

# Pharmacogenomics testing: What the FDA says

Vicki L. Ellingrod, PharmD, FCCP

**M**r. R, age 30, is referred to you by his primary care physician, who diagnosed him with depression approximately 2 years ago. When he was first diagnosed, Mr. R was prescribed sertraline, 100 mg/d, which was effective. He maintained this response for approximately 1 year, but then the sertraline stopped working. During the last year, Mr. R received citalopram, 20 mg/d, and paroxetine, 20 mg/d. Neither medication was effective for his recurrent depressive symptoms and resulted in significant adverse effects.

Mr. R says that based on his primary care physician's recommendation, he had undergone pharmacogenomics testing to help guide therapy. He presents the results to you, and you notice that he has the cytochrome P450 (CYP) 2C19 \*2/\*3 genotype and a CYP2D6\*4/\*5 genotype. Both are associated with a poor metabolism phenotype. Should you use these findings to determine which medication Mr. R should be treated with next?

While the field of pharmacogenomics is not new, within the last few years this science has begun to transition into clinical practice. A recent meta-analysis found support for using pharmacogenomics testing

Dr. Ellingrod is Associate Dean for Research and John Gideon Searle Professor of Clinical and Translational Pharmacy, College of Pharmacy; Professor of Psychiatry and Adjunct Professor of Psychology; Associate Director, Michigan Institute for Clinical and Health Research; and Director of the Education and Mentoring Group, University of Michigan, Ann Arbor, Michigan. She is the Savvy Psychopharmacology Department Editor of the CURRENT PSYCHIATRY Editorial Board.

#### Disclosure

The author reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

results in clinical practice.<sup>1</sup> This study included more than 1,700 patients who took part in 5 controlled trials that randomized participants to either pharmacogenetics-guided or unguided (ie, standard) treatment. Each participant was assessed using the Hamilton Depression Rating Scale-17 (HDRS-17) a minimum of 3 times over a minimum of 8 weeks.<sup>1</sup> While the exact inclusion and exclusion criteria for each trial differed, they all defined remission of depression as achieving an HDRS-17 score  $\leq 7$ . Overall, the authors concluded that

#### Practice Points

- Although the field of psychiatry has gained more experience with implementing pharmacogenomics testing in practice, **confusion still exists regarding how to best use this information.**
- According to the FDA, **any claims made by testing companies regarding the specific effect of a medication may not be supported by evidence.**
- The FDA recommends that **treatment decisions should be based on the pharmacogenomics information provided in the FDA-approved drug labeling.**
- **The Pharmacogenomics Knowledge Base** is a valuable resource for understanding the pharmacogenomics information for specific medications, including information from the FDA-approved drug labeling for those agents.
- **Guidelines from the Pharmacogenomics Implementation Consortium** can also be used to guide treatment.



Vicki L. Ellingrod,  
PharmD, FCCP  
Department Editor

Savvy Psychopharmacology is produced in partnership with the College of Psychiatric and Neurologic Pharmacists


  
 cnpn.org  
 mh.cpnnp.org (journal)

### Clinical Point

**Direct-to-consumer pharmacogenomics tests are FDA-reviewed only if being used for moderate- to high-risk medical purposes**

based on the random-effects pooled risk ratio, there was a significant association between pharmacogenetics-guided prescribing and remission (relative risk = 1.71, 95% confidence interval [CI], 1.17 to 2.48;  $P = .005$ ). The results of this meta-analysis are controversial, however, because all 5 studies were industry-funded, and interpretation of the testing results was based on proprietary algorithms.

