].

Neuroimaging

A systematic review of 17 studies on neuroimaging markers predicting psychotherapy response in anxiety disorders revealed the most compelling evidence for: a) mostly increased pre-treatment dorsal anterior cingulate cortex activity during relevant fMRI tasks (e.g., emotional face processing/matching, anticipation of emotional pictures, or differential fear conditioning); and b) increased resting-state anterior cingulate cortex-amygdala coupling[212].

Similarly, a quantitative meta-analysis of primarily emotion processing/regulation task-based fMRI studies observed that increased dorsal anterior cingulate cortex activity was related to CBT response in 17 datasets comprising 442 patients with various anxiety and stress disorders[217]. This meta-analysis further revealed associations between treatment response and activations spanning the larger salience and interoception networks (i.e., comprising not only the dorsal anterior cingulate cortex, but also the right inferior frontal gyrus, anterior insular cortex, and dorsomedial prefrontal cortex). A sub-analysis restricted to patients with social anxiety disorder revealed positive correlations between CBT response and activity of the bilateral Rolandic operculum, subgenual anterior cingulate cortex, right precentral gyrus, right dorsolateral prefrontal cortex, right supplementary motor area, and posterior cingulate cortex[217].

Perhaps most promising of all, the first multimodal study integrating clinical data with resting-state and structural brain connectomics imaging data using a machine learning approach predicted CBT outcome at a single-subject level in social anxiety disorder with an accuracy of 84%; there was a five-fold improvement in predictive power compared to clinical measures of severity and single connectomic measures alone[218].

Additional studies have examined potential neuroimaging biomarkers of response to pharmacotherapy. An exemplary fMRI study in social anxiety disorder applying the Multi-Source Interference Task revealed that greater pre-treatment dorsal anterior cingulate cortex reactivity predicted better response to combined psychotherapy and selective serotonin reuptake inhibitor (SSRI) treatment with 83% accuracy[219]. In a pilot study of patients with the same diagnosis, higher baseline activity in the anterior and lateral parts of the left temporal cortex and the lateral part of the left middle frontal regions, measured by Tc-99m HMPAO SPECT, predicted non-response after a six-eight week regimen of citalopram[220].

Also in social anxiety disorder, a PET study discerned task-based negative left amygdala/rostral anterior cingulate cortex and positive left amygdala/dorsomedial prefrontal cortex co-activation patterns in SSRI responders. However, this study and further comparable investigations in other anxiety disorder phenotypes applied a longitudinal pre-post design and thus followed a mechanistic rather than a predictive study approach[see221].

In GAD, a favorable response to eight-week treatment with venlafaxine was predicted by greater rostral anterior cingulate cortex activity and lower amygdala activity in response to fearful faces, and by increased pregenual anterior cingulate cortex activity in anticipation of aversive and neutral images[222,223].

Other measures

Cardiovascular markers – including tonic and/or phasic heart rate, heart rate variability, and blood pressure – as well as markers of the adrenergic system – including adrenoceptor density and plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) levels – have been proposed as potential markers of CBT response. Studies testing these biological assays, however, have largely used suboptimal study designs and/or relied on limited sample sizes[212]. Their potential to serve as biomarkers for anxiety disorders, therefore, remains to be determined.

Summary of anxiety disorder biomarkers

The majority of studies to date have failed to identify valid biomarkers of anxiety disorder pathogenesis or treatment response. Only a few studies have actually assessed sensitivity, specificity, or positive/negative predictive values[203,218,219,224,225], and are potentially actionable. For instance, ERN showed a modest overall accuracy in predicting future GAD, with an AUC of 0.60, but marked elevations of ERN were quite informative about risk, and predicted onset above and beyond clinical risk factors[203]. Notably, because EEG can be widely deployed in clinical practice and the ERN marker is malleable by attention bias modification training[226], this could be a promising and practicable risk marker of GAD.

Some task-based MRI findings have also shown satisfactory prediction of treatment response[218,219,224,225]. Biomarkers based

on connectomics neuroimaging methods (resting-state fMRI, diffusion MRI)[218] might offer some additional advantages over activation mapping markers, as connectomics-based measurements can be acquired more consistently and reliably across settings, are independent of task performance confounders, and can be performed even in infants[218]. It should be noted, however, that MRI-based biomarkers ultimately might prove less clinically viable than neurophysiology-based markers, since fMRI technology and analysis expertise are currently expensive and typically only available in large academic medical centers.

Apart from the few exceptions illustrated above, the majority of studies reported findings on a merely correlational or associative level, and did not assess sensitivity, specificity or positive/negative predictive values. According to the criteria for biomarker discovery[11], markers of anxiety disorder pathogenesis and treatment proposed so far remain at stage 1 ("target identification") and have not explicitly ruled out confounding factors such as stress, comorbidity, physical activity and/or psychotropic medication (stage 2, "internal validation"). Most presently available findings also warrant replication in validation samples independent of the discovery samples (stage 3, "external validation"), and await testing in trials demonstrating "clinical utility" (stage 4). Therefore, their potential remains unclear[223].

BIOMARKERS IN POST-TRAUMATIC STRESS DISORDER

A distinct literature has developed on biomarkers for PTSD. This research frequently operationalizes post-traumatic stress with continuous scores on measures such as the PTSD Checklist (PCL-5)[227]. The most well-established pharmacotherapies for PTSD are SSRIs, but they have limited efficacy[228]. Consequently, PTSD research has focused on developing susceptibility and diagnostic biomarkers.

Genetics

GWAS have revealed that contributions of individual genetic polymorphisms to PTSD are very small[229]. For example, in the largest GWAS to date (48,221 individuals with PTSD and 217,223 without), the effect size of the top single-nucleotide polymorphism (SNP) was trivial (odds ratio, OR=1.06)[230]. However, PRS that combine effects of hundreds of thousands of SNPs show meaningful, albeit modest effects. The strongest PRS was correlated at r=.20 with the PTSD Checklist for DSM-5 (PCL-5) score. This estimate is likely optimistic, because it was assessed using internal replication. Other studies have observed effect sizes of r=.10 to r=.16 in independent samples using an earlier version of this PRS[231,232].

