

# Doctors, Depression, and DNA

## Can a genetic test help patients get on the right antidepressant?

By: Mary Charmicael



Psychiatrists call it the “trial and error factor”: when they set out to prescribe an antidepressant, they have no clinically proven way of knowing which one to choose. Any given antidepressant tends to help only about a third of patients; the other two-thirds end up doing the prescription shuffle, trying one drug, then another, then a third or fourth in hopes of finally hitting on a treatment that works.

In theory, pharmacogenetics—the subfield of personalized medicine that focuses on how people with different DNA variants respond to drugs—is supposed to solve this problem. The idea is to allow doctors to tailor their prescribing to their patients’ genes. But so far, despite all the research that has been done in the decade since the first draft of the Human Genome Project was released, the genetics of mental illness are still a maddeningly complex mystery.

What, then, to make of GeneSightRx, a new test that identifies variants in five genes and tells doctors which antidepressant to pick based on its results?

The test’s biggest advocate—Jim Burns, president and CEO of AssureRx, which makes it—says it is “ready for prime-time clinical use,” part of a “first wave” of long-awaited pharmacogenetic progress. The test has recently become standard of care or similar at the Mayo Clinic and Cincinnati Children’s Hospital Medical Center, the two institutions where it was developed, and it’s starting to garner enthusiasm in the press. But given how little is known about psychiatric genetics, how much trust can doctors and patients put in it? Phrased another way: if you’re planning to take an antidepressant, should you have this test first?

The scientific thinking behind GeneSightRx is actually pretty solid. Pharmacogenetics may be new to medical clinics, but it’s a mainstay of labs. At the Mayo, doctors have been laying the basic-research groundwork for how it could be used in both adults and children for three decades. Although they know fairly little about the genetics of mental illness, they know much more about genes that influence the way the body processes drugs. They’ve developed a particular expertise around a group of enzymes referred to as the “cytochrome P450 superfamily,” or CYP450 for short, which is involved in how the liver metabolizes many chemicals. If you have certain variants in the genes that make proteins in the CYP450 group, you may metabolize a drug more quickly (causing it to zoom through your system, with its effects soon wearing off) or slowly (causing it to hang around in your bloodstream, remaining effective for longer) than other people.

GeneSightRx reaps the benefits of that knowledge. Three of its five genes code for proteins involved in the CYP450 pathway. (The other two code for variants in the brain’s serotonin receptors and transporters, respectively.) “These genes are well described,” says Burns. He’s not kidding: you can read far more than you’re likely to need to know about them here, in a textbook by David Mrazek, a leader in psychiatric pharmacogenomics who—not coincidentally—is based at Mayo and was instrumental in developing GeneSightRx. Two other Mayo researchers recently published an extensive article explaining how CYP450 genotyping could be helpful in choosing antidepressants for children.

The value of GeneSightRx, however, isn’t really in the fact that it identifies CYP450 variants. In theory, your family doctor or psychiatrist could do that without GeneSightRx, by employing a firm that

does “à la carte” genetic testing. The problem is that your doctor would then have to comb through the scientific literature looking for references to how your particular variants affect the metabolism of different drugs, then evaluate several antidepressants (by searching the literature some more) and choose one for you accordingly.

Few family doctors have the time to do that, if they even know it’s an option. What GeneSightRx essentially does is take all that work out, running the genetic analysis and then sorting medications into color-coded categories based on the results: green for drugs that will be safe for a patient who metabolizes them in a particular manner, yellow for those that need to be used “with caution,” and red for those to avoid.

So far, 12,000 patients at Mayo and Cincinnati Children’s have been assessed with GeneSightRx and had their meds tailored to their metabolic tendencies. “At Children’s, almost every child that comes in there [with a psychiatric diagnosis] will get a pharmacogenetic profile,” says Burns.

One of those 12,000 patients, who asked to remain anonymous, says he took the test six months ago, and it allowed him to drastically cut the dose of antidepressant he was taking—without any side effects or diminishment in its benefits. He had tried Prozac and Zoloft in the past, but those hadn’t worked. So he had switched to Effexor, which “was working fairly well,” he says. “That having been said, I thought it would not hurt to take the test, just to see the results.” The test showed the patient was metabolizing drugs slowly—meaning that a lower dose would probably be OK, because his body wasn’t burning through the drug as fast as other people’s would. The doctor cut his dose from 300mg per day to 150, and “the new dose works just fine,” he says.

Patients like him are the first targets for GeneSightRx, people who “have definitive diagnoses and have gone through multiple drug trials,” says Burns. “They’re on their third, fourth, sometimes fifth trial, or they’ve experienced adverse drug reactions and have become noncompliant. That’s who we’re targeting in the beginning.” That rationale seems to fly with insurance companies, some of which are already reimbursing for the test.

Before GeneSightRx can be expanded to all patients who might find antidepressants useful, though, there will need to be more research on its effectiveness. Specifically what’s needed is a large, well-controlled clinical trial. “With these sorts of things, the question is, what’s the state of the evidence?” says Bruce Cohen, a leading psychiatrist at Harvard-affiliated McLean Hospital who also has a Ph.D. in molecular pharmacology. “No one’s ever proven that any of these [serotonergic antidepressant] drugs are more effective than any of the others, so that’s a cautionary point right there. And no one has published and had it replicated that any set of genetic tests can be used to determine who should go on what medication. If they have gotten very strong results from 12,000 people, that needs to be published in the peer-reviewed literature and replicated before you really want to trust it.” Cohen adds that there’s a simpler way to get at whether a patient is a fast or slow metabolizer: “Ask about side effects and measure the level of drug they have in their blood.”

Still, he says, the rationale for GeneSightRx “makes some sense. Would I run off and get the test? Not on the basis of anything I know, but I’d be willing to look at their data. And there’s very low risk in doing what they’re doing. Since [choosing an antidepressant] is based on trial and error at the moment, it’s hard to imagine that adding this test could make things worse.”

The Mayo and Cincinnati doctors may soon have a response to some of Cohen’s concerns. They are running a clinical trial at three different sites in the Midwest that will ultimately involve about 500 patients. They have also begun to publish thoughtful, peer-reviewed papers (Hall-Flavin, Schneekloth, Allen, 2010) considering the challenges of bringing genotyping into psychiatric clinics.

The test, too, is changing with the times. Next week, says Burns, the company hopes to add a sixth gene to the profile it can provide, and it is “on schedule to have gene 7, 8, 9, and 10 before the end of the year.” As more well-characterized genes are added to the test, it will become a more reliable guide for picking medications. For psychiatric pharmacogenetics, then, it’s still early days—but exciting ones.

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