Experts in the field and professional societies, such as the International Society of Psychiatric Genetics (ISPG), have issued policy statements on genetic testing within psychiatry.<sup>2,3</sup> While the ISPG did not necessarily endorse use of pharmacogenomics in practice, they recommended that clinicians follow good medical practice and stay current on changes to drug labeling and adverse event reports.<sup>3</sup> The ISPG also noted that useful but not exhaustive lists of pharmacogenetic tests are maintained by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the US FDA.<sup>3</sup>

### Laboratory developed vs direct-to-consumer tests

In a previous Savvy Psychopharmacology article,<sup>4</sup> we had discussed the role of CPIC, but not the role of the FDA. This issue is key because there is a lack of clarity regarding pharmacogenomics tests and whether they are considered Class II devices by the FDA, which would require their review and approval. Until recently, the FDA was fairly quiet regarding pharmacogenomics tests because most of these tests were considered laboratory developed tests, which were regulated under the Clinic Laboratory Improvements Amendments program. The critical distinction of a laboratory developed test is that it is developed and performed in a single laboratory and is offered to patients only when prescribed by a clinician. Due to this distinction, laboratory developed pharmacogenomics tests did not need FDA 510(k) clearance, which is a premarket submission common for medical devices.

Direct-to-consumer pharmacogenomics tests are different in that the FDA has classified these platforms as medical devices; however, they are reviewed by the FDA only if they are being used for moderate- to high-risk medical purposes, or if the results of the testing may have a higher impact on medical care. As part of its review, the FDA examines test accuracy and reliably measures to determine if the measurement is predictive of a certain state of health and supported by what the company claims about the test and how well it works. Additionally, the FDA examines the company-provided descriptive information to ensure that consumers can easily understand it without the help of a clinician.<sup>5</sup>

### Conflicting FDA statements

Recently the FDA issued 2 statements—one a policy statement and the other a safety communication—about laboratory developed tests and direct-to-consumer tests. The statements appear to contradict themselves, despite focusing on using pharmacogenomics testing in practice.

**The FDA's first statement.** On October 31, 2018, the FDA released a policy statement that they had “permitted marketing, with special controls,” of the Personal Genome Service Pharmacogenetic Reports test through 23andMe (a direct-to-consumer genetic testing company) for 33 different variants within specific pharmacogenomic genes (CYP2C19, CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLC01B1, and CYP2D6) that may impact drug metabolism or response.<sup>6</sup> As part of its review of this Personal Genome Service Pharmacogenetic Reports test, the FDA found that the company-provided data showed that the test is accurate and can correctly identify the 33 specific genetic variants. The FDA review also showed that the testing results were reproducible, and the test instructions and reports could be understood by consumers.

While the specific reports related to this testing are not yet available within



Discuss this article at  
[www.facebook.com/MDedgePsychiatry](http://www.facebook.com/MDedgePsychiatry)



Table

## FDA-approved drug labeling and PharmGKB information for select antidepressants

| Medication  | Pharmacogenomics variants involved in metabolism | FDA-approved drug labeling  | PharmGKB information   |
|-------------|--|---|--|
| Bupropion   | CYP2B6 (major)                                   | Although CYP2B6 is thought to be the primary metabolic pathway for bupropion, no information is included in FDA-approved drug labeling to guide dosage changes  | Bupropion pathway, pharmacokinetics<br><a href="https://www.pharmgkb.org/pathway/PA166170276">https://www.pharmgkb.org/pathway/PA166170276</a>   |
| Citalopram  | CYP2C19 (major) and CYP2D6 (minor)               | In CYP2C19 poor metabolizers, citalopram steady state concentrations increase; therefore, 20 mg/d is the maximum recommended dose for CYP2C19 poor metabolizers due to the risk of QT prolongation. Because CYP2D6 is a minor metabolism pathway, citalopram steady state levels are not significantly different in poor metabolizers and extensive metabolizers of CYP2D6. No dosage changes based on this CYP2D6 metabolizer status are recommended | Citalopram pathway, pharmacokinetics<br><a href="https://www.pharmgkb.org/pathway/PA164713429">https://www.pharmgkb.org/pathway/PA164713429</a>  |
| Paroxetine  | CYP2D6 (major), CYP3A4 and CYP1A2 (minor)        | Paroxetine is primarily metabolized by CYP2D6 and also inhibits this enzyme; however, no dosage recommendations are included based on pharmacogenomics  | Paroxetine pathway, pharmacokinetics<br><a href="https://www.pharmgkb.org/pathway/PA166121347">https://www.pharmgkb.org/pathway/PA166121347</a>  |
| Sertraline  | CYP2C19 (major) and CYP2D6 (minor)               | No information is included in FDA-approved drug labeling regarding dosing changes based on CYP2C19 or CYP2D6 metabolizer status   | Sertraline pathway, pharmacokinetics<br><a href="https://www.pharmgkb.org/pathway/PA166181117">https://www.pharmgkb.org/pathway/PA166181117</a>  |
| Venlafaxine | CYP2D6   | Because both venlafaxine and the metabolite (formed by CYP2D6 metabolism) are active, the total amount of active drug does not change based on CYP2D6 metabolizer status or drug interactions   | Venlafaxine pathway, pharmacokinetics<br><a href="https://www.pharmgkb.org/pathway/PA166014758">https://www.pharmgkb.org/pathway/PA166014758</a> |

