yourself", "how able you are to concentrate", and "negative feelings"[9]. Patients do attach more importance to restoration of positive mood and cognitive functioning than to decrease of negative mood. However, standard rating scales do not assess positive mood.

We feel that, before we can move from artisanal prescription patterns into precision medicine, patients' characteristics, beliefs and attitudes should be better taken into account, and diagnostic and assessment tools should be revised.

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Right patient, right treatment, right time: biosignatures and precision medicine in depression

In contrast to diagnostic changes in the rest of medicine, mental disorders are still considered as behavioral, implying that an exclusive focus on symptoms would yield a precise diagnosis[1]. Thus, even though depression is characterized by biological heterogeneity and variable symptom presentation, diagnosis and treatment recommendations are traditionally given without reference to individual variability in genes, brain structure, function and/or psychological factors. Rather, clinical and health characteristics (e.g., age, weight, medical comorbidities, depression severity) serve as the sole method for treatment selection, despite limited consistency of these characteristics to yield strong associations to treatment response. As a result, treatment selection remains a trial and error process, and only one third of patients achieve remission with the first medication prescribed, with even lower rates of sustained remission in the longer term[2,3].

Much of the previous research in depression treatment has focused on predictor variables – that is, characteristics of individuals that are associated with treatment response (or non-response), independent of treatment. More recently, increased research has focused on moderator and mediator variables. Moderators are pre-treatment variables that predict differential response to different treatments; mediators are variables whose change during the course of treatment predicts eventual treatment outcomes. Clearly, our prior focus on predictor variables has yielded inconsistent and inadequate findings, and, even with the recent attention to moderator and mediator characteristics, we have yet to determine which patient will respond to which treatment. What is needed, instead, is a comprehensive panel of variables encompassing both clinical characteristics and biological factors that can lead us to identify the right treatment for the right patient.

A comprehensive approach for targeted drug treatment and prevention is precision medicine, which takes into account the complex interplay between individual variability in clinical phenotypes, genes and brain function[4]. Treatments for cancer and chronic heart disease have developed these models and, as a result, we have reduced morbidity and mortality through the development of targeted therapies for these diseases. Yet, mental illness often lags far behind. Recent focus of the US National Institute of Mental Health on the Research Domain Criteria (RDoC) and research in genetics, proteomics and brain imaging suggest that biological measures (or biomarkers) may help us to understand the heterogeneity within the symptoms of depression and other mental illnesses[5]. Identification of biomarkers of preclinical depression or of response to drug treatment will be crucial in the development of precision medicine, being propelled by recent technological advances in large-scale biologic databases (such as the human genome and connectome projects), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays), methods for detecting patterns of brain activity and structure, and effective computational tools for analyzing extremely large datasets.

Biomarkers are measurable characteristics of an organism that correspond to a particular physiological state. Biomarkers include compounds isolated from the blood, urine or other fluids as well as clinical, behavioral and neurocognitive parameters that are used to indicate the presence or severity of a particular disease state. Moderator biomarkers specify for whom or under what conditions the treatment works, and consequently help to clarify the best choice of inclusion and exclusion criteria or the best choice of patient stratification. Mediator biomarkers identify possible mechanisms through which a treatment might achieve its effect, and changes along with response to a particular intervention. Information gained from diagnostic or progression biomarkers should aid to tailor treatments for effective personalized medicine.

The development of biomarker predictors of antidepressant response languished after multiple candidates, most notably the dexamethasone suppression

test, proved to have inadequate prognostic clinical utility[6]. The recent emergence of low-cost pharmacogenomic techniques has sparked new interests in combinatorial use of allelic variations in drug transporters or metabolic genes as biomarkers that might predict drug response[7]. An initial generation of research identified a number of candidate genes with apparent validity as predictors of treatment efficacy and treatment-related side effects. These candidates include genes implicated in serotonergic function, the ABC family of xenobiotic transporters located in the blood-brain barrier, and the cytochrome P450 detoxification enzymes. However, to date, there are no effective biological methods to objectively assess depression endophenotypes, severity, or treatment response[8]. Previous efforts to achieve better treatment outcomes in psychiatry have led to the introduction of pharmacogenomics based decision-support tools[7], to help identify which patients are more or less likely to have a favorable outcome with specific pharmacotherapies, based on single nucleotide polymorphisms (SNPs) and gene variants in transporters and metabolizing enzymes.

Genome-wide association studies have revealed that common genetic variations are unlikely to explain sufficient variance in treatment response to guide selection of treatment for individual patients. Rare gene variants have greater explanatory power than common variants, but such individual markers would likely apply to relatively few patients. Thus, if neither common nor rare gene variants are likely to have widespread predictive value as "stand alone" predictors of treatment response in typical clinical trials, a new strategy is needed, one that integrates several types of clinical and neurobiological markers to guide clinical decision making for depressive disorders.

Since it is unlikely that a single biological alteration will have a one-to-one mapping with a DSM-defined or RDoC-specified mental phenomenon, a viable alternative to the single-biomarker approach is the development of biosignatures that aim to profile a diverse array of peripheral/serum growth factors, cytokines, hormones and metabolic markers. Additionally, integration with neurological, cognitive and psychological assessments will provide coverage of multiple abnormalities that contribute to the heterogeneity of depressive disorders. Such a biosignature will not only improve our ability to identify specific subtypes of depressive disorders, but will also assist with the selection of treatments that are likely to be more clinically useful[9,10].

Based on this, some of the most promising variables to evaluate include: comprehensive clinical phenotype; magnetic resonance imaging using measures of cortical structure; diffusion tensor imaging to assess cortical white matter tract integrity; functional magnetic resonance imaging assessing brain activation patterns to both emotional conflict and reward-dependent learning tasks; quantitative electroencephalography (EEG) to assess cortical and subcortical brain activation patterns; cortical evoked EEG potentials; behavioral neuropsychological tasks to assess reaction time and motor processing speed; DNA, mRNA, and plasma, urine and saliva protein and metabolomics samples, collected at baseline and throughout the study; socio-economic, demographic and life habits parameters.

Using this comprehensive approach, however, requires a large number of participants to be characterized in order to define subgroups in relation to treatment response. It also requires the use of effective computational tools to make integration of the wealth of knowledge generated from the diverse platforms possible. Herein lays our greatest challenge: developing large cohorts of depressed patients that will lead us to the discovery of not only new, meticulously-defined subtypes of depression, but also identification of precise treatments for each individual patient. If we are successful, this will propel the treatment of depression to equal the effectiveness of treatments for cancer and chronic heart disease.

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Person-centered measurement-based care for depression

It is evident that the same treatment will not work for all people with depression and that a major development is required to ameliorate the outcomes of depression in routine care. A symptom dimension of interest-activity robustly predicts treatment resistance[1], a blood test for inflammation may help select an antidepressant that works better for a given individual[2], and regular rating of symptom severity improves depression outcomes[3]. Yet, none of these simple measures that could improve treatment of depression are taken up in practice. On the other hand, some clinicians are using commercial pharmacogenetic tests in the absence of evidence that such tests could predict treatment outcomes[4,5]. R. Perlis eloquently describes how human motivations drive the paradoxes of contemporary health care[6]. Perhaps even more seriously, he argues that clinicians' insistence on artisanal prescribing hinders the accrual of data that is required