Neuroimaging

Numerous neuroimaging studies have investigated potential biomarkers of PTSD, but they have produced mixed results, also due to small sample sizes[233]. Meta-analyses have revealed clear links of PTSD to smaller hippocampal, amygdala and total brain volume, and lower structural connectivity of the corpus callosum[234,235]. Few studies examined other regions, making conclusions about them less reliable. Moreover, meta-analyses are vulnerable to publication bias (e.g., primary studies reporting only on regions where significant effects were found).

Mega-analyses can address this limitation by pooling voxel-level data from multiple samples to perform whole-brain analyses and present an unbiased picture of neural correlates. The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium performed a mega-analysis of cortical volume comparing 1,379 people with PTSD to 2,192 without[236]. Significant differences were found in 21 regions, all showing smaller volume in PTSD, but the largest group difference was only 0.17 standard deviations (SD). Another ENIGMA study examined subcortical volumes in 794 individuals with PTSD and 1,074 without[237]. Hippocampal volume was lower in PTSD by 0.17 SD. Amygdala volume and total brain volume were also smaller, but these differences did not reach significance. ENIGMA mega-analysis was also conducted on structural connectivity in 1,426 people with PTSD and 1,621 without[238]. Significant differences emerged in only one region, tapetum of corpus callosum, where structural connectivity was lower in PTSD by 0.11 SD.

Overall, these ENIGMA studies used rigorous methodology, and alignment with previous meta-analyses further increases confidence. However, their results have not been confirmed in sufficiently powered independent studies yet, and their relevance for developing biomarkers of susceptibility, prediction, or treatment response is questionable.

As links between PTSD and regional structural morphology are weak, at least for standard neuroimaging modalities, one potential avenue for improvement is if regions or voxels are combined into a composite biosignature, especially using machine learning techniques. Reliable composites will likely require larger sample sizes than currently available for PTSD. For example, research to estimate a participant's age from sMRI found that a biosignature developed in a sample of 35,474 individuals correlated at r=.69 with age in an independent sample[239]. Performance of this biosignature was proportional to the sample size used to develop it, although most of the increase occurred by the sample size of 5,000.

Peripheral biomarkers

Numerous peripheral measures have been explored as potential biomarkers of PTSD, and we consider only the most studied ones.

Psychophysiology research has linked PTSD to autonomic nervous system functioning. Meta-analyses of heart rate variability and respiratory sinus arrhythmia found differences between people with and without PTSD of 0.16 to 0.50 SD[240,241], though some of this signal may be due to potential confounders such as low socioeconomic status or physical comorbidities. Another possible marker is startle response to an acoustic probe (i.e., sudden loud sound) when the person expects danger (e.g., possible electric shock) (fear-potentiated startle). This paradigm produces reliable differences in startle magnitude between danger and safety conditions,

but the link to PTSD is unclear. It appears that some patients with PTSD show potentiation, while others are indistinguishable from healthy participants[242]. This casts doubt on fear-potentiated startle as a viable biomarker.

Biomarker research has also focused on developing relevant assays from blood, urine and saliva. Evidence suggests that these assays are informative, albeit imperfect, surrogates for brain tissue[243-246]. Initially, peripheral tissue studies focused on candidate markers, such as cortisol and inflammation markers[247,248]. They reported elevated inflammation in PTSD, but the findings were quite mixed and may have been confounded by physical comorbidities.

Omics studies seek to investigate tissues comprehensively. The largest methylome-wide study included 878 participants with PTSD and 1,018 without, finding four significant methylation sites, all in gene *AHRR* [249]. Two of these sites were replicated in an independent sample[250]. However, the difference between groups was small even for the top site, and a composite methylation signature was not attempted.

The largest transcriptome-wide study included data on 977 participants and did not find any significant associations between PTSD and expression of individual genes[251]. However, it did not attempt to develop a transcriptomic signature. Two previous studies constructed such signatures and observed moderate accuracy, with an AUC of 0.64 to 0.76[252,253], but neither signature was evaluated in an independent sample.

Proteomics is a new modality in PTSD research. The most comprehensive study to-date included 276 plasma proteins, finding significant links between numerous proteins and PTSD[254]. A multiprotein signature showed a moderate association with PTSD within-sample, but these results require replication.

Summary of PTSD biomarkers

PRS for PTSD has passed the first three stages of biomarker development. It is an informative measure of susceptibility, reliable and non-invasive. However, its links with PTSD are too weak to be useful clinically. Even as performance of PRS improves with increasing discovery sample sizes, it is unlikely to reach the level needed for clinical utility. Nevertheless, it may become useful when combined with clinical and demographic risk factors[255].

The other potential biomarkers need rigorous replication and careful control for confounds. Moreover, their links to PTSD are quite weak. Integration of data across the whole brain, methylome, transcriptome and proteome is needed to improve effect sizes and replicability. However, this approach requires very large sample sizes.

BIOMARKERS IN MOOD DISORDERS

Mood disorders (MDD and BD) are among the most prevalent and costly illnesses[167], and the development of clinically actionable biomarkers is therefore a critical research and therapeutic goal. Early biomarker efforts throughout the 1970s and 1980s centered on urinary levels of various catecholamine metabolites, measures of platelet monoamine oxidase activity, and hypothalamic-pituitary-adrenal axis (HPA) function[256,257], with inconclusive results.