CYP: cytochrome P450; PharmGKB: Pharmacogenomics Knowledgebase  
**Source:** Reference 11

### Clinical Point

**Tell patients that they should not stop taking any medication based on pharmacogenomics testing results**

23andMe, this approval allows for greater oversight by the FDA with regard to the pharmacogenomics information provided through this company's Personal Genome Service Pharmacogenetic Reports test. The FDA noted that this approval was only for adults age >18<sup>5</sup> and that consumers "should not use the test results to stop or change any medication."<sup>6</sup> Further, the FDA stated that the results of the direct-to-consumer

test should be confirmed with independent pharmacogenomics testing before making any medical decision. Unfortunately, the FDA did not offer guidance on what would be an appropriate independent pharmacogenomics test, but it did provide a link to a list of FDA-approved nucleic acid-based tests, on which 23andMe's Personal Genome Service Pharmacogenetic Reports test is included.<sup>7</sup>

continued

### Clinical Point

**Consult the FDA-approved drug label for information about how genetic information should be used in making treatment decisions**

**The FDA's second statement.** On November 1, 2018, the FDA issued a separate safety communication that cautioned clinicians and patients that most of the current commercially available testing platforms for pharmacogenomics have not been FDA-reviewed, meaning that they may lack clinical evidence supporting their use.<sup>8</sup> Further, the FDA safety communication stated, "Changing drug treatment based on the results from such a genetic test could lead to inappropriate treatment decisions and potentially serious health consequences for the patient."<sup>8</sup>

Taken together, these FDA statements appear to support pharmacogenomics testing with approval of the 23andMe's Personal Genome Service Pharmacogenetic Reports test but warn that the testing results should not be used to make treatment decisions, and that they should be verified. However, the FDA does not offer any guidance on what an appropriate testing platform would be to confirm the results.

### What the FDA advises

The FDA has provided some guidance to clinicians and patients regarding next steps for patients who are interested in having pharmacogenomics testing or who have already undergone testing. The FDA's first point is that both clinicians and patients need to be aware that pharmacogenomics testing is not FDA-reviewed, that patients should discuss the results of their testing with their clinicians, and that they should not stop their medication based on the results of the testing. Additionally, the FDA recommends that clinicians and patients should be aware that any claims made by the testing companies regarding the specific effect of a medication may not be supported by evidence. Furthermore, the FDA strongly recommends that clinicians consult the FDA-approved drug label, or the label of the FDA-cleared or FDA-approved genetic test, for information regarding how genetic information should be used in making treatment decisions. The FDA recommends reviewing the

Warning section, as well as the Indications and Usage, Dosage and Administration, or Use in Specific Populations sections of the FDA-approved drug labeling.

