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ON THE WEB

## A Special Drug Just for You, at the End of a Long Pipeline

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A new drug for acne, Aczone, was approved in July, but with a catch. The Food and Drug Administration said it would require that patients first be tested for an enzyme deficiency that could put them at risk of developing anemia from the drug.

The age of personalized medicine is on the way. Increasingly, experts say, therapies will be tailored for patients based on their genetic makeup or other medical measurements. That will allow people to obtain drugs that would work best for them and avoid serious side effects.

But the case of Aczone illustrates a barrier to this new era. Pharmaceutical companies fear that if testing for such genetic markers is required, that will discourage doctors from prescribing a drug or limit a drug's sales to a subset of patients.

Upon learning of the testing requirement for Aczone, Astellas, one of its developers, abandoned the drug.

The other developer, QLT, is planning another clinical trial in hopes of having the testing requirement lifted. It argues that in a previous clinical trial, only 1.4 percent of patients had the enzyme deficiency and none developed anemia.

Tailoring drugs to patients can introduce problems for doctors, as well as drug makers. Transfused blood is an example. Many transfusion centers would love to have a single type of blood suitable for everyone, rather than having to keep different types in stock and worrying that severe problems may occur if the wrong type is transfused.

Still, many physicians, regulators, market analysts and pharmaceutical executives agree that despite the obstacles, personalized medicine is inevitable.

About 40 of the 50 psychiatrists at the Mayo Clinic use genetic tests to help choose which drugs to prescribe, said Dr. David A. Mrazek, chairman of psychiatry at Mayo. And some companies are offering tests directly to consumers.

Mary Jane Q. Cross, an artist in Newport, N.H., developed a permanent tremor on the right side of her body after taking the antidepressant Prozac 14 years ago. She now paints with her fingers because she cannot hold a brush.

A year ago, she paid about \$600 to Genelex, a company in Seattle, for genetic tests that showed she would have trouble tolerating certain drugs, possibly including Prozac. "Had I known that 14 years ago, I would not have used the drug," Ms. Cross said.

Recently, when she had an emergency appendectomy, she advised the doctors to use a low dose of anesthesia based on her genetic test results. "My husband had to go home in the middle of the night to get the material, bring it back and make it clear to them that this was an important issue," she said.

Scientists are finding numerous examples of variations in genes that help predict who will respond to a drug or who will suffer side effects. Most drug companies now routinely collect DNA samples from patients in clinical trials to look for such markers.

In March, the F.D.A. issued guidelines to encourage drug companies to pursue personalized medicine, and

the agency is adding information about genetic tests to the labels of a few drugs.

Since June, the label for Camptosar, a Pfizer drug for colon cancer, has advised doctors that a lower starting dose may be appropriate for the 10 percent of people who have a particular version of a gene called UGT1A1. The variant makes them more prone to a side effect, serious decline in white blood cells.

But despite progress, many more years of work will be required before combinations of drugs and tests, sometimes called theranostics, could reach the market.

"I don't see any indication that there is a drug that will come to market in the next five years that will have a DNA-targeted market," said Dr. Gualberto Ruaño, president of Genomas, a company working on genetic tests for drug use.

For that to happen, Dr. Ruaño said, the drug and the genetic test would have to be tested together in a clinical trial. "What Phase 3 trial is ongoing now where they have selected the patients based on genetic markers?" he asked.

Choosing a drug based on a patient's genes is called pharmacogenetics or pharmacogenomics. But pharmacogenetics is just one part of personalized medicine.

In fact, all medicine is already personalized to some extent. Cancer patients are treated based on their body size; the type, size and extent of a tumor; and so on.

Genetic testing would add just one element to this. Some experts say genes, which provide the instructions for making proteins, may not be the best approach, because a gene, even if present, is not always active.

"Genetic markers per se will be less useful than things further downstream, like proteins in the blood," said Dr. Mark Fishman, head of drug discovery research at Novartis.

Asked for examples of pharmacogenetics, experts usually cite Herceptin, a breast cancer drug given to the 20 to 30 percent of patients whose tumors have abundant levels of a protein called Her2. That Herceptin was approved seven years ago and remains the best example attests to the difficulties in the field.

Another example is that doctors treating patients with H.I.V. or AIDS often test a patient's virus for mutations that induce resistance to particular drugs.

In both cases, however, it is the disease-causing agent that is being tested, not the patient's genes. Tumor genes are very different from normal genes. So the tests are really diagnostic rather than pharmacogenetic, not much different from characterizing a bacterial infection to prescribe the proper antibiotic.

The first widespread use of testing a patient's own genes is likely to be for variations in enzymes involved in metabolizing drugs, particularly those in a family called the Cytochrome P450 enzymes.

People with genetic variations that limit the effectiveness of a particular enzyme may not be able to break down a drug quickly enough, allowing dangerously high levels to build up. In June, The American Journal of Psychiatry published a letter from doctors in Fargo, N.D., about a patient who died after receiving a low dose of the antidepressant Paxil, apparently because of an inability to metabolize the drug.

Enzyme testing may allow people who metabolize a drug poorly to receive a lower dose to avoid side effects. In contrast, ultrafast metabolizers may need more than the usual dose for the drug to be effective.

In some cases, however, the opposite is true. Codeine provides pain relief because it is turned into morphine in the body through an enzyme called 2D6.

In December, The New England Journal of Medicine printed a report of a fast metabolizer who received a small dose of codeine as a cough suppressant and developed a life-threatening overdose of morphine. A slow

metabolizer, in contrast, would experience little pain relief because the codeine would not be effectively converted into morphine.

