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PSYCHIATRY IN PRIMARY CARE (BN GAYNES, SECTION EDITOR)

The Promise of Biomarkers in Diagnosing Major Depression in Primary Care: the Present and Future

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Abstract Major depressive disorder (MDD) is the most prevalent psychiatric disorder, but it can be underdiagnosed or misdiagnosed. Most people with depression are seen in primary care settings, where there are limited resources to diagnose and treat the patient. There is a lack of clinically validated objective laboratory-based diagnostic tests to diagnose MDD; however, it is clear that these tests could greatly improve the correct and timely diagnosis. This review aims to give a cross-sectional view of current efforts of DNA methylomic, transcriptomic, and proteomic approaches to identify biomarkers. We outline our view of the biomarker developmental steps from discovery to clinical application. We then propose that better cooperation will lead us closer to the common goal of identifying biological biomarkers for major depression. "The important thing is not to stop questioning. Curiosity has its own reason for existing." Albert Einstein.

Keywords Biomarkers · Major depression · Primary care · Methylation · Transcriptomics · Proteomics

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Introduction

Major depressive disorder (MDD) is a prevalent, serious, and multifaceted illness that affects the patient, their family, and society. The average age of onset of the illness is in the early twenties, and the manifestation is often recurrent or chronic, with depressive episodes overshadowing most of the patient's life. It is known that early diagnosis, leading to early treatment, could beneficially affect the progression and severity of MDD [1, 2]. Unfortunately, diagnosis of the illness is fraught with many objective and subjective problems. The objective difficulties begin with the lack of an objective diagnostic tool such as a blood test, an imaging measure, or anything that is quantifiable without the patients' or physician's interpretation. Depression is not a homogeneous illness, and without specific measures to aid subgrouping, unusual presentation of the illness could interfere with the correct diagnosis. Subjective difficulties include the stigma associated with mental illness diagnosis, the patients' willingness or ability to communicate with the health care provider, the amount of time a health care professional spends with a patient, and differences in specific medical training between psychiatrists and other physicians.

Primary care providers carry a large share of the burden to diagnose and treat MDD. A majority of individuals who commit suicide have contact with their primary care providers, and not mental health providers, in the months before their suicide [3]. This choice to engage primary care providers over specialty health professionals is not unique. In a 12-month period, 10–20 % of the adult population will visit their primary care physicians with mental health-related symptoms, most commonly depression [4]. Thus, it is not surprising that the prevalence of MDD in primary care is estimated between 4 and 18 % [5], higher than the prevalence in the general population. Unfortunately, in primary care, both overdiagnosis and underdiagnosis as well as misdiagnosis of clinical depression occur.

A recent meta-analysis indicated that in the primary care setting, individuals with depression were correctly diagnosed less than 50 % of time [6]. These and other data suggest that aiding MDD diagnosis in the primary care setting has the potential to significantly and positively affect precision of diagnosis and speed of treatment. Specificity of diagnosis is as essential as its reliability; biological markers correctly identifying MDD patients would greatly contribute to improving both.

This review will begin by summarizing the state of research aiming to identify biomarkers for the diagnosis of MDD. We focus on fit-for-purpose biomarkers that have the potential to diagnose the illness rather than biomarkers that predict treatment response, as several recent reviews have already covered this area [6, 7]. Next, we propose how to characterize a diagnostic biomarker and analyze some of the studies by these criteria. Finally, we paint a picture of the future where MDD is diagnosed and treated like any other chronic illness.

Biomarkers for MDD Diagnosis

Biomarkers are widely used in general medicine; however, the foray into biomarker discovery in psychiatry is relatively new. From genetic susceptibility markers through transcriptomic changes or altered functional activity of neurons, biomarkers can cover a large range of biological modalities. A sensitive and specific diagnostic noninvasive test for MDD would be greatly beneficial, as brain tissue cannot be obtained from the live patients. Practical biomarkers would be measured from tissue that is easily accessible, without a complicated procedure. Therefore, most biomarkers discussed here are measured from saliva, buccal, or, most commonly, blood samples. The idea of using blood as a surrogate tissue for the brain has been generating substantial controversy in psychiatry, although it is already an accepted approach in other areas of medicine [8]. These studies only had to prove that blood measures are commensurate with those in the target organ of the illness. While this criterion is easier to fulfill in cancer research, it is more difficult in the case of psychiatric illnesses. Not only does using postmortem brain tissues have its own inevitable complexities, but also the exact brain region or regions responsible for psychiatric diseases is still under investigation.

