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Letter to the Editor: Pharmacogenomic testing is not ready for general use in psychiatry

Letter to the Editor:

It was with great interest that we read Greden et al.'s (2019) study that evaluated the impact of pharmacogenomics on clinical outcomes in major depressive disorder (the GUIDED trial). This is the largest randomized controlled trial thus far of any of the commercially available pharmacogenomic tests. At first glance, avoidance of medications that might prove problematic due to genetic polymorphisms that impact metabolism could be very attractive to patients and their physicians. However, the potential utility of these tests is dependent on the prevalence of CYP450 polymorphisms affecting metabolism of psychiatric medications, the likelihood of a given patient being prescribed a medication they metabolize faster or slower than expected, and then on the clinical significance (in terms of side effects and clinical efficacy) of this mismatch. For example, 2D6 and 2C19 enzymes are involved in the metabolism of many psychiatric medications. While poor and ultrarapid phenotypes of these genes vary in their prevalence among different ethnic groups, they remain uncommon (Hicks et al., 2017).

The study was restricted to patients with moderate to severe depression who failed an average of 3.5 antidepressant trials. Although 18.3% of patients at baseline were prescribed medications in the "use with increased caution and more frequent monitoring" category, reflecting high rates of pharmacokinetic polymorphisms, the study failed to demonstrate a statistically significant impact of genetic testing on its primary outcome measure, the change in HAM-D17 score. The authors' choice to highlight relative risk reduction of the secondary variables (response and remission rates) obscures the fact that the absolute risk reduction was modest—6.1% more patients responded by week 8 and 5.2% more patients remitted by week 8. If the effect size is expressed in terms of Number Needed to Treat (NNT), 16.4 patients would require pharmacogenetic testing in order to have one additional patient show a clinical response, and 19.2 patients to have one additional patient achieve remission. NNT would be expected to be even higher in patients with no prior treatment failures given the increased prevalence of poor and ultrarapid CYP450 phenotypes in this sample, particularly for 2D6. Other important clinical outcomes (hospitalization, suicide attempts) were not reported. While the small subset of patients who were changed from incongruent to congruent medications by week 8 enjoyed significant improvement on all study measures, there is already evidence to suggest that medication doses reflect a patient's metabolic status even when their genotype is unknown to their physician (Mas et al., 2012).

More than 16 million adults in the U.S. have experienced major depression (SAMHSA, 2017). Assuming a cost of $3000 per test, the potential economic impact of widespread pharmacogenomic testing in patients with depression or other psychiatric disorders is enormous. While the findings of Greden and colleagues are encouraging, we believe that the generalizability to patients presenting with depression is unknown. Given that these products are marketed for use with the gamut of psychiatric medications, future studies should incorporate cost-effectiveness of pharmacogenomic testing on a wide range of psychiatric patients, followed over a longer time period.

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