This year, the F.D.A. approved a test developed by Roche that uses a new type of DNA chip to detect variations in the 2D6 and 2C19 genes, which play a role in metabolism of about 25 percent of prescription drugs. Other clinical laboratories offer their own tests, which do not require F.D.A. approval.

Gwynne Wolin, a retired medical transcriber from Coconut Creek, Fla., said she had become sick from taking certain drugs like the heart drug Inderal. A few months ago, she paid \$550 to Genelex to test the genes of four drug-metabolizing enzymes. The results showed that she was a poor metabolizer in using the 2C19 enzyme and somewhat slower than normal for the 2D6 enzyme.

Mrs. Wolin said the findings gave her evidence to help her refuse certain drugs. "I've been labeled uncooperative a couple of times," she said, referring to her doctors' reactions. "But I've shown them my records, and they've accepted it."

Dr. Mrazek of the Mayo Clinic said he used the tests to help choose antidepressants, particularly for children. There has been concern that some children can turn suicidal or aggressive on antidepressants, and some evidence suggests this may be linked to high drug levels, he said.

Dr. Mrazek said Prozac and Paxil were metabolized by the 2D6 enzyme. About 10 percent of Caucasians have a variation in the enzyme that make them poor at eliminating the drugs from their bodies. For those patients, he said, he may prescribe Celexa or Lexapro, antidepressants metabolized primarily by another enzyme, 2C19.

So far, though, few psychiatrists, or any doctors, use these tests. The pharmacogenomics laboratory at the University of Louisville, one of the main clinical labs that offer metabolism tests, performed 3,500 to 5,000 in the last year, according to its director, Roland Valdes Jr.

Many doctors are unfamiliar with tests, Dr. Valdes said. Some say that their usefulness has not been proven and that it is not always clear how much to raise or lower a dose based on the test results.

Doctors' reluctance to change habits is another factor. One of the oldest examples of a pharmacogenetic test is for 6-mercaptopurine, or 6MP, a drug used to some forms of childhood leukemia and inflammatory bowel diseases.

About 1 Caucasian in 300 is a very slow metabolizers of 6MP, because he has two copies of a variant of a gene for a protein called TPMT. In these poor metabolizers, the drug can cause a severe, even fatal, decline in white blood cells.

But when the F.D.A. held a meeting in 2003 to consider requiring the test for patients prescribed 6MP, some doctors opposed the idea.

They argued that the test was not needed because they were already watching for side effects and reducing the drug's dose if necessary. Testing everyone, they argued, would be too costly, given the relatively low incidence of the gene variant. And, they said, requiring the test might scare doctors away from using a drug that could cure cancer.

The F.D.A. decided to put information about the test on the drug label, but not to require testing.

Health insurers are in some cases balking at paying for pharmacogenetic tests. It might seem that insurers would welcome tests that allowed side effects to be avoided or drugs to be used only in patients who would benefit from them. A test for a single enzyme like 2D6 costs \$100 to \$500.

But a person would need to have the test only once in a lifetime, and it would apply to all the drugs metabolized by that enzyme.

Yet Blue Cross Blue Shield concluded that the usefulness of the metabolism tests was not established. In particular, the insurer said, there have been no prospective studies, in which some patients are given the test and others are not to see whether those who are tested do better.

Such a genetic test would be useful for the blood thinner warfarin. Even a little bit too much warfarin can cause potentially fatal internal bleeding. In this case, however, the challenge is to find a genetic marker.

The 2C9 enzyme metabolizes warfarin. But it is only one of several factors that control the level of the drug in the blood. A recent study pointed to another gene, vitamin K epoxide reductase, as a better predictor.

Finding genetic markers is not always easy. "There are a lot of drugs where simply it's not the right tool," said Richard S. Judson, former chief scientific officer of Genaissance, a pharmacogenomics company.

Dr. Judson said his company had tried but failed to find genetic variations to help determine which cholesterol-lowering statin was best for a particular patient.

Other problems might arise, as well. It might be hard for doctors to deny a drug to a desperate patient, even if a genetic test predicted that it was unlikely to work.

"There would be no way with a safe drug for a serious condition that you could tell people they can't take the drug," said Dr. Allen Roses, senior vice president for genetics research at GlaxoSmithKline. "It wouldn't be ethical."

Pharmacogenetics, however, does offer drug makers some advantages that might offset the risk that a particular drug would be limited in its use to a subset of patients. For example, a company may be able to charge a higher price if the drug is highly likely to be effective.

"We're not going to have a single blockbuster," Dr. Roses said. "We'll take five minibusters."

Clinical trials could also be far smaller, cheaper and quicker if a drug was tested just on patients for whom it was likely to work. Several companies are trying to rescue drugs that failed in clinical trials by retesting them only on people they are likely to work for.

Dr. Roses said drug companies were likely to test their drugs on all patients and hope for a broad approval. But if that failed they would request approval for a subset of the patient population.

One spur to the use of such tests in the future could be the fear of malpractice lawsuits. If a patient suffers side effects from a drug, doctors might be sued for not using an available test.

Pharmaceutical companies might also want to direct drugs at specific patient groups to avoid liability, as in the thousands of lawsuits filed against Merck by people claiming to have been harmed by the pain reliever Vioxx. Merck, which pulled Vioxx from the market last year, marketed the drug very broadly, increasing the company's legal risk when Vioxx was found to cause heart attacks.

"I think you are seeing a change in the air," said Lawrence J. Lesko, who heads the pharmacogenomics working group at the F.D.A.

"With the concern that everybody has about risk management there's not a lot of pushback from the companies," Dr. Lesko said.