There are various ways to categorize biomarkers such as by their physiological function, as it has recently been done [7], or by the nature of the product: DNA, methylated DNA, RNA, and proteins. Here, we have chosen the latter organization.

Genetic Markers

Genetic risk factors as biomarkers for disease have been used as diagnostic tools [9]. In complex illnesses, genome-wide association studies (GWAS), which examine sequence variations linked to disease among a large population, are needed to provide the most informative genetic risk factors. GWAS have helped identify genetic risk factors for a number of polygenic diseases including type 1 and type 2 diabetes, inflammatory bowel disease, prostate cancer, and breast cancer [10]. Two large GWAS performed with 18,759 and 34,549 subjects, respectively, were unable to determine any significant associations with MDD [11, 12]. However, when an addition replication set of 16,709 subjects were included, the 5q21 region containing the rs161645 sequence variation reached genome-wide significance. Nevertheless, GWAS analyses have proved to be mainly unsuccessful in MDD [13••].

The correspondence between the presence of a single genetic marker and the illness is not 100 % even in the case of monogenic illnesses, and in polygenic ones, as MDD or any common disease, it is not a feasible approach. Yet, there have been numerous attempts to associate a genetic variation with MDD in candidate genes such as brain-derived neurotrophic factor (*BDNF*) [14, 15], serotonin 2a receptor (*5HTR2A*) [16, 17], and solute carrier family 6 (serotonin transporter), member 4 (*SLC6A4/5HTT*) [18, 19]. Several recent meta-analyses and reviews have begun to question the association of polymorphisms in these genes with MDD [13••]. For example, a recent meta-analysis of 28 studies by Gyekis found no association between BDNF polymorphisms and MDD risk [20]. Similarly, another meta-analysis found no association between 5-HTR2A rs6311 and MDD risk [21].

Epigenetic Markers

As opposed to the permanence the DNA sequence variations provide, DNA methylation is a dynamic process and therefore, can report on the physiological state of an individual. DNA methylation, the addition of a methyl group to the cytosine or adenine DNA nucleotides, is one of the major mechanisms that can regulate the expression of genes. The unbiased search for DNA methylation markers for MDD prompted genome-wide DNA methylation studies. In the ideal paradigm, sequence variation would not contribute to variations in DNA methylation, such as in monozygotic twin studies. Higher variation of overall DNA methylation is found in the twin with MDD compared to their control twin in both blood and buccal cells [22, 23]. Most significantly, the latter study confirmed buccal cell hypermethylation of *STK32C* in the depressed twin and independently, in post mortem cerebellar tissue of depressed patients [23]. Another study found no significant genome-wide methylation differences in the blood between twins discordant for depression [24]. However, one of the top suggestive candidates, *ZBTB20*, was shown to be hypermethylated in the coding region using an independent replication sample. When using medication-free subjects,

Numata and colleagues found 363 CpG islands that were hypomethylated in depressed subjects [25••]. Using the top methylation markers, they were able to distinguish patients with MDD from controls.

Candidate genetic markers for MDD have more recently been the focus of interest for their environmentally induced DNA methylation signatures. For example, childhood adversity was significantly associated with hypermethylation of the *SLC6A4* promoter in the blood [26]. In a monozygotic twin study, higher depression scores were again associated with hypermethylation of the *SLC6A4* promoter in blood leukocytes [27]. However, a recent study was unable to distinguish MDD patients from controls by means of blood DNA methylation profiles at CpG islands of *SLC6A4* [28]. Therefore, though *SLC6A4* promoter methylation seems to be a possible biomarker target, further work is needed to determine if it has actual discriminatory potential.