Neuroimaging modalities, such as gaseous encephalography, were used as early as the 1950s[258], and structural imaging methods were increasingly employed throughout the 1980s in attempts to define major structural and volumetric differences in the brains of individuals suffering from mood disorders[259]. The use of neuroimaging in mood disorders dramatically increased in popularity over the last 20 years, with the introduction of novel, minimally invasive MRI and MRS techniques that allow for structural, functional and neurochemical investigations. These emerging modalities were paired with novel pathophysiological and treatment concepts such as neuroinflammatory pathology, neurometabolic contributions to behavioral disorders, circuit/network based disorders, and neuroplasticity enhancing treatments. The field of psychiatric genetics has also leveraged technical and conceptual advances to perform ever larger studies aiming to identify genetic variation contributing to disease risk and treatment response.

However, despite decades of work attempting to identify clinically meaningful diagnostic tools and procedures, there has been limited progress in developing biomarkers that meaningfully aid in the diagnosis, prognosis, or personalization of treatment choices for mood disorders. Below, we present an overview of the current state of knowledge.

Susceptibility biomarkers

Genetics

The hope of identifying genetic biomarkers for mood disorders is bolstered by the clear epidemiological evidence of heritable factors contributing to these disorders, such as the moderate level of genetic contribution found in the Scottish Family Health Study for MDD[260], and the heritability estimates of approximately 70-90% for BD[261]. However, the identification of specific genetic contributions to these disorders has proven extremely challenging.

Several large, recently-completed GWAS have provided new information on the genetics of mood disorders. For example, a GWAS study identified 17 loci – relating to aspects of brain function ranging from excitatory neurotransmission to neuron spine/dendrite functions – that were associated with depressive phenotypes in ~114,000 people[262]. These findings are generally in line with a meta-analysis of post-mortem studies, which reported lower levels of synaptic protein or mRNA across MDD and BD (protein levels of SNAP-25, PSD-95 and syntaxin in MDD, and PSD-95 mRNA levels in BD)[263].

More recent GWAS efforts with growing sample sizes continue to expand the number of genome-wide significant hits[264,265]. These large studies provide additional evidence that the genetics of depression maps onto the broader genetic structure of mental disorders and cognition. Furthermore, transcriptional signatures in MDD have been found to be gender-specific[266,267], suggesting an important further area of investigation.

A GWAS study in ~42,000 patients identified 15 genes linked to BD[268]. However, the pattern that emerges most consistently is that BD shares many common weak genetic risk factors with MDD and schizo-

phrenia[269]. Ultimately, it seems likely that these genes will each have a small impact on the susceptibility to mood disorders, and progression to disorder will importantly depend on interactions with environmental factors, such as (perceived) uncontrollable stress.

Neuroimaging

Much of the neuroimaging work related to mood disorder susceptibility seems to parallel the effects of stress on the central nervous system. Large meta-analyses of the structural correlates of mood disorders show volume reductions in the areas commonly associated with the stress response, including the hippocampus and frontal lobe[259].

The large multi-site ENIGMA consortium study, comprising ~2,000 participants, found reduced hippocampal volume, lower cortical thickness in multiple regions, and white matter alterations in MDD[270]. Similar to the genetic studies, the ENIGMA findings indicate relatively small overall effect sizes and common abnormalities in MDD, BD and schizophrenia, making it unlikely that the measures will prove useful in providing diagnostic biomarkers at the individual level. However, newer work using PET and MRI methodologies may be uncovering the cytoarchitectural correlates of the above structural findings, by demonstrating reductions of synaptic density in MDD[271].

Functional imaging studies, conducted at rest or during the performance of emotional or cognitive tasks, have increased dramatically over the last decade. Although these studies have provided support for circuit and network contributions to mood disorder pathophysiology, few findings reliably distinguish mood disorders from other conditions[272], similar to the structural and genetic findings previously described. Overall, prefrontal dysfunction may be a trait feature of mood disorders, while increased activation in limbic regions such as the anterior cingulate cortex and the amygdala may be associated with symptom expression[273]. However, medication and the presence of comorbid conditions – such as anxiety or substance abuse – may affect these findings. Much more work is needed at both the technical and conceptual levels before functional imaging can have more direct clinical applications in mood disorders.

The findings of MRS studies are far from consistent or conclusive, and are often complicated by methodological and technical heterogeneity. However, they have provided evidence to suggest the involvement of the amino acid neurotransmitter systems, including GABA and glutamate, in the pathophysiology of mood disorders[274-277]. These findings again appear not to be pathognomonic of these disorders, but common among a range of psychiatric conditions[278-282].

Early-stage MRS studies also suggest a role for pathophysiological effects related to oxidative stress as a contributor to mood disorders. Newer proton-MRS has enabled the quantification of glutathione concentrations in the brain, allowing for *in vivo* investigations of oxidative stress neurochemistry[283]. Although only a limited number of MRS studies have been completed to date, there is some indication of reduced glutathione measures in mood-disordered patients compared with healthy controls, with possible differences between MDD and BD[284], and specific regional associations with anhedonia in MDD[285]. Most recently, glutathione concentrations in the anterior cingulate cortex were found to be inversely correlated with depression scores and white matter hyperintensities associated to COVID-19 infection, further suggesting a link between neuroinflammation, oxidative stress, and mood[286].

In sum, the emergence of novel MRS methodologies has allowed unique *in vivo* explorations related to neurochemistry, brain metabolism, and neuroenergetics of mood disorders. While various technical and methodological limitations of the existing studies prevent firm conclusions about relationships to mood disorder susceptibility, the emerging data are generally in line with rodent models and post-mortem studies[287,288], and with predictions from large genetic studies showing effects on synaptic density and excitatory/inhibitory neurotransmitter pathways[265,268], and may reflect the reduction of synaptic density observed in MDD[271]. However, the methodology to date is not meaningfully helpful in providing prognostic markers, or in differentiating clinically relevant phenotypes of mood disorders.

