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Psychiatric Pharmacogenomics: How Close Are We?

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A patient presents to your clinic with the results of a commercially available genetic panel and asks whether her medication regimen should be adjusted based on this information. How would you respond today? If you are an oncologist, you might be excited, and it is likely that you have invested significant time and energy learning how to interpret these results. However, if you are a psychiatrist, you might feel uncomfortable because of your relative unfamiliarity with this approach.

Over the past decade, the field of pharmacogenomics—once the stuff of science fiction—has become a leading topic in the pursuit of precision medicine (1). The goal of pharmacogenomics is to predict how patients will respond to specific medications based on their genetic profile. This allows clinicians to optimize both the choice of which medications to prescribe and also how to dose them for maximum efficacy and minimal adverse effects (Figure 1).

To date, the field of oncology has seen the most success in leveraging the power of pharmacogenomics. Multiple gene-response associations have been discovered that are used to guide routine clinical practice for the selection of chemotherapeutic agents (2). Furthermore, across medical specialties, the Food and Drug Administration has approved commercially available tests that are purported to predict medication efficacy and toxicity, and a growing number of insurers are subsidizing some costs (3). Which is to say, in some fields, pharmacogenomics has arrived.

In contrast, psychiatric pharmacogenomics is in its infancy; there are currently few validated and clinically useful gene-response associations that can be used to reliably guide psychotropic medication choice (4). Reasons that psychiatry may be lagging behind other specialties include the heterogeneity of psychiatric illnesses [e.g., DSM-based diagnoses may coincide more with general syndromes than distinct pathophysiologically based diseases (5)], the lack of biomarkers for specific illnesses, and the difficulty in defining and standardizing clinical outcomes (4).

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Commercially available genetic tests that claim to guide psychotropic prescribing are now widely available (and are often advertised directly to consumers). These tests offer patients information primarily about how their specific genetic profile might affect their metabolism of psychotropic drugs. Although the presentation of the results differs among companies, in general, patients are presented with a list of psychotropic drugs grouped into different categories that correspond to different prescription recommendations: use as normally prescribed, use with caution, or use with extreme caution. The companies' recommendations are based on an integrated analysis of multiple genetic variants thought to affect the functioning of enzymes involved in metabolizing psychotropic drugs. The patients are then classified as poor, intermediate, extensive, or ultrarapid metabolizers for each drug, and corresponding prescription recommendations are offered. Practically speaking, what these results suggest is that patients who are slower metabolizers of a given medication (based on their genetic profile) are more likely to benefit from lower doses of that medication to avoid toxicity, and, conversely, more rapid metabolizers may require higher doses to achieve therapeutic effect. Some companies will also provide information about how a patient might respond to a drug based on genetic variants in drug receptors or transporters.

Unfortunately, the evidence supporting the regular use of these commercial panels has significant limitations. Many of the genetic variants that are commonly analyzed have not been found to have independent associations with treatment response or clinical outcome across multiple large studies (4). Further, few studies have been conducted directly comparing clinical outcomes between patients who are treated with the aid of pharmacogenomic information and those treated by standard trial-and-error approaches. The studies that have been completed are small, are limited by design and analysis flaws, are funded by industry, and have yet to be replicated (4).

While this is the current state of the field, there is promising research on the horizon that may allow clinicians to use pharmacogenomics to truly enhance patient care. Perhaps the most progress has been made in identifying genetic variants that are associated with adverse effects of psychotropic medications (in contrast to those that try to predict therapeutic efficacy). This may be because the presence of a side effect is more easily defined and quantified than clinical efficacy. In addition, clinicians need to first reduce adverse medication reactions before addressing targeted symptoms.

As of this writing, the best data for pharmacogenomic testing in psychiatry relates to the use of carbamazepine. As with many psychiatric medications, carbamazepine can have rare but dangerous adverse effects; in this case, Stevens-Johnson syndrome and toxic epidermal necrolysis. From a study of Taiwanese patients (6), the Food and Drug Administration now recommends that all patients of Asian descent be tested for a specific variant of the HLA-B gene before initiating therapy to avoid carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. While this is a valuable, and potentially lifesaving, discovery, it is clearly only a first, small step toward a broader application of pharmacogenomics in psychiatry. For example, currently unanswered questions include: What are the effects of environmental exposures (e.g., diet, toxins) on this genetic predisposition and drug response? How do demographic factors, such as age and sex, affect this gene-response finding?

In this setting, one of the most challenging clinical situations is when a patient with treatment-refractory schizophrenia develops potentially life-threatening, severe neutropenia (7), also known as clozapine-induced agranulocytosis (CIA)/clozapine-induced granulocytopenia (CIG; referred together as CIAG). Both choices are fraught. Should one continue treatment with clozapine, thereby accepting the risk of a potentially grave adverse effect, or discontinue a treatment that may be a patient's last hope for relief from a debilitating disease? A pharmacogenomic test that could predict who is likely to develop CIAG (and/or who could be safely re-challenged with clozapine after the resolution of an episode of CIAG) would be an extraordinarily valuable tool (8). To this end, multiple research groups have tried to identify genetic variants that may predispose individuals to this outcome. Thus far, several variants in human leukocyte antigen genes, which play a key role in immune function, have been associated with CIAG (9). While promising, these initial results require additional investigation and replication.

In this issue of *Biological Psychiatry*, Saito *et al.* (10) advance our understanding of the pharmacogenomics of CIAG. They compared a group of Japanese individuals with schizophrenia who developed CIAG with a control group of Japanese individuals who were exposed to clozapine but did not develop CIAG. With the use of an iterative series of increasingly specific genetic scans to identify variants that distinguished the two groups, they found that the presence of the genetic variant HLA-B*59:01 was associated with a tenfold increased risk of CIAG.