BDNF promoter hypermethylation was found in mononuclear blood cells from MDD subjects compared to either controls or bipolar patients [29, 30]. However, the opposite, hypomethylation of BDNF CpG sites including the promoter region in subjects with MDD, was found in saliva when compared to controls [31]. This may raise the question regarding the appropriateness of comparison between methylation status using various tissue sources. It is possible that one tissue type could provide methylation biomarkers with a reliable clinical readout, while another may not.

Transcriptomic Markers

Transcriptomic biomarkers have been gaining ground, as the ease of collecting blood or other fluids and preserving RNA has increased [32•]. The transcriptome is the sum total of all RNA molecules expressed from the genes. Transcriptomic biomarkers can provide insight into one's current physiological condition through the measurement of specific transcript levels. The use of genome-wise approaches allows for the potential of novel, unbiased discoveries. The human transcriptome was investigated in studies using genome-wide approaches to look for hitherto unknown transcriptomic markers for MDD. A large study using next generation sequencing of blood RNA found no significant expression differences by MDD status after controlling for many covariates. However, there was high enrichment of the IFN α/β signaling pathway supporting the hypothesis that altered immune signaling has a role in MDD pathogenesis [33••]. Using microarray-based genome-wide analysis of whole blood, 17 mRNA were found to be differentially expressed between MDD patients and controls [34]. They also found differentially expressed long noncoding RNAs of which four are known to regulate four of the 17 differentially expressed mRNAs. Functionally, the candidate marker mRNAs were primarily related to basic metabolic processes and signal transduction. A genome-wide exploration from dermal fibroblast resulted in differentially expressed mRNAs between subjects with and without MDD. Candidate markers mainly fell into the functional categories of cell-to-cell communication, innate/adaptive immunity, and cell proliferation [35•]. In addition, a distinct group of differentially expressed microRNAs (miRNAs) was found. The differentially expressed mRNAs are targets for the thereby identified miRNAs, and the directionality of the mRNA and miRNA differences was opposite as would be expected.

Another approach to the unbiased identification of transcripts through genome-wide analyses uses induction of gene expression. This approach could be particularly useful in uncovering the relationship between inflammation and MDD. Incubating blood from people with MDD and controls with liposaccharides resulted in seven differentially expressed mRNAs, mainly immune system-related transcripts involved in cellular proliferation and differentiation [36]. Inducing gene expression by in vivo administration of dexamethasone yielded increased discrimination of MDD patients from controls [37]. While only levels of five transcripts differed between MDD patients and controls at baseline, 18 differed after stimulation. Genes showing the most significant expression differences, *FKB15*, *DUSP1*, and *ZBTB16*, have previously been associated with mood disorders or neuroprotection.

Among studies that investigate candidate biomarkers, the one by Powell and colleagues is particularly interesting as it focuses on only inflammation-related genes in the blood [38]. The two most robust and reliable biomarkers identified were *CCL24*, with higher transcription in MDD patients compared to both controls and bipolar patients, and *CCR6*, with decreased expression in MDD patients compared to controls.

Two biomarker discovery approaches are unique in that they combine multiple levels of information. Niculescu and colleagues measured genome-wide expression differences in the blood between bipolar disorder subjects with low or high mood [39]. Additionally, they identified unique gene expression patterns in the brain and blood of a mouse pharmacogenomic model. Using their convergent functional genomic strategy, they identified candidate blood biomarkers involved in myelination (*Mbp*, *Edg2*, *Mag*, *Pmp22*, and *Ugt8*) and in growth factor signaling (*Fgfr1*, *Fzd3*, *Erbb3*, *Igfbp4*, *Igfbp6*, and *Ptprm*).

