I started promoting pharmacogenetic tests in the 1990s—before they were fashionable—and now, after going through the 3 phases of pharmacogenetic testing (fear, failure, and hype), I am embarrassed.

Early in the 1990s, a couple of pharmacologists opened my eyes to cytochrome P450 (CYP), which is involved in clozapine metabolism. Then a patient taught me that a CYP-mediated drug-drug interaction between caffeine and clozapine was important. Thus, after 20 years of studying pharmacology and treating many complex patients, I reached the conclusion that drug-drug interactions are frequently important and that pharmacogenetic tests are occasionally indicated in psychiatry.

In the early 2000s (the fear phase), pharmaceutical companies were scared of pharmacogenetic tests. In the later 2000s (the failure phase), I figured out that I was not going to become famous, since the early pharmacogenetic tests failed. In the current hype phase, I am embarrassed that nonvalidated pharmacogenetic tests are aggressively promoted by some companies.

The onset of the year of embarrassment
In January 2015, I was scheduled to lecture my department residents on psychopharmacology when one of them asked my opinion about a pharmacogenetic test that tells which drugs are good or bad for each patient. Another senior psychiatry resident had started ordering the test and was encouraging other residents to do so. My pharmacological arguments about the limitations of that test did not impress the resident. Who can blame him?

A company gave him a free test (saving him at least $2000) that told him in simple terms which psychiatric medication to use in each patient. Yet a professor lectured him about the need to study pharmacology and told him the following regarding selection of psychiatric drugs:

1 Using science to select the right drug for a patient is beyond our current scientific knowledge;
2 Once you choose a drug, selecting the right dosage may be relatively easy for some drugs; however,
3 Drug dosing is influenced not only by genetics, but also by environmental and personal factors.

The year of embarrassment continues
This experience of failure to convince my psychiatry residents of the appropriate use of pharmacogenetics tests led me to design a PowerPoint presentation to teach residents which pharmacogenetic tests are indicated and the complexity involved in interpreting them. Pharmacogenetic tests in the clinical environment should be limited to:
Nonvalidated Pharmacogenetic Tests, Part I: Confessions of an Embarrassed Psychiatry Professor

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1. HLA-B*15:02 testing before starting carbamazepine in patients with Asian ancestry
2. CYP2D6 and/or CYP2C19 genotyping under the following conditions: always before prescribing tricyclic antidepressants, preferably combined with blood levels; and occasionally when seeing lack of effectiveness or adverse drug reactions with SSRIs, venlafaxine, pimozide, atypical antipsychotics dependent on CYP2D6 for their metabolism (aripiprazole, brexpiprazole, iloperidone, and risperidone)

On the other hand, genetic testing is not needed for CYP1A2, CYP2B6, CYP3A4, or CYP3A; brain neurotransmitters and/or transporter genes; and diagnosis of schizophrenia, depression, or bipolar disorder.

The embarrassed professor learns a few things

The PowerPoint presentation became useful when I was invited to speak on the same topic to confused clinicians in Spain and Italy. During the presentation, I attempted to explain to psychiatrists, who had no clue about CYP pharmacology, the various CYP alleles and the terminology differences among phenotypes: poor, intermediate, and ultrarapid metabolizers. Unfortunately, this does not explain that there is no need to test for normal alleles—the only tests required are for CYP abnormal variants. Unless an abnormal allele is found, the allele is normal by default.

If a lab tests 15 CYP2D6 alleles (although few test for so many), findings will show many patients with abnormal alleles and fewer with normal alleles; the 3 metabolizer phenotypes will also be identified. If a poorly equipped lab tests only 5 alleles associated with lack of activity, this lab will find only a few poor metabolizers and consider the remaining normal or almost normal. This can be confusing for psychiatrists. During the question period, one of the top Spanish researchers suggested to me that it may better to order the test and have the company tell you what medication to use than to try to learn how to interpret CYP testing. Instead of being cool-headed, this professor responded that his children frequently accuse him of being demented, and maybe the researcher was getting demented too and could not learn to interpret CYP testing.