One might be tempted to conclude that patients of Japanese descent with schizophrenia should be routinely screened for the HLA-B*59:01 variant before being prescribed clozapine, but as the researchers warn, their results must be interpreted with caution. The HLA-B*59:01 is rare in Japanese populations and almost nonexistent in non-Asian populations. Therefore, presence of this variant could not account for the full risk of developing CIAG; such a test would have low sensitivity. Saito *et al.* (10) recognized this shortcoming and looked for other situations in which this genetic test might be more informative. They applied the observation that HLA-B*59:01 confers a much greater risk of CIA (the more severe form of CIAG) than CIG (the milder form) to formulate a new question: For patients who have already developed CIG on an initial clozapine trial, does a negative HLA-B*59:01 genotype make it less likely that they will progress from CIG to CIA on clozapine re-challenge? Their results suggest that Japanese patients would, in fact, have a reduced risk of progressing from CIG to CIA on clozapine re-challenge if they did not carry the HLA-B*59:01 genetic risk variant.

Where does this leave us for other patients of non-Asian descent who are at risk of developing CIAG? In a previous study that also attempted to identify genetic variants associated with CIAG, Goldstein *et al.* (9) identified two different genetic variants in human leukocyte antigen genes that were linked with CIAG in cohorts of European descent. Similar to Saito *et al.* (10), they concluded that their genotype markers were not sensitive enough to completely rule out CIAG risk on re-challenge; however, they did not evaluate the utility of these genetic markers to assess risk of conversion from CIA to CIG. These subtle, yet crucial, differences in results between these two studies highlight some of the complexities and challenges of translating pharmacogenomic research into clinical practice; namely, the

importance of considering ethnic and population-level genetic differences in psychiatric pharmacogenomics.

The study by Saito *et al.* (10) is representative of the dynamic, rapidly evolving nature of pharmacogenomics and illustrates its dramatic potential to transform clinical care in psychiatry, as is already occurring in other medical fields. It will be exciting to follow future studies that link genetic changes and psychopharmacologic drug response in the coming years. Those studies will also need to account for other important factors in drug response (such as environmental exposures and drug adherence) and to include larger sample sizes. Until then, psychotropic medication prescribing remains a careful art of trial and error.

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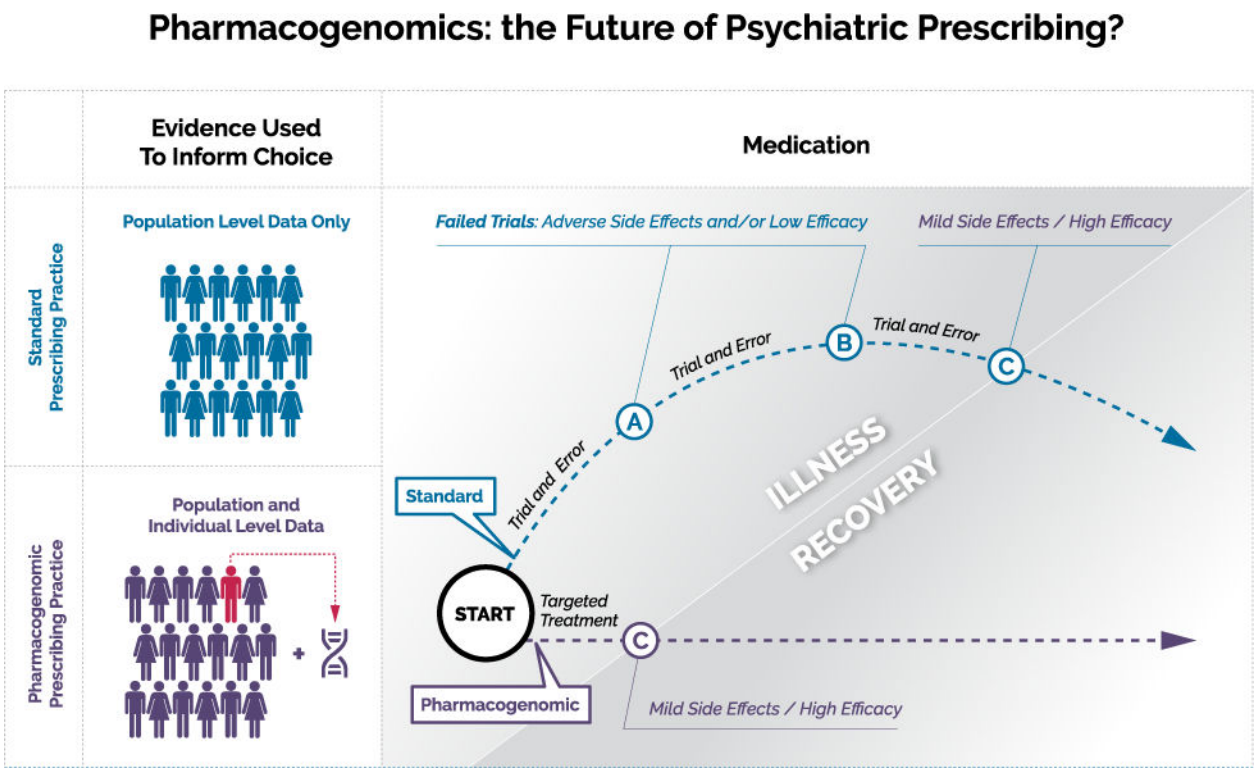

Figure 1.

Shown is a schematic representation of the current standard-of-care approach for prescribing psychotropic medications vs. an imagined future of prescribing using pharmacogenomics.