Our group took a different route to MDD biomarker discovery [40]. We identified a prospective panel of blood transcriptomic biomarkers by genome-wide expression analysis of both a genetic and a chronic stress-induced animal model of depression. These biomarkers were tested in human patients, and a subset of them was able to differentiate adolescents with depression from their nondepressed controls [41]. This study was followed up in adult primary care patients with MDD and their controls. Blood transcript levels of *ADCY3*, *DGKA*, *FAM46A*, *IGSF4A/CADM1*, *KIAA1539*, *MARCKS*,

PSME1, *RAPH1*, and *TLR7* differed significantly between patients and controls. Abundance of *DGKA*, *KIAA1539*, and *RAPH1* remained significantly different between MDD patients and controls even when the patients remitted after cognitive behavioral therapy. This suggests that levels of these three transcripts are trait markers of MDD.

Protein Markers

There has been less unbiased exploration of protein biomarkers of MDD for unknown reasons. Protein biomarkers derive from the proteome, which is the complete set of proteins expressed in an organism at a given time and condition. Ditzen and colleagues analyzed the cerebrospinal fluid (CSF) proteome of subjects with MDD and controls [42]. Mass spectrometry analysis identified 11 proteins with differential expression levels: PEDF (two isoforms), apolipoprotein E precursor (ApoE), prostaglandin D2 synthase (PGDS; 21 kDa), transthyretin precursor, a-1B-glycoprotein, vitamin D-binding protein (DBP, two isoforms), cystatin C, b-2-glycoprotein, and hemopexin. Granted, collecting CSF is a far more invasive method than blood collection, and the procedure is unlikely to be performed in a primary care setting. Still, CSF biomarkers could provide a close readout of proteomic changes occurring in the MDD brain. In another proteomic approach to biomarker discovery, AlAwam and colleagues identified three peptides with significantly different signals between depressed and control subjects [43•]. However, these peptides were not further identified.

Progressive work has continued in the attempt to further explore and validate the role of interleukins, tumor necrosis factors, C-reactive proteins, and COX-2 among other inflammatory response proteins as biomarkers of MDD. A rich prior literature supports these explorations. Several reviews have recently integrated these findings aiming to provide a comprehensive explanation of the inflammation model of depression [44–46]. Recently, blood serum levels of nine biomarkers were selected based on their relevance to pathways reported in the literature to be associated with MDD [47•]. These biomarkers were able to distinguish patients from controls with 91 % sensitivity and 81 % specificity in both a pilot and replication experiment.

Two recent studies sought to determine depression biomarkers in the elderly. This focus is important because diagnosis is more difficult in this population. Testing blood with a panel of systemic inflammation markers revealed a linear or prospective relationship between depressive symptoms and levels of IL-6 and IL-8, respectively, in the elderly [48]. Another study in elderly MDD patients employed a multiplex panel previously developed on the Luminex platform to measure proteins from the cancer, cardiovascular disease, metabolic disorders, inflammation, and Alzheimer's disease literature [49]. Analytes that were most highly associated with depressive symptoms included hepatocyte growth factor, insulin polypeptides, pregnancy-associated plasma protein-A, and vascular endothelial growth factor.

Criteria for a Clinically Relevant Biomarker for Depression

Those who oppose the advancement in identifying biological markers for psychiatric illness have very varied reasons to do so. Some suggest that diagnosing major depression is an art not science, while others discount conclusions from an independent study [50] when it does not replicate their initial findings [51•]. Animal studies are dismissed as having limited direct relevance or specificity to the human condition [51], even if the results can be translated into humans [40]. Sometimes, the replication studies are done in subjects with differing diagnosis from the original discovery population [39, 52]. For these reasons, we would like to point out concepts that could be useful in the critical evaluation of the different biomarkers proposed for MDD.

The definition of a biomarker varies by its proposed usage and the intended level of regulatory approval. Recent white paper guidelines [53], in agreement with FDA regulations, are helpful in the discussion of biomarker assays aiming to become diagnostic tools.

A biomarker assay can vary greatly in quality and robustness from non-FDA-approved assays (in-house developed assays, commercial-research use only kits, and lab-developed tests) to FDA-approved diagnostic kits that can be run in a central clinical lab. Validation stringency is the highest in the definitive quantitative assay, which presents a phenotype-concentration association to calculate absolute values for unknown samples. The results could help to define the severity of the target disorder. In contrast, the relative quantitative assay uses calibrators when the reference standard is not available in a pure form, or is not fully representative of the endogenous biomarker. Finally, the qualitative assay gives a categorical readout with yes or no answers or scoring scales.

