



Up Close With

Julie Johnson

CLINICAL PHARMACIST

"I kept dabbling at things, trying out different career options until I found a really good fit."

FAMILY VACATIONS

Scuba diving in the Caribbean

CHILDHOOD HOBBY

Raising beef cattle

PETS

One dog, two cats, a bunny, three fish

FAVORITE AUTHORS

Richard Russo,
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SARAH KEWELUP HEALTH SCIENCE CENTER NEWS



The Right Fit

BY ALISA ZAPP MACHALEK

“All things are poison
and nothing is without poison.
Only the dosage distinguishes
the killer from the cure.”

(loose translation from the original German)

—Paracelsus, Swiss scientist (1493–1541)

If that sounds crazy to you, consider

the case of the blood thinner warfarin. Now one of the most widely prescribed drugs in the world, warfarin was originally marketed—and is still commonly used—as a rat poison.

Killer or cure? The difference is in the dose.

But it gets more complicated: A safe dose for one person might be dangerous—even lethal—for another.

So how do doctors know how much of a medicine to prescribe? Essentially, they make an educated guess. Then, depending on how well the patient responds, they might adjust the dose.

Unfortunately, for very sick patients—or for very strong drugs—the delay caused by this trial-and-error process can be harmful or even life-threatening.

Julie Johnson, a clinical pharmacist at the University of Florida in Gainesville, hopes to speed things up, getting the right prescription to each patient right away. To do this, she focuses on genes.

“The hope is that through a person’s genetics, we can minimize the trial-and-error process and quickly identify the drug therapy that will work best for that person,” Johnson says.

The ultimate goal is to enable doctors to tailor prescriptions for each patient.

This area of research is called pharmacogenetics or pharmacogenomics. Johnson’s team is one of a dozen groups that are part of a nationwide pharmacogenetics research network (see “Genes, Disease and Drugs,” page 14).

Steering in the Right Direction

Before she landed in her current career, Johnson went through her own trial-and-error process. She was raised in rural Ohio, where her parents had a small farm.



The same substance that kills rodents protects the lives of millions of people.



Your genes influence how your body responds to medicines.

While growing up, she was very active in 4-H and showed beef cattle every summer at the county and state agricultural fairs. She even won the Grand Champion award for her steer when she was a senior in high school.

Although raising cattle may seem far afield from medical research, it actually taught Johnson skills that help her excel in the laboratory, says Deanna Kroetz, a fellow scientist (and pharmacogenetics network member) with whom Johnson has been close friends for more than 30 years.

“Julie has been doing long-term projects and setting goals since she was a kid. It contributes to how she works on things, how she thinks,” says Kroetz.

As a girl, when Johnson thought about what she wanted to be when she grew up, she looked to the careers of her family and neighbors. She considered being a kindergarten teacher, veterinarian, hospital pharmacist or drugstore owner. For one reason or another, none of these was a good fit. Eventually, she considered being a faculty member in a college of pharmacy.

While studying pharmacy in college, she took an elective class in research.

“Much to my surprise, I really, really liked it,” she says. “It fit. It was intellectually stimulating and allowed me to address clinically important questions.”

What’s Genetics Got to Do With It?

Johnson’s continued interest in medical issues led her to focus on the pharmacogenetics of cardiovascular drugs.

In addition to determining whether you will be tall or short, black-haired or blond, your genes influence how your body responds to medicines.

But genes aren’t the only factor. Your age, weight, lifestyle and other characteristics also play a role.

Here’s how it works. When you swallow a pill, it lands in your stomach and soon moves to the small intestine. From there, it is absorbed into nearby blood vessels, then carried to your liver.

Among its many functions, the liver is your body’s main toxic waste-processing plant. It is chock-full of enzymes that metabolize drugs, alcohol and toxins, changing these substances into new chemical forms.

Within the liver is a large family of enzymes known as cytochrome P450s, or CYPs (pronounced “sips”), which together are responsible for metabolizing about 75 percent of all medications.

Some CYP enzymes change toxic compounds into harmless ones. Others chemically alter substances to prepare them for elimination in urine or feces. Still others convert drugs into their active form.

There are five main CYP enzymes involved in drug metabolism, each of which comes in many variations.

Every person has a unique combination of CYP enzymes, genetically

selected from countless possibilities. Whether your combination is advantageous, pharmacologically speaking, depends on which medications you take.

Take a CYP

Take for example CYP2D6, an enzyme that is responsible for processing about one-fourth of all prescription drugs. This enzyme has more than 100 versions, based on tiny differences in the genes that code for it. Depending on which versions you inherit, your CYP2D6 enzyme activity could be normal, superfast or nonexistent.

Why should you care what kind of CYP2D6 activity you have? Because it could make a big difference in how well medicines work for you.

Say you broke a bone or had surgery. A doctor might prescribe codeine for your pain. In order to work, codeine needs CYP2D6 to transform it into the potent painkiller morphine.