Unfortunately, this information might be difficult to locate due to the lack of consistency regarding where it is placed in the FDA-approved drug labeling. The Pharmacogenomics Knowledgebase (<https://www.pharmgkb.org/>) can help clinicians quickly identify information regarding medications, their metabolic pathways, CPIC dosing guidelines, and the FDA-approved drug labeling information.<sup>9</sup> By searching for specific medications within the Pharmacogenomic Knowledge Base, information regarding the FDA-approved drug labeling can be easily found, which is important because currently >120 medications contain pharmacogenomics information in their FDA-approved drug labeling.<sup>10</sup>

### CASE CONTINUED

Overall Mr. R's pharmacogenomics testing results indicate that he has 2 genotypes that are associated with poor metabolism phenotypes and could result in reduced metabolism of medications that are metabolized by these CYP enzymes, leading to higher blood levels and an increased risk of adverse effects. The **Table<sup>11</sup> (page 31)** lists pharmacogenomics information from the FDA-approved drug labeling and from the Pharmacogenomics Knowledgebase for both the medications Mr. R has previously been prescribed and for several potential medications to consider.

It would be prudent to first discuss with Mr. R the FDA's recent policy statement and safety communication. While you could recommend that he pursue additional pharmacogenomics testing, it is unclear which specific laboratory is available to conduct this confirmatory analysis.

Because Mr. R has had unsuccessful trials of several medications that primarily fall in the selective serotonin reuptake inhibitors class, it might be time to consider a medication from a different class. A quick review of the FDA-approved drug labeling

continued on page 42

Savvy Psychopharmacology  
continued from page 32

for bupropion indicates that its metabolism is not dependent on CYP2D6 or CYP2C19, which might make this drug a good choice. Furthermore, the metabolism of venlafaxine does not appear to be influenced by CYP2D6 poor metabolism, which might also make it a good choice for Mr. R.

#### References

1. Bousman CA, Arandjelovic K, Mancuso SG, et al. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. *Pharmacogenomics*. 2019;20(1):37-47.
2. Zubenko GS, Sommer BR, Cohen BM. Pharmacogenetics in psychiatry: a companion, rather than competitor, to protocol-based care-reply. *JAMA Psychiatry*. 2018;75(10):1090-1091.
3. International Society for Psychiatric Genetics. Genetic testing statement: genetic testing and psychiatric disorders: a statement from the International Society of Psychiatric Genetics. <https://ispg.net/genetic-testing-statement/>. Revised January 26, 2017. Accessed January 1, 2019.
4. Ellingrod VL, Ward KM. Using pharmacogenetics guidelines when prescribing: what's available. *Current Psychiatry*. 2018;17(1):43-46.
5. U.S. Food and Drug Administration. Medical devices: direct-to-consumer tests. <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm624726.htm>. Published November 1, 2018. Accessed January 1, 2019.
6. U.S. Food and Drug Administration. FDA news releases: FDA authorizes first direct-to consumer test for detecting variants that may be associated with medication metabolism. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624753.htm>. Published October 31, 2018. Accessed January 1, 2019.

## Related Resources

- Gammal RS, Gardner KN, Burghardt KJ. Where to find guidance on using pharmacogenomics in psychiatric practice. *Current Psychiatry*. 2016;15(9):93-94.
- Clinical Pharmacogenomics Implementation Consortium. What is CPIC? <https://www.pharmgkb.org/page/cpic>.

#### Drug Brand Names

|                                  |   |
|----------------------------------|---|
| Bupropion • Wellbutrin,<br>Zyban | Paroxetine • Paxil<br>Sertraline • Zoloft |
| Citalopram • Celexa              | Venlafaxine • Effexor                     |

7. U.S. Food and Drug Administration. Medical devices: nucleic acid based tests. <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm>. Published February 5, 2019. Accessed March 1, 2019.
8. U.S. Food and Drug Administration. Medical devices. The FDA warns against the use of many genetic tests with unapproved claims to predict patient response to specific medications: FDA Safety Communications. <https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm>. Published November 1, 2018. Accessed January 1, 2019.
9. Whirl-Carrillo EM, McDonagh JM, Hebert L, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2012;92(4):414-417.
10. U.S. Food and Drug Administration. Drugs. Table of pharmacogenomic biomarkers in drug labeling. <https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm>. Published August 3, 2018. Accessed January 1, 2019.
11. U.S. Food and Drug Administration. Drugs@FDA: FDA approved drug products. <https://www.accessdata.fda.gov/scripts/cder/daf>. Accessed March 4, 2019.