The definition of the biomarker can be complex (for example, [54]), but for our purposes here, we define biomarkers of an illness as characteristics that are objectively measured and evaluated as indicators of pathogenic processes. The process from discovery to clinical validation of a biomarker is indicated in Fig. 1.

Biomarker discovery is a fascinating process. It can be unbiased, such as genome-wide expression analyses in human samples [33••, 55], in samples from a valid animal model [40, 41], or a combination of both [56]. An alternate, unbiased process integrates genome-wide expression and genetic findings to identify biomarkers [39]. Candidate biomarker analyses, on the other hand, are motivated by either the results of prior literature [57–59] or the availability of a panel of markers with nonspecific purposes [38, 49, 60]. An explanation of terminology commonly

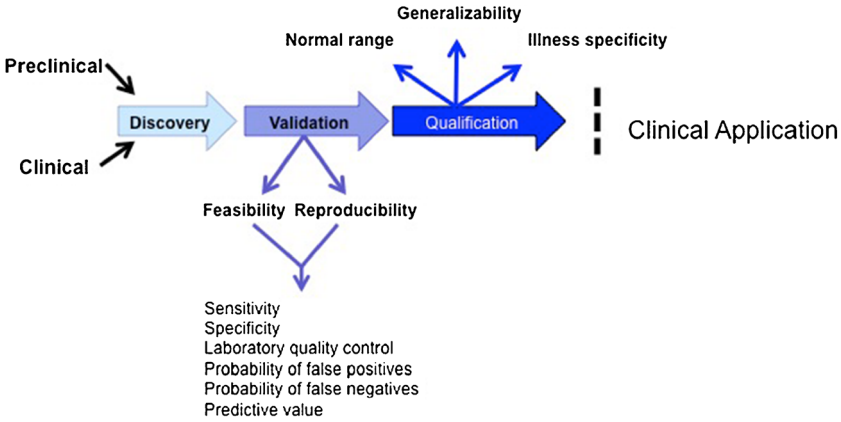

Fig. 1 Schematic representation of the steps to clinical applications for a fit-to-purpose biomarker

used in the discussion of biomarkers will help hone in on the definition of a biomarker and interpret Fig. 1.

A valid biomarker is defined as "a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results" [61]. Validation of biomarkers from genome-wide gene expression in human samples is very difficult. Due to the large number of covariates that superimpose on the genetic heterogeneity of the subjects sampled and the disease heterogenetity that is inherent in MDD, identification of genome-wide significant association for single genes is seldom achieved [33]. Although Mostafavi's study estimated 80 % power to detect genome-wide significant *P* values, it is clear that just like the MDD GWAS studies [11, 13••], transcriptomic analyses of MDD in surrogate tissues will need large sample sizes.

In the validation process, *feasibility* implies that the biomarkers perform to expectation in a human study, distinguishing subjects with MDD from their age-gender and race-matched controls. Almost all studies discussed in this paper fulfill this criterion. *Reproducibility* can be achieved in two ways; a study can be reproduced by the same group that made the initial finding, or by independent investigators. The first criterion is fulfilled by several studies, although most commonly, the available patient population is divided into a pilot and a replication sample, which do not differ demographically from each other [39, 47•]. Other times, the same group carries out independent studies on two separate and differing populations, such as we have done [40, 41]. Unfortunately, published studies that independently confirm biomarker panels for MDD are still lacking [55].

