Pharmacogenomic Tests in Psychiatry: Not Ready for Prime Time

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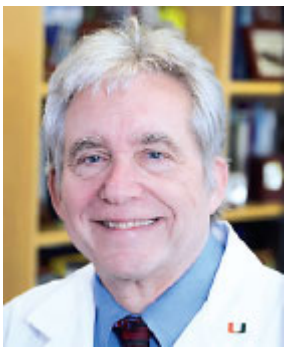

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The remarkable advances in pharmacogenomics in other branches of medicine, notably oncology and cardiology, have served as an impetus for its application to psychiatry, where we urgently need predictors of treatment response in individual patients with depression, bipolar disorder, schizophrenia, and, in fact, all of our disorders.

In recent years, several commercially available laboratory tests have appeared, and their substantial cost is reimbursed by Medicare, the Veterans Affairs system, and many private insurers. These commercial, combinatorial pharmacogenetics tests utilize algorithms that are composed of gene variants of pharmacokinetic- and pharmacodynamic-relevant genes. The pharmacodynamic relevant genes are largely associated with monoamine systems, such as the serotonin transporter, and one or more of the serotonin and dopamine receptors. Several clinical trials assessing the utility of these tests have been conducted, most of poor quality, and these data have been reviewed (see first reference below).

The APA Workgroup for Novel Biomarkers and Treatments, which I chair, published our findings in the *American Journal of Psychiatry* last year and concluded that “at present

there are insufficient data to support the widespread use of combinatorial pharmacogenetics testing in clinical practice. …" This position was endorsed by the APA Council of Research. Since that publication, additional findings and commentary even more critical of these tests have appeared in several journals, and perhaps even more importantly, the Food and Drug Administration (FDA) has now weighed in.

On November 1, 2018, the FDA released a consumer warning, stating, "The relationship between DNA variations and the effectiveness of antidepressant medications has never been established." The FDA goes on to point out that changes in patients' medications based on these test results "could potentially lead to patient harm."

A number of noted investigators in the field have strongly concurred with this view, according to George Zubenko, M.D., Ph.D., and colleagues in the August 2018 *JAMA Psychiatry*. Since that FDA announcement, a large clinical trial sponsored by Myriad Genetics failed to achieve its primary outcome measure—namely, any difference in depression symptom severity as assessed by the Hamilton Rating Scale for Depression between the pharmacogenomics-guided treatment group and the treatment-as-usual group. Several claims have been made based on improvements in secondary outcome measures, but these have been severely criticized on statistical grounds (Goldberg et al., *Journal of Psychiatric Research*, in press). On the positive side, a more recent study by Paul Bradley, M.D., and colleagues in the January 2018 *Journal of Psychiatric Research*had more promising findings, though patients with depression and anxiety were lumped together into a single group to mimic real-world experience.

On April 4, the FDA issued a warning letter to Inova Genomics Laboratory: "FDA is concerned that the clinical validity of your MediMap tests has not been established for their intended uses. Specifically, we are unaware of data establishing the relationships between genotypes assessed by your tests and your assertions regarding drug response for multiple drugs. For example, the relationship between CYP2C19 genotype and drug response to escitalopram and sertraline is not established, and the relationship is not described in the FDA-approved labeling for these drugs. Given these issues, these tests pose significant public health concerns as inaccurate test results could impact the decision making of health care providers and patients in ways that are seriously detrimental to patient health. Health care professionals may make inappropriate treatment decisions based on these test results, including inappropriate dosing adjustments, prescribing an ineffective therapy, and not prescribing a therapy that could benefit the patient. Such inappropriate treatments could

lead to immediate serious health consequences to the patient. In the case of escitalopram and sertraline, for example, such inappropriate treatments pose a significant risk of illness, injury, or death where health care professionals may avoid prescribing or may prescribe insufficient doses of these potentially life-saving antidepressant drugs to severely depressed and/or suicidal patients."

Pharmacogenomics, as an integral component of personalized medicine in psychiatry, however, has a very bright future. Many breakthroughs in this area are here now or will be forthcoming shortly. In particular, many recent findings with individual gene variants such as the norepinephrine transporter and the CRF binding protein are promising, but the current commercial entities marketing the available tests do not own the intellectual property for such gene variants and therefore cannot include them in their offerings. A related problem is that all the companies that market commercial assays utilize proprietary information in developing their algorithms, which they will not disclose in scientific publications, precluding any ability for scientists in the field to truly evaluate them.

I have little doubt that in the next decade a combination of pharmacogenomics and functional brain imaging will lead to usable, sensitive, and valid predictive tests for treatment response. In addition, there are emerging and promising developments in pharmacoepigenomics. Unfortunately, the currently available tests do not exhibit the requisite scientific evidence for routine clinical use today.

This article represents the writer's opinion, not that of the APA Workgroup on Biomarkers and Novel Treatments or the APA Council of Research. ■