how to accomplish our clinical tasks, including treatment selection. However, we seem to get entrenched in our beliefs and routines, and our own administrative, reimbursement and legal cultures. I'll bet that the Liberian "doctors" are still able change practices more easily than we can!

Perlis highlights the issue of slow adoption with his experience in pharmacogenetic testing research. Clinicians are moved almost entirely by what impacts their patients' outcomes, despite evidence of cost-effectiveness. There is still a paucity of research capable of changing the minds of clinicians and patients. Uptake and changes in practice would speed up if we had more research that focused on questions pivotal to clinician-patient decisions that result in clear evidence of benefit to substantial numbers of patients[3]. Issues in implementation would be clarified and uptake facilitated by addressing specific questions, such as: when in the course of treatment steps and with which medications is pharmacogenetic testing useful? Or, can we identify which patients have treatment-resistant depression at the outset?[4]

Let's assume that we have engineered consistent high-quality, measurement-based care, and have electronic health records and a cadre of educated and collaborative patients. Having somehow set this table to aggressively pursue precision medicine, the question becomes: do any of our prior successes in matching treatments and patients suggest a preferred path forward?

One major focus might be on identifying with a high degree of certainty which patients are very likely to not respond or succeed (i.e., to go after treatment failures). Depression is not unchecked cancer, with its generally predictable downhill and often terminal course. Success is an exception in cancer without treatment. Therefore, in cancer treatment research, a focus on success makes sense. Even after a successful cancer treatment begins to fail, we can learn from these failures. Depression, on the other hand, is a heterogeneous syndrome that has a highly variable course which is affected by changes in support, stresses, comorbidities and substances to name but a few. Adding to these challenges is the fact that only a small proportion of the "successes" will be specifically responding to the medication.

By focusing on depressed persons whose treatments have failed, we can learn which features of our patients or their treatments are contributing to the failures. An example of this in another area of study would be the pool of anemic patients who have been non-responsive to iron. This group would be enriched in patients with B12 deficiency. This B12 deficient subset might be easier to detect, especially in large patient samples and with the use of machine learning.

As a further illustration of the potential value of a focus on failures, consider how atypical depression grew out of a recognition that some depressed patients, often with atypical features, fared poorly with tricyclic antidepressants but succeeded with monoamine oxidase inhibitors[5].

Perlis' own work to define risk factors for treatment-resistant depression[4] also illustrates how a failure focus can be productive. His results indicated that there is a meaningful proportion of treatment-resistant patients (maybe 25%) who can be specifically identified by the measures used. Uher et al[6] also hit pay dirt with a failure focus, finding that anhedonic depressed patients do poorly with serotonin/noradrenaline reuptake blockers. Hedonically-impaired patients with treatment-resistant depression may have a dysfunctional mesolimbic dopamine system. Fawcett et al[7] recently found higher doses of adjunctive pramipexole to be associated with substantial and largely sustained benefits to treatment-resistant depression patients with severely impaired interest/activity.

Finally, to advance precision medicine, do we really need to wait to change psychiatric practices broadly? Culture changes are led by the few; almost never by the many. Multi-site registries that engage only those providers who are willing to make the changes above could generate large numbers of subjects for computations that involve large numbers of variables. I suspect that even randomization after the first step (though not essential) would be feasible in such registries and might well speed up discovery, given providers that possess the requisite curiosity and humility.

In conclusion, I largely concur with the challenges raised by R. Perlis in moving into the precision medicine space. These problems are all solvable as they are all man-made. Certainly better patient education, widespread use of measurement-based care and a willingness to throw away those bones are essential next steps for a coalition of the willing. A focus on failures may be a fertile field to till.

A. John Rush
Duke-National University of Singapore, Singapore

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Can we at least learn to fail faster?

For clinicians and (more important) patients, the current trial-and-error process of finding an effective depression treatment is frustrating and discouraging. Our ability to accurately match individual patients with specific medications is embarrassingly poor[1]. And, given the delayed symptomatic response to most depression treatments, the cycle time for each trial-and-error is as long as two months. It is therefore not surprising that many patients starting depres-

sion treatment become discouraged and never return.

As R. Perlis[2] clearly describes, more accurate prediction or personalized treatment selection is not yet in sight. It may not even be just over the horizon. Much of the research that claims to support personalization of treatment is really more relevant to general prediction of depression outcome or general prediction of treatment response than to selection of specific treatments for individuals[1]. I refer to this mis-application of evidence as "trying to answer a four-group question with a two-group research design".

Stated statistically, personalized or precision treatment selection depends on interaction effects rather than main effects. If we hope to detect interactions rather than just main effects, research to support precision medicine for depression will certainly require much larger samples than we are accustomed to. More important, selection of and testing for promising interactions or moderators will likely require a clearer understanding of treatment mechanisms and more precise measures of outcome.

While accurate prediction of treatment success may be off in the distance, we are probably closer to faster detection of depression treatment failure. And "failing faster" would be a significant improvement on the current state. Even though depression treatment guidelines often advise waiting six weeks or more to assess the effectiveness of antidepressant medication, evidence from placebo-controlled trials consistently demonstrates separation between active medication and placebo as early as seven days[3]. Even more promising, direct assessment of the neuropsychological "building blocks" of depression may allow even more rapid discrimination of treatment success or failure – identifying treatments unlikely to work earlier than traditional clinical measures.

For example, C. Harmer and colleagues at Oxford have shown that biased processing of emotional information (measured by a computerized task resembling a video game) can change within hours of a first dose of antidepressant medication[4]. We may soon welcome the day when we tell patients: "Download this app, take this pill tonight, and send me your test results in the morning. We can decide tomorrow if this medication is worth continuing". That scenario would be a dramatic improvement over our current advice to "take this medication for a month, and we can decide then if it was worth the wait".

The National Institute of Mental Health's Research Domain Criteria (RDoC) scheme[5] helps to reveal the connection between these two goals (precision prediction of treatment success and rapid detection of treatment failure). Under the RDoC scheme, we hope to resolve the heterogeneous category of depression into more crisply defined components or building blocks. Any individual case of depression would represent some admixture of more fundamental elements such as decreased sensitivity to reward, impaired executive function, and overvaluation of negative emotional stimuli.

Following this scheme, performance-based assessment of those RDoC components could facilitate advances in both directions: faster detection of treatment failure and more accurate prediction of treatment success. Stated statistically, discovery of mediators (processes that explain or account for the success of any specific treatment) will inform the discovery of moderators (pre-treatment characteristics identifying individuals for whom that treatment will be successful). Ultimately, this "experimental medicine" approach would also facilitate the development of more specific (and more effective) new treatments.

I expect that advances in precision medicine for depression will likely come sooner from neuropsychology than from genomics.

Gregory E. Simon
Group Health Research Institute, Seattle, WA, USA

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