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

to meaningfully enhance the treatment of depression.

There may be a consensus that a serotonin reuptake inhibiting antidepressant is the first treatment to try in most individuals with the diagnosis of major depressive disorder, but we know that fewer than half of patients benefit sufficiently, that many experience side effects that are not matched by benefits, and that there is little evidence on what treatments should be attempted next. Many have lamented how it is possible that we still do not have personalized treatment given the amount of work that has been done. The number of articles published on this topic may be misleading. The reason why second and third line treatment for depression is still artisanal is that there is far too little data to personalize treatment choice.

The largest study of depression treatment completed to date – the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study – has failed to personalize the second and third line treatment choices for depression because it was too small. By the time STAR*D participants progressed to the third step, the numbers of patients allocated to specific treatments were too low to allow meaningful analysis of predictors. Genetic data were available for only half STAR*D participants, further compromising the power to find biomarkers that could facilitate the choice between second and third line treatments. Genetic case-control association studies of schizophrenia, depression and other disorders have taught us that sample sizes of many thousands are needed to leverage genomic information and enable meaningful predictions. For treatment predictions, these sample sizes have to be multiplied by the number of alternative treatments that need to be tested.

With today's technology, it is possible to create, combine and exploit datasets of hundreds of thousands for common disorders like depression. The way to do it may need to work with human motivation so that the process and not just the outcomes are meaningful for patients and for clinicians. The first step will be to motivate the collection of diagnostic information and regular outcome ratings in routine clinical practice. Person-centered care with active engagement of patients in clinical decisions offers a framework for achieving such routine information collection[7].

People living with depression come with their values and preferences and want to be actively involved in discussions about their care. Patients will complete regular outcome measures if they know that these meaningfully contribute to their care. Investigators of the Canadian Depression Research and Intervention Network have piloted a person-centered measurement-based care model where patients are given the option to complete regular measures on Internet-enabled devices and request feedback that serves to enhance their participation in collaborative decision making with their clinicians. Clinicians are able to access the information and also contribute diagnosis and rating scales. Based on the information provided by clinicians and patients, a feedback is generated that selects relevant recommendations from current best practice guidelines. In this model, patients are motivated to contribute data that serve both clinical and research purposes because they see the impact of the information on their care. They in turn motivate their clinicians to participate in the information gathering and feedback process. Patients are also asked for consent to use their data for clinical research and link their data with health care databases. The platform is improving outcomes of depression in real time, allows efficient evaluation of services, and at the same time contributes to the accrual of data that will eventually help personalize treatment for depression.

In a large database, it will be possible to look up individuals who resemble a given patient on a number of factors and recommend treatments that worked for that patient. Where two or more treatments are at equipoise, they can be compared using the efficient randomized registry design embedded in routine health care[8]. The results of such large pragmatic comparisons will gradually allow exploring further steps in treatment selection or testing novel treatments.

The vision outlined above has only been partially piloted. The early experience leads us to believe that the treatment for depression has to be person-centered and measurement-based before it can be meaningfully personalized.

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Carving depression at its joints?

Personalization of treatments has long been an aspiration for medicine and has recently evolved into a sophisticated practice for the treatment of some diseases. Although in psychiatry treatment decisions are usually based on the individual patient and his/her needs, there is a lack of information about how the benefits and harms of individual pharmacological agents (and indeed treatments in other modalities) differ from patient to patient and very limited data on which to base the choice between treatment options for individual patients. The thoughtful paper by R. Perlis[1] addresses the challenges in