Peripheral biomarkers

A myriad of peripheral measures attempting to capture monoaminergic neurotransmitter functioning have been employed over the years, with limited to no success in modifying diagnostic or treatment approaches. More recently developed metabolomics approaches, however, allow dynamic measures of large numbers of metabolites over time. Meta-analyses of these studies have found several metabolic abnormalities associated with mood disorders, including decreased levels of tryptophan, kynurenic acid and kynurenine, and increased glutamate levels in MDD patients. Pathway and network analyses of these data indicate disturbances of amino acid and lipid metabolism, especially the tryptophan-kynurenine pathway and fatty acid metabolism[289]. Overall, these findings support the involvement of several pathophysiological processes – including cellular signaling systems, components of the cell membrane, various neurotransmitter systems, hormonal regulation, moderators of circadian rhythm and sleep, as well as inflammation and immunological factors. However, no specific abnormalities can be associated with clinically meaningful differences to date.

Peripheral HPA axis measures have also been studied in large numbers of patients over the last five decades. The findings generally indicate HPA hyperactivity in depression, providing evidence of a link between MDD and comorbid conditions such as diabetes, dementia and coronary heart disease, especially in older and more severely depressed inpatients with melancholic or psychotic features[290]. However, the results are quite heterogeneous, and the effect sizes are modest, limiting the utility of these measures as diagnostic tools[291].

A relatively large number of studies, conducted over the past two decades, have examined peripheral measures of relevant neurotrophic factors. Much of this work has demonstrated a relationship between abnormally low peripheral measures of brain-derived neurotrophic factor (BDNF) and mood disorders. Reduced plasma and serum BDNF levels are commonly reported in depressed

patients and may be altered with treatment response[292,293]. Although fitting nicely with data suggesting that BDNF gene expression and function contributes to the pathophysiology of depressive-like behaviors, these findings lack specificity, and notable inconsistencies pervade research related to gene expression changes in human and rodent studies[294].

Interest in peripheral markers of immune function and inflammation has also increased over time. Abnormalities in several inflammation markers – including C-reactive protein (CRP), IL-6, IL-12 and tumor necrosis factor alpha (TNFα) – are consistently observed in major depression, often with medium sized effects. Nevertheless, the specificity and selectivity of these markers has not yet been convincingly demonstrated[295].

Finally, an emerging but potentially exciting body of research has begun to examine susceptibility biomarkers related to circadian rhythms. Mounting evidence suggests that abnormalities in circadian phase may precede mood disorders[296-304]. Indeed, change in sleep is one of the diagnostic criteria for MDD[305], and sleep difficulties are present in >85% of cases[298,306-308] and are correlated with greater depression severity[309,310]. Depressed patients exhibit reduced motor activity during the day[309,311], and lower rhythm-adjusted mean (or midline estimating statistic of rhythm, MESOR) has been reported as a diagnostic indicator of depression, with up to 80% accuracy[312]. A phase shift in activity is also present, as time to peak activity (acrophase) is delayed[309,312,313], and this delay may be associated with greater depression severity[309,313]. Disrupted sleep is also a diagnostic criterion for BD[305,314]. BD patients are also likely to have lower amplitude of motor activity when depressed[315] or euthymic[316].

Interestingly, circadian markers may have the potential to distinguish MDD from BD[317]. In particular, while further studies are needed, initial evidence suggests that MDD is associated with a phase delay[318,319], whereas BD is associated with a phase advance during mania[320], and a phase delay during euthymia[321], mixed mania, and depression[320,322]. Additional information may be gleaned by measuring melatonin during sleep/wake cycles[304,323,324], or by measuring awakening cortisol levels in euthymic BD patients[325].

Further work has indicated that the 3111T/C clock gene polymorphism, related to circadian rhythms, is associated with a higher recurrence of initial, middle and early insomnia in homozygotes for the C variant and a similar trend concerning decreased need of sleep in BD patients[326]. Moreover, expression of the clock genes *PER1* and *NR1D1* from saliva of BD patients in manic episodes is phase advanced relative to depressive episodes[327].

Prediction of treatment response

The best predictors of treatment response in mood disorders have traditionally included demographic and clinically-defined factors, such as age, severity and duration of illness, number of comorbidities, and the presence or absence of psychotic or mixed features[328,329]. However, several large-scale efforts aiming to identify biological predictors of treatment response have been implemented in the last decade. The international Study to Predict Optimized Treatment of Depression (iSPOT-D)[330], the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT)[331], and the Genome-Based Therapeutic Drugs for Depression (GENDEP)[332] studies all used large sample sizes to study and identify possible biomarkers for treatment response in depression.

The iSPOT-D study randomized over 1,000 depressed patients to 8 weeks of treatment with escitalopram, sertraline or venlafaxine, and assessed a large number of outcome variables, including clinical, daily functioning, cognitive, genetic and psychophysiological (e.g., EEG, event-related potentials, heart rate) markers. At least some outcome predictive value was found for various EEG measures (such as alpha connectivity)[333]; genetic factors (including variants in the *CRHBP* gene[334], and regulators of the gene coding for P-glycoprotein, which limits brain concentrations of certain antidepressants[335]); structural markers (such as hippocampal tail volume[336]); functional measures (such as activation in the frontoparietal network during response inhibition[337]); and environmental factors (such as early childhood trauma[338]). Further evidence also suggested that measures of functional connectivity of cognitive control and reward circuits could selectively and differentially predict antidepressant treatment responses[339,340].

The GENDEP study identified baseline levels of macrophage migration inhibitory factor (MIF), IL-1β, and TNF-α as "predictors" of antidepressant treatment response. That is, higher levels of pro-inflammatory cytokines predicted lack of antidepressant response, but lower levels did not predict a positive antidepressant response[341]. Interestingly, modulation of the glucocorticoid receptor complex and measures related to neuroplasticity were associated with a therapeutic antidepressant effect.

The Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study was a randomized sequential treatment study. In phase 1 of the study, nearly 300 patients were randomized to either sertraline or placebo. In phase 2, non-responders were randomized to placebo, sertraline (except previous non-responders), or bupropion. The goal was to identify potentially treatment-predictive endophenotypes of MDD, using electrophysiological methods, functional imaging, and peripheral markers[342-344]. Pre-treatment brain reward was somewhat predictive of individual antidepressant response[345]. Similar to reports from the CO-MED trial[346], the study also found evidence suggesting that CRP levels had some value in predicting treatment response, though the effect may be gender-specific[347].

The familial aggregation of BD (particularly the lithium-responsive type) among responders to lithium prophylaxis[348] has prompted recent attempts to identify genomic correlates of lithium response. The largest GWAS study[349] found a single associated locus on chromosome 21. The authors demonstrated that the response-related alleles were associated with lower rates of relapse in an independent sample of 73 patients treated for two years of lithium monotherapy. However, the predictive power of genomic data remains unknown, since GWAS are not designed to evaluate predictive capacity[350].

Summary of mood disorder biomarkers

Numerous biomarkers have been proposed in MDD and BD, and multiple studies including large-scale initiatives have identified potential candidates for future validation. There are several reasons underlying the limited gains achieved to date. These include the extreme heterogeneity of mood disorder diagnoses, limited treatment options, incomplete understanding of how the biomarkers actually reflect pathophysiological states, and the specific technical limitations and costs of the individual modalities.

Neuroimaging modalities, particularly those based on emerging spectroscopy approaches, may hold promise for improving prediction. However, at present, it remains a challenge to distinguish such findings in MDD or BD from similar effects in other mental disorders, such as schizophrenia, perhaps partly due to the imaging measures capturing a generalized "stress" phenotype rather a disorder-specific signature.

Similar challenges of sensitivity and specificity confront the use of peripheral biomarkers, such as neurotrophic factors as well as markers of immune function and inflammation. Future research may aim to integrate these measures with emerging approaches, such as those related to circadian rhythms, which may have the capability of differentiating MDD and BD biologically and behaviorally.

Acquiring combinations of available markers may also be useful[351-353], potentially providing complementary information while reducing noise and alternative explanations that compromise internal validation efforts. Future studies will also need to continue unraveling the formidable heterogeneity in mood disorder prediction, which may depend on factors such as gender and early childhood adversity, among many others.

BIOMARKERS IN SUBSTANCE USE DISORDERS

Among psychiatric disorders, SUDs are unique in the sense that the presence of a potentially addictive drug within the context of use-related dysfunction provides biological evidence for a disorder. Yet, beyond the presence of a drug in individuals' biological fluids, SUDs reflect repeated, compulsive substance use patterns mediated by complex (and not well-understood) interactions between biological drug effects, genetic predispositions, early life experiences, external stressors, and central and peripheral nervous system adaptations. Only an estimated 1 in 7 individuals who use substances will progress to use disorder[354], and such estimates vary according to which substance is used[355]. Considering that stable use with limited adverse consequences may describe a substantial group of substance-using individuals[356], it is vital to determine which susceptible individuals will eventually transition into full SUD.

Furthermore, among those diagnosed with SUD, there is a huge treatment gap. Epidemiological data indicate that 19 out of 20 individuals classified as needing treatment for SUD do not think that they need it[357], and this low perception of treatment need tends to persist over time[358]. Multiple factors likely drive this low perception, including minimization of the signs/symptoms of dysfunction associated with substance use, fear of stigmatization[359], and possibly neurocognitive impairments that might affect insight[360,361]. Thus, it is vital to develop and validate biomarkers that can help predict who is more likely to engage and succeed with treatment.

The area of neuroimaging has attracted the greatest attention in the search for biomarkers in SUDs[362,363], for several reasons. First, there are now well-established substance-related brain circuitry changes that involve: a) disruption in executive control, underpinned by dysregulation of prefrontal-subcortical processing, and b) increased salience processing of substance-related stimuli, spanning subcortical and cortical structures[364]. Second, neuroimaging can be used to integrate mechanistic models of substance effects (e.g., increasing dopaminergic tone via the transporter[365] or vesicular sources of intracellular dopamine[366]) with adaptations of brain systems to repeated use (e.g., decreased dopamine receptor availability and release measured with PET), which are some of the most reliable findings in the addiction literature[367,368]. Third, some studies support the idea that individual differences in neuroimaging assays may be of sufficient effect size to be used for predictive purposes[369]. On the other hand, several studies show clear evidence of limited associations between brain and behavior[370], and even large-scale studies show only modest correlations between psychopathology and structural or functional brain characteristics[371]. Despite these challenges and uncertainties, several studies have successfully used neuroimaging markers to predict important substance use outcomes.

Susceptibility biomarkers of transition to problematic use

In one large cohort study, transition from no use to frequent drinking in early to mid-adolescence was predicted by blunted activity of the medial orbitofrontal cortex during reward outcome[372]. Also in adolescents, structural characteristics – such as a larger cingulate gyrus – were predictive of resilience to problematic use after 3 years[373]. In a review of 44 longitudinal neurobehavioral studies predicting substance use in youth[374], functional vulnerability markers of substance use – i.e., markers that predict onset of subsequent substance use – included increased fMRI activation during reward feedback and risk evaluation in prefrontal and ventral striatal regions, and fronto-parietal hypoactivation during working memory. Altered neural patterns during response inhibition and differences in structural markers, including smaller fronto-parietal and amygdala volumes and larger ventral striatal volumes, were also observed.