The end of 2015 brought further embarrassment. Some of the residents reported attending a dinner lecture supported by one of the pharmacogenetic companies because they receive no training in this area. Not having access to unbiased information about new products highlights the potential risk of receiving misinformation about these products by way of the company’s marketing messages. A pharmacogenetics expert told me that each test costs “only” $2000 (one article quotes a higher price of $3800). Nevertheless, whether it is $2000 or $3800, one test ordered by a resident is sufficient to pay for dinner for all my program residents at the best restaurant in town.

In the spring of 2016, I again started lecturing residents on psychopharmacology. My embarrassment over the continued failure to convince my psychiatry residents of the appropriate use of pharmacogenetics tests led me to the foolish idea of using, as my first lecture, the one titled “Pharmacogenetic Testing in Psychiatry.” I had to start with the confession that my wife thinks I am incompetent in marketing. I then acknowledged that this was a complex issue, mainly interesting to experts in CYP testing but relevant for patient care. I also conceded that hearing this lecture at 4 pm after a full day of lectures couldn’t possibly beat an enticing sales pitch (“You do not need to worry about psychiatric drug selection! Our test gives you all the answers!”) during dinner at a nice restaurant.

Analytic validity, clinical validity, and clinical utility

Analytic and clinical validity as well as clinical utility are required to market a genetic test. Analytic validity addresses accurate and reliable measurement of the gene variations; clinical validity, the ability to detect or predict the associated disorder—in this case, that genetic variations predict drug response in the clinical environment; and clinical utility, the risks and benefits of the test in clinical practice. The FDA has tried to control pharmacogenetic testing by limiting the promotion of genetic tests to the general population. It has not had success in limiting the genetic tests offered to clinicians. US clinical laboratories are regulated not by the FDA but by the Clinical Laboratory Improvement Amendments (CLIA). Following CLIA, accreditation by the College of American Pathologists, the Joint Commission on Accreditation of Healthcare Organizations, or state health departments allows any laboratory to legally offer pharmacogenetic testing in the US. Unfortunately, CLIA regulations only deal with very basic aspects of analytic validity.

Any US clinical lab can offer CYP genotyping without the need to demonstrate clinical validity or clinical utility, and the FDA cannot do anything about it. Some US managed care companies pay in some cases for CYP testing. This professor cannot understand why Medicare has approved payment for one of these tests in psychiatry, even though the test has problems with analytic validity and
shows no demonstrated clinical validity or clinical utility. In my view, Medicare should not get involved in approving complex pharmacogenetic tests that should be regulated by the FDA.

**Conclusion**

This professor of psychiatry believes that personalized prescription in psychiatry is a complex pharmacological puzzle that:

1. Can focus on drug dosing or drug selection
2. Requires combining genetic, environmental, and personal variables
3. Necessitates understanding pharmacokinetic and pharmacodynamic mechanisms to predict efficacy and safety

Furthermore, as each patient is a unique individual with different drug responses governed by pharmacological laws, each drug may also be a different individual governed by its specific pharmacological mechanisms. The most frequent cause of being a poor metabolizer is not a genetic variant but rather taking an inhibitor, such as an antidepressant; and the most frequent cause of being an ultrarapid metabolizer is not a genetic variant but taking an inducer, such as an antiepileptic. Genetic testing does not tell you about these very frequent and clinically relevant drug-drug interactions. However, as stated above, it can help in a few psychiatric patients.

As there is no way that this set of conclusions is going to satisfy you and you may prefer to order a pharmacogenetic test that provides an easy answer (eg, a red, yellow, or green signal for each drug), you will need to read the sequel to this piece—about the consequences of ordering pharmacogenetic tests. Look for it in the next issue of *Psychiatric Times*.

**Disclosures:**

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**References:**


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