VIEWPOINT

On the Marketing and Use of Pharmacogenetic Tests for Psychiatric Treatment

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Clinicians hope to see translational uses of powerful new technologies, such as brain imaging and genomic testing, guiding care of patients. In genomics, many newly risen companies promise to address this hope by vigorously marketing pharmacogenetic (Pgen) tests, especially for the treatment of major depressive disorder (MDD). One company's website reports sales of over 650 000 Pgen tests.[1] Does the evidence support such use? The heterogeneous and complex underlying causes and mechanisms of illness and clinical response to treatment in MDD strongly suggest that there will be serious issues limiting or preventing the development of Pgen approaches to treatment choice. Simply put, MDD is determined by a large number of genes, and, except in rare cases, no single gene or limited gene set, even those for drug metabolism and drug targets, determines more than a few percent of the risk of illness or course of treatment.[2-4] Environmental factors (age, sex, diet, alcohol use, hormonal status, general health) and comedication are usually more important factors than inherited determinants of drug metabolism and response.[5] While the activity of metabolic enzymes is heritable, extremely rapid or slow metabolism is rare, and dosing needn't be guided by Pgen rather than by careful dose choice and monitoring therapeutic and adverse effects.[6] Thus, the available evidence suggests that Pgen tests will not contribute much to care.

Still, it is reasonable to continue to study whether some gene variants or combination of gene variants are strongly associated with medication response. However, attention must be given to what would be required to demonstrate adequate predictive power to warrant clinical use. Clearly, such protocols should look much like protocols used to determine the efficacy of new medications. That is, studies must be of appropriate populations and adequate size to avoid false-positive findings. They must be properly randomized and achieve good matching for demographics and type and severity of illness, comorbid illness, and coprescribed medication. All participants, including the treating clinician, as well as raters and patients, must be blinded, as unblinded studies are biased in favor of any intervention. Comparison with an appropriate control is essential, as standard treatment (treatment as usual) cannot be blinded and assured to be of good quality. Conflicts of interest must be considered. Pharmacogenetic tests are proprietary and may not specify on what basis treatment recommendations are made. Some companies base their advice on diagnostic, demographic, and symptom information obtained by the clinician in addition to Pgen results. When that occurs, it cannot be clear whether the Pgen results made a substantial contribution. Analyses should account for multiple measures of effect, and reports should include examples of the advice given, that is, what drug changes were recommended and why.

Table. Summary Features of Published Clinical Studies of Pharmacogenetic-Guided Medication Treatment of Major Depressive Disorder[a]

Type of Study	No. of Studies	Total No. of Participants
Open/nonblinded and uncontrolled	5	1700
Retrospective/nonblinded and uncontrolled	1	333
Partially blinded and no protocol-based comparison	4	1186
Blinded and with protocol-based comparison	0	0

[a] Published studies were obtained through Google searches of websites of companies offering pharmacogenetic testing and PubMed searches for genetics, pharmacogenetics, or pharmacogenomics and depression or psychiatry and genetic, pharmacogenetic, or pharmacogenomics testing and depression or psychiatry. Only a few studies showed a statistically significant result, and these results were not corrected for multiple comparisons or nonrandomized assignment.

The literature contains 10 studies evaluating Pgen efficacy, all for MDD (**Table**). All of these studies demonstrate problems of conflicts of interest in that an author or institution had a commercial stake in the tests used. Most studies were small, including well below the hundreds of participants needed for definitive trials. Comparison groups were not well balanced for a variety of factors affecting response, such as age, sex, type of MDD, and medical and psychiatric comorbidity, including substance abuse, severity of illness, social and family history, current medications, and prior treatment. There was little information on types of prescribers, validity of the chosen ratings, reliability of raters, the clinical significance of group differences, and the contribution of therapeutic vs adverse effects to outcome. Most studies were neither controlled nor blinded, and none were adequately blinded and properly controlled. That is, the treating physician knew which patient was receiving a novel procedure, which can have a powerful placebo effect. In addition, controls were at best given treatment as usual, often provided by nonpsychiatrists, and medication choices were in some cases outdated or inappropriate. Specifically, some medications used in the treatment-as-usual group and advised against in the Pgen-guided group had known lesser efficacy or greater adverse effects and would not be used under available best-treatment clinical protocols.

In fact, no study used a proper comparison, such as free, readily available published protocols for the treatment of MDD (eg, STAR*D and the Texas Medication

Algorithm Project, both available online). Therein lies a key issue: to be valuable, Pgen should outperform good care. It should not be an expensive alternative for attending to standard protocols.

Recently, other independent assessments of Pgen testing were published.[7,8] Those authors also came to the conclusion that the evidence does not support the clinical use of Pgen. We are emphasizing both the reasons why Pgen may not be able to exceed the value of protocol-based treatment and detailing the minimal criteria expected to show that a particular Pgen test offered to clinicians and consumers has value. Reports of the success of Pgen will continue to be published by interested parties. Clinicians must be careful to follow independent reviews of Pgen testing (eg, the website of the International Society of Psychiatric Genetics) and be wary of the claims made in advertisements from companies selling these tests.

The desire to discover biological tests to guide treatment is sincere and studies should continue, but with the usual attention to careful design and with skepticism about claims. The claims on company websites may be good marketing, but they are not balanced and the time-pressured clinician or the uninformed consumer, often in distress, may be especially vulnerable to the pitch. Medicine has a history of use of improperly evaluated treatments and some persist because consumers demand help and can find clinicians who will comply.

Lastly, there are cost issues. Some costs may be covered by public and private insurance. Patient copayments from $249 to $399 are listed, but total costs for the tests are not disclosed. Additional billing for conducting, interpreting, or implementing the results may occur. Is it best to spend money on unproven procedures or put that money into purchasing more time for clinicians to evaluate patients or get a consultation? In this regard, the decision of insurers to pay for Pgen testing seems unwise. Pharmacogenetic tests, unproven and poorly documented, may distract from careful history taking and assessment of drug effects and interactions and cannot replace knowing and following the precepts of the large literature on appropriate serial drug choice. In these ways, Pgen tests carry the possibility of wasting resources and choosing the wrong treatment.

Genomic testing is valuable in a modest number of well-documented circumstances in medicine. We may yet achieve the goal of useful biological tests to assist clinical decision making in psychiatry. That time has not come. Nor should we undervalue the knowledge that we have on matching medications and other treatments to illness presentations. Psychiatric treatment, as sometimes claimed, notably in some materials from the purveyors of Pgen tests, is not trial and error. That is an oft-repeated and harmful canard, which only increases the difficulties in getting people into effective treatment. Proper assessment and treatment choices are well documented and usually produce substantial improvement. Monies spent to support such knowledge-based psychiatry and its application in thoughtful care is our current need.

ARTICLE INFORMATION

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Additional Information: Dr Zubenko is retired from the Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

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