In one examplary study of this approach, occasional stimulant users completed a Risky Gains Task during fMRI and were followed up to three years later to determine whether or not they transitioned to problematic use. Compared with participants who stopped their occasional stimulant use, those who later transitioned to problematic use made riskier baseline decisions after winning feedback, and exhibited lower baseline frontal, insular and striatal blood oxygen level dependent (BOLD) responses to win/loss feedback after making risky decisions[375]. In another study, initially alcohol-naïve adolescents were tested with fMRI during a reward task and were followed for 3 years to determine whether or not they initiated alcohol drinking. Compared with adolescents who

did not initiate alcohol use, those who did displayed increased baseline fMRI activation to loss in the left dorsal striatum (putamen) and right precuneus[376]. Finally, a study used connectome-based predictive modeling with leave-one-out cross-validation to uncover stress-linked connectivity patterns that differentiated risky from non-risky drinkers, finding that the stress-linked network profiles of the risky drinkers predicted loss of control of drinking in the entire sample[377].

These brain-based assays complement well-established behavioral predictors of problematic substance use. Investigators have found that non-planning and affect-based impulsivity, as well as reward-related valuation, were predictors of SUD vulnerability[378]. Other investigators have additionally found support for relatively poor control, early substance use initiation, binge patterns of use[379], and lower efficiency of evidence accumulation[380]. However, regardless of whether these neuroimaging or behavioral markers can serve as predictive biomarkers, a fundamental question persists of how these markers can be used in a predictive context. In fact, no study in SUD has used prospectively predictive biomarkers to examine their ability to affect outcomes or guide clinical decisions.

Predictive biomarkers of relapse and abstinence

Among individuals who have already met criteria for SUD, another important goal for biomarker development is the prediction of relapse versus abstinence. Prediction of relapse to substance use has been a major focus for biomarker development in SUD research for some time[381], and several investigators have been intrigued by findings that individual differences on various biological or behavioral measures provide predictive information[382,383], although there is increasing recognition that such outcomes are only a small part of the many possible clinically relevant measures[384], and that a comprehensive approach using complementary outcomes for prediction has been missing.

In a cue-reactivity study conducted among individuals with alcohol use disorder, fMRI activation in the ventral striatum during viewing of alcohol vs. neutral pictures predicted a shorter time to relapse[385], perhaps reflecting a heightened vulnerability to drug cues that culminates in drug-seeking and drug-taking behavior during abstinence. Consistent with this, an EEG study was conducted in a cohort of individuals with cocaine use disorder who were subsequently subgrouped based on length of cocaine abstinence. Results showed that the EEG-measured late positive potential (LPP), acquired in response to viewing cocaine images (and previously linked to craving[386]), showed a quadratic (inverted U-shaped) pattern as a function of abstinence length[387]. These results were interpreted as potentially reflecting an objective biological marker of craving "incubation", where drug-cue reactivity is counterintuitively potentiated after short- and medium-term abstinence[388,389].

In cue-reactivity research, one potentially important consideration is the contrast examined. While many studies have historically tested a standard drug vs. a neutral contrast, a drug vs. a pleasant contrast may be more ecologically valid[390,391]. This latter contrast better reflects diagnostic criteria, for example as specified in the DSM-5, where time, effort and resources need to be allocated toward the pursuit and consumption of the addictive drug at the exclusion of other activities[392,393]. They also better tap into theories of addiction that emphasize a shift in salience and hedonic value from pleasant reinforcement to drug reinforcement[394,395].

Beyond cue-reactivity, other studies have reported that reduced functional resting-state connectivity within the executive control network, and between the executive and salience networks, could serve as a marker of relapse risk[396]. There may also be important clinical outcome predictive effects of brain areas involved in inhibitory control, such as the inferior frontal gyrus, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex[397], as well as brain areas involved in stress reactivity, such as the ventromedial prefrontal cortex and ventral striatum[398]. For stress reactivity, a recent study of patients with alcohol use disorder first found case-control differences (i.e., ventromedial prefrontal cortex and ventral striatal hypoactivity to stressful, threatening images) (Study 1), and then found that these same imaging phenotypes predicted a faster relapse to drinking in a new sample (Study 2)[399]. The finding of clinical implications in a new sample lends support to this imaging phenotype as a target for biomarker development into the future.

An alternate, but related strategy has been to examine functional and structural correlates of sustained abstinence[400]. A recent systematic review concluded that drug abstinence tracked with increased gray matter volume in multiple cortical regions spanning the frontal, temporal, parietal and occipital lobes. There were also volumetric increases in the insula, cerebellum, hippocampus and thalamus, though not the striatum[400].

Functional studies were relatively less clear, though some evidence indicates changes in subcortical areas such as the midbrain and striatum. For example, an earlier study scanned individuals with cocaine use disorder using a drug-Stroop task that incorporated monetary payouts for correct performance. Results showed that midbrain activation during this rewarded cognitive control task increased from baseline to six-month follow-up, during which participants were abstinent and/or treatment-seeking. Furthermore, the more the midbrain task activation increased from baseline to follow-up, the greater was the reduction in scores on a simulated drug-seeking task[401] that itself has been associated with real-world drug use/severity[402,403] and dopamine D2-type receptor availability[404].

The finding of midbrain activation enhancement to monetary reward in cocaine addiction was since independently replicated: relative to pre-treatment measurements, post-treatment was associated with increased activity in anticipation of reward in the midbrain, thalamus and precuneus; and increased activity in midbrain correlated with one-year cocaine abstinence, while an increase in ventral striatal activity during loss anticipation correlated with fewer negative urine screens[405]. Insula functioning may also play a role, depending on the task: in one examplary study with methamphetamine-addicted individuals in early abstinence, insula fMRI activation during risky decision-making predicted relapse with greater sensitivity and specificity than standard clinical variables (e.g., days since

last use)[406]. Studies like these highlight the utility of imaging phenotypes as complementary markers of relapse prediction, but further development and validation needs to occur before they may be deployed as clinically-actionable biomarkers.

