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Is pharmacogenomic testing ready for prime time?

Loren Bonner

Pharmacogenomic testing has become more popular with each passing year. In late October 2018, the consumer genetics testing company 23andMe announced that it gained FDA approval for a first-of-its-kind, direct-to-consumer pharmacogenomics test that can bypass a health care practitioner completely.

“We’ve seen 23andMe’s classic ancestry kit stocked on pharmacy shelves alongside diabetic testing supplies and other direct-to-consumer products that the pharmacist is an expert on. We can assume this new test will be right there,” said Elvin Price, PharmD, PhD, FAHA, an associate professor in the department of pharmacotherapy and outcomes science at Virginia Commonwealth University in Richmond.

While 23andMe has yet to say when the test will be available to the public and for how much, pharmacists across the board see it having a major influence on the popularity of pharmacogenomics going forward.

Albertsons Companies, like many pharmacies, saw the rise in pharmacogenomic testing coming. Last year, it partnered with a genetic testing company to bring pharmacogenomic testing to patients who have struggled to find the right medications for depression and other mental illnesses.

“We wanted to see how we could proactively get involved with pharmacogenomic testing and make our pharmacists feel comfortable enough to answer basic questions that patients have,” said Kimberly Hecht, PharmD, who spearheaded the new service at Albertsons Companies.

Albertsons Companies is currently piloting the testing at two Sav-On pharmacies at Acmes in the Philadelphia area, as well as several Sav-On pharmacies in Boise, ID, and Jewel-Osco pharmacies in the Chicago area.

Melissa Frontino, PharmD, BCACP, from Acme Sav-On pharmacy in the Philadelphia area, discusses the benefits of pharmacogenomic testing with a patient, including what genes will be tested and what can be determined from the results based on the patient’s medications.

Pain and Psychiatric gene/drugs with CPIC guidelines					
Gene	**Drug**	**CPIC level**	**PharmGKB level of evidence**	**PGx on FDA label**	**CPIC publications (PMID)**
CYP2C19	Citalopram	A	1A	Actionable PGx	25974703
CYP2C19	Escitalopram	A	1A	Actionable PGx	25974703
CYP2C19	Sertraline	B	1A		25974703
CYP2D6	Fluvoxamine	A	1A	Actionable PGx	25974703
CYP2D6	Paroxetine	A	1A	Informative PGx	25974703
CYP2D6	Codeine	A	1A	Actionable PGx	22205192; 24458010
CYP2C19	Amitriptyline	A	1A		23486447; 27997040
CYP2C19	Clomipramine	B	2A		23486447; 27997040
CYP2C19	Doxepin	B	3	Actionable PGx	23486447; 27997040
CYP2C19	Imipramine	B	2A		23486447; 27997040
CYP2C19	Trimipramine	B	2A		23486447; 27997040
CYP2D6	Amitriptyline	A	1A	Actionable PGx	23486447; 27997040
CYP2D6	Nortriptyline	A	1A	Actionable PGx	23486447; 27997040
CYP2D6	Clomipramine	B	1A	Actionable PGx	23486447; 27997040
CYP2D6	Desipramine	B	1A	Actionable PGx	23486447; 27997040
CYP2D6	Doxepin	B	1A	Actionable PGx	23486447; 27997040
CYP2D6	Imipramine	B	1A	Actionable PGx	23486447; 27997040
CYP2D6	Trimipramine	B	1A	Actionable PGx	23486447; 27997040
CYP2D6	Tramadol	A	1B	Actionable PGx	22205192; 24458010
CYP2D6	Atomoxetine	B	2A	Actionable PGx	In review

Note: The full list includes many more for psychiatric medications that, as of now, do not have CPIC guidelines.

“Whether community pharmacists want to be involved with [pharmacogenomic testing] or not, eventually we are going to have patients bringing pharmacogenomics results into our pharmacies and asking the pharmacist about them because they see us as the medication experts,” said Hecht.

Is that antidepressant the right one?

Mental health has become a popular area for pharmacogenomic testing, and several genetic testing companies have sprung up to offer it to patients.

