Genetic variation in the enzymes involved in the metabolism of drugs can have a huge impact on the efficacy and/or risks of a drug. See examples below.

Is Your Medicine Right for Your Metabolism?

More genetic tests aim to help predict how people might respond to many common medications.

People can respond to drugs very differently. A medication that brings relief for some patients might show no benefit at all in others, or even cause harmful side effects.

A growing array of genetic tests is designed to help predict how people are likely to respond to many common medications, from antidepressants and antihistamines to pain relievers and blood thinners. The tests, which are controversial, look for tiny variations in genes that determine how fast or slow we metabolize medications.

Because of such gene variations, codeine, frequently prescribed to relieve pain, has little effect on as much as 20% of the population, while 2% of people have such a strong reaction that a normal dose can be life-threatening. About 25% of people can’t effectively absorb Plavix, a clot-busting drug, putting them at increased risk for a heart attack or stroke.

Even everyday drugs such as Advil and Motrin, for pain relief, and Zocor, to lower cholesterol, can have widely varying effects.

Testing patients for gene variations could avoid some of the 700,000 serious drug reactions in the U.S. each year, some experts say. Proponents of the tests, which are done with a cheek swab, say they also could help doctors rely less on trial and error in choosing the right drug and the right dosage for individual patients.

The Food and Drug Administration has included cautionary information for people with certain gene variations on the labels of more than 100 prescription medications. As yet, only about 20% of doctors order such tests, according to a survey by the American Medical Association, and many patients don’t know they exist.

Some major medical associations, including the American College of Cardiology and the American Psychiatric Association, have been slow to endorse the testing, mainly because there are no large, randomized controlled trials showing the technique significantly improves patient care. And the tests, which range from $500 to $2,000, are only covered by some insurers in some cases.

Alan Pocinki, an internist in Rockville, Md., says he orders gene testing for patients who have a history of unexplained symptoms or who haven’t gotten relief from drugs in the past. In many cases, he is able to find a better treatment based on their DNA, he says. “It makes a huge difference clinically among people I see every day.”
How people’s genes affect their response to medications is called pharmacogenetics. One of the first such drug-gene interactions was identified at the Mayo Clinic in Rochester, Minn., in the 1970s. Researchers discovered that about 1 in 300 children being treated for childhood leukemia had a gene variation that made the drug thiopurine destroy their bone marrow. Now, children are routinely tested before undergoing treatment with the drug.

Scientists have since discovered that about 75% of prescription and over-the-counter drugs depend on a handful of liver enzymes to be absorbed and eliminated from the body. Minor variations in the genes that regulate those enzymes are very common—95% of people have at least one.

People who get two impaired copies of an enzyme gene—one from each parent—are likely to be “poor metabolizers” and absorb drugs so slowly that even a normal dose can become toxic. “Intermediate metabolizers”—with one impaired and one normal gene—allow drugs to build up in the body and over time can cause side effects. People sometimes get extra copies of enzyme genes, which can make them “ultrarapid metabolizers” of some drugs and flush them out of the body so fast they have little effect.

Gene variations that affect drug metabolism tend to run in families and ethnic groups. Other factors, including alcohol and dietary supplements, can also affect how a person reacts to a drug. Some medications, such as Plavix and the acid-blocker Prilosec, shouldn’t be taken together because they can impair each other’s ability to be absorbed. Cigarette smoking speeds up the absorption of the schizophrenia drug clozapine, so patients who smoke need a higher dose.

Some people say learning they have drug-gene sensitivities explains a lifetime of health mysteries. Elise Astleford, 75, a retired Episcopal priest in Vancouver, Wash., says she experienced hallucinations, a deep depression and symptoms of dementia while taking various drugs over the years. After spotting a newspaper ad for gene testing, she convinced her primary-care doctor to order it. She learned she has variations in three key liver enzymes that make her an intermediate metabolizer of dozens of common drugs.

Ms. Astleford still takes a variety of medications for thyroid, blood pressure and other conditions, but she makes sure they all use different enzyme pathways. “Now, whenever I get a new prescription, I check with the pharmacist to see how they are metabolized,” she says.

Some tests for gene reactions to individual drugs have been available for years. More lab companies, including Assurex Health Inc., in Mason, Ohio, and OneOme LLC, in Minneapolis, offer panels of tests aimed at advising patients with psychiatric, cardiac or chronic-pain conditions what medications would be the best fit based on their genes. Genelex Corp., in Seattle, says its YouScript software program analyzes how multiple medications, over-the-counter drugs and supplements react with each other and with patients’ DNA. The testing and analysis costs roughly $1,000. “Your results don’t change; you’ll have that information the rest of your life,” says Genelex Chief Executive Kristine Ashcraft.
Medicare pays for pharmacogenomic tests in some cases, such as before patients take certain antidepressants and anticoagulant drugs, but stopped covering many others last year after one company was investigated for allegedly making improper payments to doctors. Private-insurance coverage is spotty but costs for the tests are dropping. NorthShore University HealthSystem in Evanston, Ill., opened a pharmacogenomics clinic last year that offers a panel of 14 gene tests for less than $500.

More top medical centers—including those at Vanderbilt University, the University of Pittsburgh, the Mayo Clinic and St. Jude Children’s Research Hospital—are testing patients’ DNA and studying whether gene-based drug targeting makes a difference in their care. Insurers sometimes cover the cost of testing for such research trials; other times grants or the hospitals themselves provide the funding.

In many cases, hospitals are incorporating the information into patients’ electronic-medical records, so it can help doctors choose the most useful drugs and dosages for them in the future.

“Pharmacogenomics is never going to be a crystal ball to tell you which medications will work and which won’t. Too many other factors come into play,” says Dr. Mark Dunnenberger, who heads the NorthShore University clinic. “But we can take advantage of a patient’s DNA and say, ‘You have a high likelihood of a suboptimal response from these drugs, so let’s try another medication that works a different way.’”

Many common medications can affect people differently depending on minor variations in the genes that regulate key enzymes. The variations can make people metabolize certain drugs either more slowly or rapidly than normal. Some examples:

**DRUGS**

Pain relievers codeine or oxycodone, including Tylenol 3 and Percocet

**ENZYME PATHWAY AT WORK**

CYP2D6

**IMPACT**

A standard dose can have little effect in up to 20% of people, while as many as 2% can have a life-threatening reaction.

**DRUGS**

Blood thinner Plavix (clopidogrel) and acid reducers Prilosec (omeprazole) and Prevacid (lansoprazole)

**ENZYME PATHWAY AT WORK**

CYP2C19

**IMPACT**

Up to 15% of people metabolize these drugs very slowly, resulting in a higher effective dose and greater risk of side effects.
Blood thinner Coumadin (warfarin)

**ENZYME PATHWAY AT WORK**
CYP2C9

**IMPACT**
People with some gene variants have twice the risk of severe bleeding, but other factors are involved and population percentages are unclear.

**DRUG**
Cholesterol reducer Zocor (simvastatin)

**ENZYME PATHWAY AT WORK**
SLCO181

**IMPACT**
Up to 40% of people have impaired ability to metabolize this drug, giving them increased risk of muscle pain and other side effects.
Source: Clinical Pharmacogenetics Implementation Consortium

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