The application of rigorous machine learning approaches to avoid overfitting has provided evidence that it should be possible to use markers for disease stage prediction. In a recent review, a state-of-the-art approach was proposed to develop predictive biomarkers within the context of relapse, which entailed computing connectivity patterns that generated out-of-sample predictions of outcomes[369]. For example, in one of the studies[383], cocaine abstinence was predicted by increased connectivity between frontoparietal and medial frontal networks; increased connectivity among salience, motor/sensory and subcortical networks; and decreased connectivity between these two systems. Importantly, the results were replicated in an external sample, providing some predictive validity. Such studies and perspectives provide a blueprint for addiction biomarker research into the future.

Summary of substance use disorder biomarker research

The development of biomarkers for addiction has been impeded by multiple difficulties. First, as this field is still maturing, study designs have been largely limited to case-control or longitudinal follow-up approaches, and even most longitudinal studies predicting substance use outcomes have not provided additional data or methodologies confirming the predictive value of the measurements. Randomized intervention trials, such as neurostimulation approaches that directly modulate addiction-related neural signatures[407], will be important to use prospectively in order to examine the utility of these markers.

Second, addiction describes the compulsive use of different classes of substances that, while usually acting upon a largely common final neural substrate, have fundamental differences in their mechanisms of action and treatment approaches – even for different classes of "stimulants", encompassing cocaine and methamphetamine[408]. This substance heterogeneity also complicates the search for genetic biomarkers in addiction. For example, as much as 38% of the variation in opioid addiction may be due to genetic factors specific to opioids (i.e., not shared with other substances)[409,410].

Third, different biomarkers may be more appropriate depending on a person's current stage of addiction trajectory. For example, a large body of preclinical work has shown that initial drug-taking may be largely mediated by ventral striatal ("reward") pathways, whereas later-stage addiction may be largely mediated by dorsal striatal ("habit") pathways, and some human neuroimaging work has revealed a similar pattern of results[411-413].

Fourth, arguably more than in other psychiatric disorders, environmental exposure is important, as someone can never become addicted if he/she never tries a particular substance. As an illustrative example, estimates have suggested that as much as 62% of the variance in cannabis misuse was shared with cannabis initiation[412,414], highlighting the importance of substance availability for the eventual addiction phenotype. It should be noted that one exceptional counterexample is the alcohol dehydrogenase genes protecting against alcohol consumption and dependence[415].

Fifth, SUDs do not exist in isolation, but frequently co-occur with other behaviors and mental health conditions that are likely to have a profound influence on various biological markers. For example, most clinical studies of SUDs, by necessity, allow some amount of commonly occurring psychiatric comorbidity, such as depression or PTSD. Such constraints argue against the utility of potentially accessible, scalable and affordable – but largely non-specific – biomarkers such as genetic or blood-based measures, because these kinds of non-specific assays may be difficult to interpret mechanistically.

In this vein, recent work suggests that extracellular vesicle-associated miR-29a-3p plays a crucial role in methamphetamine use disorder and might be used as a potential blood-based biomarker for detecting chronic inflammation and synaptic damage[416]. However, blood-based measures indicating substance-induced metabolic or inflammatory changes[417] may be additionally influenced by poor lifestyle (e.g., lack of exercise, poor diet and disrupted sleep) and other mental health conditions (e.g., comorbid mood or anxiety disorders), and so specificity remains a concern.

Nevertheless, an objective marker of substance use severity, not unlike a blood glucose or hemoglobin A1c measurement, might help to facilitate evaluation of treatment need (among clinicians) and treatment acceptance (among patients), and could be a low-hanging fruit in the search for biomarkers in SUDs if an appropriate biomarker could be devised and confirmed for efficacy.

GENERAL DISCUSSION AND RECOMMENDATIONS

A review of candidate biomarkers for predicting diagnosis and treatment responsivity in ASD, schizophrenia, anxiety disorders and PTSD, MDD and BD, and SUDs, encompassing genetic, molecular, neuroimaging and/or peripheral phenotypes, reveals that most are in the very early stages of development and validation, and, for this reason, an assessment of their clinical utility is premature.

The immature state of the biomarker development in mental disorders is unsurprising, given its many challenges. One of the most fundamental challenges to overcome is that psychiatry research to date has most often relied on case-control designs, contrasting behavioral and/or biological assays between patients with chronic illness and healthy comparison participants. This is even the case for large-scale imaging datasets such as ENIGMA and similar consortia. Such consortia have been, and will likely continue to be, important for summarizing statistically robust group differences and associations in patients and controls, and will have the power to illuminate novel brain-behavior findings that might otherwise remain hidden. Nevertheless, consortia data built from case-control studies are unlikely to deliver clinically applicable biomarkers for relevant clinical indications understood in terms of the FDA, because the constituent case-control studies themselves generally lack an actionable biomarker target (i.e., not diagnosis, but rather susceptibility or treatment response).

Our perspective is that studies should be designed from the outset to have as their designated end goal the development of a biomarker for a particular indication, in the right population for that indication (e.g., CHR for conversion, drug-naive adolescents to predict development of SUD, acute unmedicated psychotic patients to predict response to first-line treatments). In this way, psychiatry as a field can begin to move away from pursuing large studies relying on non-specific big-data approaches, and instead pivot toward designing a pipeline for a given target in a manner more akin to drug development. The Adolescent Brain and Cognitive Development (ABCD) study [418] has the potential to drive new biomarker knowledge on SUD susceptibility, for example. The PRONIA consortium has the potential to advance biomarker development for CHR for psychosis. Even then, it is not the case that massively large datasets are necessarily required for biomarker development; smaller studies could suffice, provided that a particular biomarker produces sufficiently high discrimination accuracy for its indication.