According to the Clinical Pharmacogenetics Implementation Consortium (CPIC), which issues guidelines and gene-based prescribing recommendations based on a standard system for grading levels of evidence, strong evidence currently exists for *CYP2D6* and *CYP2C19* genotyping for SSRIs and tricyclic antidepressants. CYP2D6 and/or CYP2C19 are responsible for the metabolism of many commonly prescribed medications—not only antidepressants but also some antipsychotics, analgesics and antitussives, beta adrenergic blocking agents, antiarrythmics, and antiemetics.

However, when genes like *CYP2D6* and *CYP2C19* have multiple isoforms, genetic testing companies do not have to consult each other about which allele, or different variations of the gene, they put on their test. This has created an environment where patients can receive different results if they have testing done through different companies.

Frontino and Linh Huynh, PharmD, a PGY-1 community-based pharmacy resident, are looking at a drug that has guidelines for pharmacogenomic testing. They discuss how the patient's gene profile can affect therapy.

CPIC levels for evidence		
Levels A & B	**Level C**	**Level D**
Prescribing action recommended; alternative therapies or dosing are highly likely to be effective and safe.	No prescribing action recommended; alternatives are unclear, but testing is common.	No prescribing action recommended; alternatives are unclear or evidence is weak; testing is rare or nonexistent.
Pharmacists can go to **www.PharmGKB.org** , enter any gene or drug in the search engine, and get information on what is currently known about any gene and/or drug association.		

Source: https://cpicpgx.org/.

Note: CPIC assigns CPIC levels to genes/drugs with

1) PharmGKB Clinical Annotation Levels of Evidence of 1A, 1B, 2A and 2B, or

2) PharmGKB PGx level for FDA-approved drug labels of "Actionable PGx", "Genetic Testing Recommended", or "Genetic Testing Required," or

3) Based on nomination to CPIC for consideration.

With *CYP2D6,* for example, there are more than 100 known variants, but a certain company may only test for 10 of those. If an individual does not have any of those 10, they will be considered a normal metabolizer.

"That's a caveat with the tests—just because a test like *CYP2D6* comes back normal isn't a guarantee you actually have normal *CYP2D6* metabolism. You may have a genetic variant that causes altered metabolism and is relevant for your medications but wasn't included in the test," said Roseann Gammal, PharmD, BCPS, assistant professor of pharmacy practice at MCPHS University in Boston.

As a generally accepted practice, most companies test for the most common alleles, since it's expensive to test for all of them.

"It's important to know that companies may market a variety of pharmacogenomic tests, but just because a pharmacogenomic test is available to be ordered clinically doesn't mean it has clinical utility at this time," said Gammal. "Patients may be coming to the pharmacy with these test results in hand, and pharmacists need to recognize which test results can be used to guide therapy decisions and which ones can't at this time due to insufficient evidence. Resources like CPIC guidelines are available to help pharmacists make this important distinction."

CPIC guidelines help practitioners interpret genotypes and come up with appropriate prescribing decisions (see tables). CPIC has its strongest level of evidence assigned to about 90 drugs on the market.

Likely because of the uptick in companies that offer genetic tests for antidepressant prescribing, FDA seems to be taking an interest and has signaled that it would like labs to be transparent and to reference clinical guidelines, such as those by CPIC.

Pharmacogenomics in community pharmacy

Melissa Frontino, PharmD, BCACP, who offers pharmacogenomic testing through the Albertsons Companies pilot at an Acme Sav-On pharmacy just outside of Philadelphia in Flourtown, PA, said there are two categories of patients she sees most often with the new service, and for whom she would also recommend the test.

The first are patients who are having issues managing their depression. "Maybe they have tried many antidepressants and are failing them or having side effects," she said.

However, the patient population that has quickly become very common at both pilot locations in Philadelphia, as well as in other pharmacies that offer this type of testing, is kids and adolescents who struggle with ADHD medications.

"We have had success with the parents who are frustrated," said Frontino. "They come in and have tried so much. This is something we can recommend to them to help."