Validation is also the process of assessing the molecular and reliability characteristics of the biomarker (Fig. 1). *Sensitivity* describes the quality of the relationship between the magnitude of change in the biomarker and the magnitude of change in the clinical endpoint. *Specificity* is the ability of the biomarker(s) to distinguish those with the illness from those without; the greater these measures are, the better the biomarker(s) is. *Laboratory quality control* refers to the measurements' accuracy, reproducibility, limit of detection, unit values, etc. The specific questions that can specify laboratory quality controls include the following: were the methods of the diagnostic test described in sufficient detail; is there enough information that the tests could be replicated; do the results include how indeterminate results, missing results, and outliers of the test were handled? *Probability of false positives* refers to the odds that when the biomarker suggests the presence of the illness, the subject is not ill. Conversely, the *probability of false negatives* is the probability that a biomarker fails to signal the presence of the illness when it is present. Finally, high *predictive value* is a very mighty goal. It requires a prospective screen using the biomarker(s) and assessment at follow-up time points to determine if the biomarker successfully predicted the occurrence of the illness.

"Fit for purpose" validation is a more tailored approach, whereby the biomarker should be deemed to be reliable for the intended application [62]. There are several caveats for a peripheral biomarker of MDD. First, the validation of accuracy depends on the "gold standard" of MDD diagnosis, which of course has its own accuracy problems. Many of these are described in the introduction, particularly as they are related to MDD diagnosis in primary care. Then, surrogate biomarkers, which are the ones we deal in psychiatry, are mostly blood-based biomarkers that serve as a substitute for a clinically meaningful endpoint, such as how a patient feels and functions. Relatively few biomarkers will meet the stringent criteria that are needed for them to serve as reliable substitutes for clinical endpoints. The most rigorous standards are those of Fleming and DeMets who state that a "correlate does not a surrogate make" [63]. Instead, a surrogate biomarker should predict the effect of an intervention on the clinical outcome—a much stronger condition than correlation. Finally, in a complex disorder as MDD, multianalyte assays are the rule, rather than the exception. Here, the analytes need to be validated individually and then in combination, and the results will need specific algorithms to be interpreted.

Qualification is to provide evidence that the biomarker is linked with specific clinical end points. In this stage, determining the *normal range* by gender, age, and race is very important, as no biomarker will become a diagnostic tool unless this is established. Then, specifics of *generalizability*, whether the biomarkers can detect the illness in different subject populations, stratified by gender, age, and race, or at different geographic location, needs to be established. And finally, *illness specificity*, whether MDD biomarkers will detect depression in bipolar disorder, or can differentiate MDD from all other psychiatric illnesses, is the last criteria before the determination of suitability for clinical application.

Conclusions and the Future

Developing biomarkers is particularly important in psychiatry where no measures that are quantifiable without the patients' or physician's interpretation are available to date. Well-characterized and valid markers could distinguish and confirm the specific diagnosis of disorders with similar symptoms, predict the course of the disorder, and determine how to treat an individual with the disorder. Meeting these goals is important because, in psychiatry, the close association between symptoms and pathology is tenuous and varied and "…in the absence of any definitive neurobiological underpinning for neuropsychiatric diseases, psychiatric classification remains dependent on eliciting signs and symptoms of mental illness. This is the central problem from which many other difficulties in psychiatry arise" [64].

An additional high-priority research goal is to develop biomarkers that can identify "at risk" individuals and diagnose and/or estimate severity of mental illness, which is often on a continuum, into a clinical disorder. Although there is no doubt that on the one hand, objectively measured, valid biomarkers could alleviate the stigma of psychiatric disorders, there are also many ethical questions regarding their potential use. "… What is the best way to communicate the idea of a 'risk profile', and how might this affect personal identity? Given that human behavior and psychiatric disorders arise from a complex set of factors, how can this complexity be respected when using biomarker information in the clinic and community? And what issues might arise from commercialization of biomarkers, and how should they be addressed" [65]? Although these concerns are valid, they are primarily related to the societal view of psychiatric diseases. Some chronic illnesses are viewed as "benign" to the society while other as "malignant." After the tragic incident when the Germanwings co-pilot committed suicide by crashing a plane full of passengers, there was great outcry against Lufthansa for allowing a pilot with a history of depression to fly. However, for example, a pilot with diabetes is required to carry and use a whole blood glucose-measuring device with memory during his/her flight to avoid a hypoglycemic incident. If a similar portable device existed, which could diagnose one's acute depressive/suicidal state, the Germanwings co-pilot could not have boarded that plane. This seems an utopist view now, but so did many novel ideas in medicine before they were brought to reality. For much of 20th century, cancer immunology was a contentious field where immunologists questioned whether the immune system could recognize cancer cells and mount a response that could reject tumors. Today, the paradigm shift in oncology targets the immune system rather than cancer cells, in some risky but increasingly successful treatments.