Another fundamental challenge for biomarker development in psychiatry is the heterogeneity of the disorders themselves. The diagnostic criteria for psychiatric conditions continue to rely on constellations of symptoms and signs that group patients together even if they exhibit very different illness presentations. For example, there are ~1,500 combinations of symptoms that result in a diagnosis of MDD[419]. Therefore, the cohorts of individuals we study are necessarily heterogeneous, and samples in which biomarkers are developed may not be representative of the larger population of patients who meet criteria for a given diagnosis. While newer diagnostic and classification systems, which are more quantitative and/or biologically-based[420,421], may help address this concern to some degree, a fundamental impediment to progress pertains to our insufficient knowledge of the human brain, and this likely can only be fully addressed with novel technologies that fundamentally increase the precision of measurement. Moreover, biomarkers will still be subject to potential confounds – including medication status, age and gender, among others – which threaten internal validity. For neuroimaging in particular, there are even more factors to consider, such as variability stemming from the processing pipeline[422].

Despite these formidable challenges, several strategies and recommendations – either considered individually or in combination – may improve sensitivity and specificity in the search for biomarkers of pathogenesis, treatment response, and safety in psychiatric disorders. First, adequately powered collaborative (epi)genetic studies are needed, involving mega-samples of patients who are deeply phenotyped for clinical course and treatment response, thereby allowing for the generation of poly(epi)genic risk in combination with poly-environmental scores. PRS have been developed for many forms of psychopathology, but must continue to be updated and refined as more GWAS data become available; other psychopathologies would similarly benefit from the creation and validation of PRS and related tools. Collaborative efforts would also further allow for the inclusion of biosystems beyond genetics and neuroimaging, such as proteomics, metabolomics[423] or blood transcriptomics[424], as well as potentially integrating some or all of these markers together in a multimodal framework to improve personalization and prediction.

Second, as alluded to above, alternate forms of classification and diagnosis may be useful for conceptualizing and testing potential biomarkers. This includes the investigation of intermediate phenotypes, which are related to the disorders but are more narrowly defined and putatively more proximal to the underlying neurobiological mechanisms (e.g., for anxiety disorders, the Research Domain Criteria "negative valence systems" traits[425]).

Third, long-term and cohort study designs are needed in order to evaluate the longitudinal course of disorder and remission/relapse after treatment, which may be more promising for biomarker development than diagnosis, being a clearer and more actionable target. Mechanistic confirmation may be achieved via experimental approaches that can demonstrate causality (by modifying the neural substrates thought to drive the disease states), such as neuromodulation techniques[426] or translational approaches incorporating animal models[427].

Fourth, studies could include online remote acquisition of selected measures in a naturalistic setting using mobile health (mHealth) tools (e.g., ecological momentary assessment of physiological data[428,429]). The identification of multimodal and multivariate signatures can be accomplished by means of mathematical modeling using artificial intelligence (e.g., machine learning, pattern recognition methods) in a systems biology approach[430,431]. Finally, *a priori* stratification approaches may be employed to clinically test preventive and therapeutic strategies individually tailored to the individual person's biological risk factor constellation.

In conclusion, although the general consensus is that we do not yet have clinically actionable biomarkers in psychiatry, considerable efforts and investments have fostered useful developments over the last couple of decades. We have reviewed some substantial advances made during this time, while also describing the additional work and complications that need to be addressed in order to accelerate and finalize the development and eventual roll out of candidate biomarkers into clinical settings. In doing so, some shifts in priorities may be necessary, particularly moving from diagnostic biomarker studies, which are currently overrepresented in the literature[84], to targeting questions for which biomarkers may be most clinically actionable.

Recent examples highlight difficulties yielding highly accurate classifiers even when rich datasets and strong incentives for biomarker development are available[432], and have specifically emphasized issues with external validation and robustness to sample-specific factors. For a biomarker to be actionable, however, it will need to be clinically predictive at the individual-person level. It will also need to be economically viable, which includes non-prohibitive cost and the ability to deliver unique information that cannot be gleaned with traditional, less expensive alternatives.

These needs will evolve in parallel to the development of novel therapeutics and technologies, and so the menu of biomarker possibilities in psychiatry is likely to expand in the future. Even with the current state of affairs, though, suboptimal biomarker-based predictions may still be helpful for high-stakes applications if they improve upon

what is possible when relying on clinical information alone, in ways that substantively decrease the individual and societal burden of mental illness. Setting specific benchmarks for well-defined target applications that can be used today where possible, in conjunction with developing appropriate funding and partnership mechanisms for end-to-end biomarker development into the future, will be critical to ultimately reap the societal benefits of this critical scientific and clinical endeavor.

ACKNOWLEDGEMENTS

A. Abi-Dargham is supported by grants from the US National Institute of Mental Health (NIMH) (R21MH 125454) and the US National Institute on Drug Abuse (NIDA) (R61DA056423); S.J. Moeller by grants from NIDA (R01DA051420, R01DA049733, R21DA048196, R21DA051179 and R61DA056423); C. DeLorenzo by grants from the NIMH (R01MH114972, R01MH123093) and the US National Institute on Aging (RF1AG064245); K. Domschke by grants from the German Research Foundation (CRC-TRR58, projects C02 and Z02; DO 1241/8-1) and the German Federal Ministry of Education and Research (FKZ 01EE1402A, PROTECT-AD, project P5); G. Horga by grants from the NIMH (R01MH 117323 and R01MH114965); R. Kotov by a grant from the US National Institute of Occupational Safety and Health (U01OH011864); M.P. Paulus by the William K. Warren Foundation and the US National Institute of General Medical Sciences (1P20GM121312); G. Sanacora by the G.D. Gross and E.S. Gross Endowment and the Yale New Haven Health System, and J. Veenstra-VanderWeele by the NIMH (R01MH114296) and the Simons Foundation. A. Abi-Dargham and S.J. Moeller are joint first authors of the paper.

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DOI:10.1002/wps.21078