Frontino said most of the time it's the pharmacist who talks to the patient about the test and then gets a prescription from their physician to order it. Physicians also order the test directly, but Frontino said it's been

challenging getting physicians she works with on board—perhaps because they are less comfortable with requests coming from a pharmacist than would be the case in states where scope of practice laws are more progressive. Testing can also be costly.

“I think physicians are more skeptical because it’s expensive, which is good to keep in mind, but they are not realizing that it’s also very expensive to keep changing drugs,” said Frontino.

“I’m never convincing a patient about the test—it’s something they want because they are at a point where they are frustrated with their medications,” said Frontino.

Once Frontino or another pharmacist she works with have a patient’s prescription for the pharmacogenomic test, they can immediately perform the test with a simple cheek swab, done right in the pharmacy’s private consultation room, and send it back to the lab. Results from the genetic testing company come back fairly quickly, and an appointment with the patient and a specially trained pharmacist, like Frontino, is set up to go over the results.

In Albertsons Companies’ case, the genetic testing company bills the patient’s insurance (but not all insurance covers it), and the pharmacist is compensated from the testing company for the cognitive services they provide to the patient, but at no cost to the patient.

Evidence to back metabolism of pain medications

Determining appropriate pain management therapy for patients is another in-demand area for pharmacogenomics — but the evidence is still growing for most opioids, except for a few.

In pain management, there is substantial evidence supporting a relationship between the *CYP2D6* genotype with efficacy and safety of codeine and tramadol. On this basis, CPIC members have created a guideline that makes clinical recommendations for prescribing these two drugs. As a metabolizing enzyme, CYP2D6 controls how codeine and tramadol are metabolized into morphine and O-desmethyltramadol, respectively. Pharmacogenomic testing can determine if individuals are ultra-rapid metabolizers and at-risk of toxicity from normal doses, or poor metabolizers who may receive a limited therapeutic benefit from these drugs. The evidence is less strong for oxycodone or hydrocodone with CYP2D6 or other relevant drug metabolism enzymes.

“I think the limiting factor in pain is the fact that we don’t have recent large clinical trials that have used pharmacogenomic testing to personalize pain control or therapy for commonly used drugs like hydrocodone or oxycodone,” said Price. “We need those studies.”

Although randomized controlled trials are the gold standard, they can be challenging with pharmacogenomics because patients who will benefit are just a small percentage. These trials are also expensive and time-consuming.

“A minority of patients have a rare genetic variant that will make them respond differently,” said Gammal. “If you enroll a general cohort of patients and try to do a randomized controlled trial, you may not get enough patients in your group who have the variants that would benefit, so it’s hard to get those outcomes data. In certain cases, it may also be unethical to conduct these types of studies because we have other data that strongly links the gene to the drug, and therefore [we] may not want to randomize patients who we know have a genetic variant and subject them to standard dosing.”

The evidence is building, nonetheless, especially as it becomes more common for pharmacogenomics to be translated from research to the clinical setting.

Do your homework

“Pharmacists always have to remember that genetics is not the end-all-be-all of personalized medicine,” said Gammal. “You can’t just look at the guidelines and the information in isolation—it’s one piece of the puzzle and has to be considered with other clinical factors, like drug–drug interactions [and] the patient’s age, weight, and organ function.”

Frontino and her team check which other medications the patient may be on and also consider their lifestyle factors, such as smoking and caffeine intake, which can affect enzymes. They also consult several resources, including CPIC and other clinical guidelines, as well as FDA information in the package insert of some medications, which includes genetic information.

Pharmacists also need to know that genetic testing companies promote their products directly to pharmacies. It’s common for companies to give pharmacists a consulting fee when interpreting results for patients. However, some companies compensate pharmacists for referring patients for testing.

Price said he’s also seen company’s market heavily to long-term care facilities in states where consultant pharmacists are required by law.

He said it’s important to gauge companies on the basis of the accuracy of their claims. This means familiarizing oneself first with the CPIC guidelines as well as FDA-approved biomarkers.

“Then when they come sell a product, pharmacists can take their time, review the claims they are making, and see if they are overreaching the evidence that is out there,” Price said.

Loren Bonner, senior editor