So far, most putative biomarkers of psychiatric disorders have been promoted as "markers of the disease state." In reality, some of these markers may have altered levels as a consequence of the illness, while others were and remain causative. These causative markers could bring us closer to the identification of the multiple biological etiologies that contribute to complex neuropsychiatric diseases such as MDD. Despite the reasonably high genetic contribution, approximately 38 %, to depression [13••, 66, 67] compared to other common complex diseases, the limited successes of GWAS studies in depression are not unique, and the explanation for the "missing heritability" is not forthcoming [68]. Trait markers, such as those we identified in our study of blood-based biomarkers for MDD [40], may be in the pathway of genetic risk factors contributing to depression. Thus, if the pathways unique to these markers can be identified, hypothesis-driven targeted sequencing could determine the presence of common or rare sequence variations in subjects with MDD.

Additionally, using current computational methods, biomarkers could lead to new therapeutics. The biological pathways to which they belong could be identified, existing or potential new drugs targeting these pathways could be inferred in silico, and finally, these drugs could be confirmed by screening. For example, with the help of the Connectivity Map (CMap), novel drug targets can be identified. The CMap is a collection of gene expression profiles of drug compounds tested in various doses on one or more cell lines [69]. One can find drugs in the CMap, which would reverse the expression profile of the MDD markers in well-selected primary cells or cell lines. The CMap has been used to reposition catalogued drugs for other diseases where gene expression can be reversed by the drugs from their original patterns [70, 71]. Despite imperfect translations between different cell types and doses, repositioning with the CMap has been successfully demonstrated for inflammatory bowel disease by validating the inferred drugs used in in vivo models [72]. This approach could be improved by using a well-characterized animal model of the disease in question. For example, since most of the biomarkers identified by our group originated from the genome-wide expression analysis of the brain and blood of our genetic animal model of MDD [41, 73], these animals are particularly useful for screening novel targets for antidepressants.

Generating a panel of biomarkers that are highly reproducible as an indicator of MDD state would fulfill a great need in psychiatry, but an even greater one in primary care. At this time, we

have no biomarker panel that can fulfill all the criteria we schematically outlined in Fig. 1. However, there are several promising panels in the pipeline, which should be and could be promoted for diagnostic testing. At first, the greatest benefit for primary care physicians would come from these biomarker panels, which could easily and specifically diagnose MDD. Subsequently, biomarkers relevant for use in primary care would be able to identify patients' who are at risk for MDD. As soon as these potential diagnostic panels become approved and clinically available, primary care physicians could use them as the basis for referral to mental health professionals. The feedback from this process would enhance the use of these tests. When biomarkers are developed that can predict the optimal treatment for the specific patient, primary care physicians would be equipped to diagnose and treat most patients with MDD. Thus, only the difficult cases would require treatment by psychiatrists, allowing for a precise treatment opportunity for all patients.

The greatest success in recent years has come from consortiums, such as the International Cancer Genome Project, Psychiatric GWAS consortium, which put aside rivalry for the greater good. Sharing samples, methods, and ideas could be a game changer in psychiatry, allowing for objective, laboratory-based diagnostic tests that will confirm, devise diagnosis, predict treatment outcome, and aid in developing novel treatments.

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Compliance with Ethics Guidelines

Conflict of Interest Neha S. Mehta declares no conflict of interest. Eva E. Redei reports grants from NIH and from the Davee foundation, some of which is on topics outside the submitted work. In addition, Dr. Redei is named as an inventor on three pending patents owned by Northwestern University: Redei EE, Andrus B: Methods for Detection of Depressive Disorders, Redei EE: Biomarkers predictive of predisposition to depression and response to treatment, and Redei EE: Compositions and methods for characterizing depressive disorders.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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