If you have nonexistent CYP2D6 activity (along with about 5 percent of Americans), codeine will do nothing for you because your body can’t convert it into morphine. Your pain will just keep throbbing.

But having too much CYP2D6 activity could have even worse consequences.



A single liver enzyme, CYP2D6, is responsible for processing about one-fourth of all medicines, including these.

ALISA Z. MACHALEK

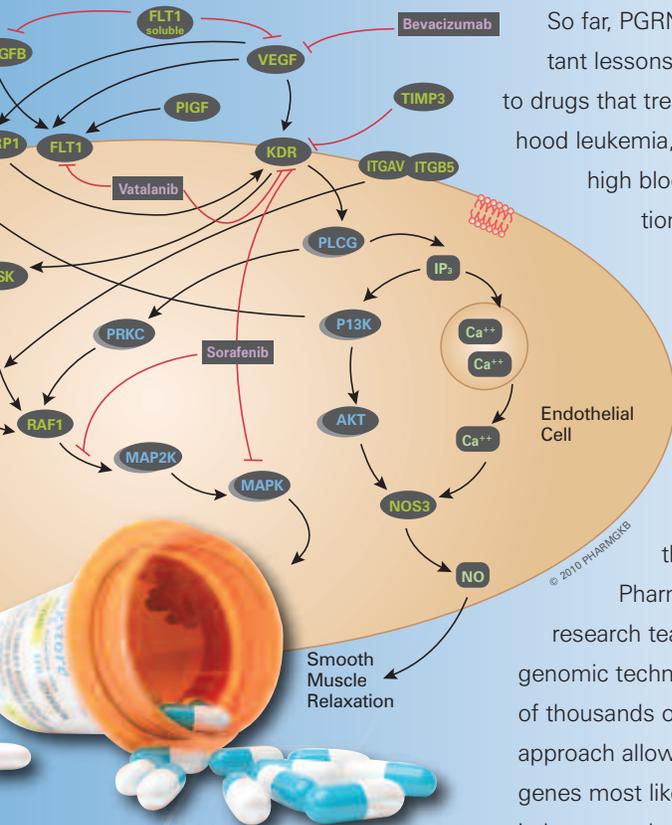
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Genes, Disease and Drugs

Have you ever taken a medicine that didn't work or that caused bad side effects? If so, you know that not everyone responds the same way to medications.

Recognizing the importance of understanding these differences, the National Institute of General Medical Sciences, together with other components of the National Institutes of Health, created the Pharmacogenetics Research Network (PGRN) in 2000.

Scientists in this nationwide collaboration study genes and medicines relevant to a wide range of diseases. The researchers expect that the knowledge they uncover will help doctors use genetic information to tailor treatments for each patient, in essence making drugs safer and more effective for everyone.



So far, PGRN scientists have learned important lessons about gene-based responses to drugs that treat asthma, breast cancer, childhood leukemia, depression, heart disease, high blood pressure and other conditions. Discoveries made by the network have already led to changes in the prescribing instructions for some medications.

In 2008, members of the PGRN joined forces with scientists in Japan to form the Global Alliance for Pharmacogenomics. The new research teams use state-of-the-art genomic technology to examine the sequences of thousands of genes simultaneously. This approach allows scientists to get a fix on the genes most likely to play an important role in how people respond to drugs.

You can find more information about the Pharmacogenetics Research Network at <http://www.nigms.nih.gov/Initiatives/PGRN>. —A.Z.M.

And here's the kicker: the ideal dose varies widely—one person may require 10 times more than another—so it's nigh impossible to get every prescription right the first time.

How do doctors even know where to start?

Typically, they begin with a generic dosage adjusted for factors like the patient's weight, age and gender. Then they wait up to a week, check the patient's blood for its clotting ability, and tweak the dosage as needed.

They repeat these steps for a few weeks until they've found the optimum dosage. The patient then remains on the final, stable dosage (with regular tests to check that it's still the right fit).

Fortunately, doctors have been doing this for decades and have carefully worked out the technique. But Johnson and her colleagues think there's a better way—through pharmacogenetics.

Johnson discussed this idea with other scientists from the pharmacogenetics research network and from the online knowledge base PharmGKB. They all knew that to fully investigate whether pharmacogenetics could improve warfarin dosing, they would need a worldwide effort.

So they created the International Warfarin Pharmacogenetics Consortium. The consortium is made up of about a hundred researchers on four continents.

The scientists already knew that variations in two genes, CYP2C9 and VKORC1 (an enzyme that activates vitamin K), could influence warfarin's effectiveness. But no one was really sure whether knowledge of a patient's CYP2C9 and VKORC1 variations could help doctors arrive at the optimal dose of warfarin more quickly. That's what the consortium set out to determine.

up when doctors repeatedly change the medicine.



By combining their data, consortium members had access to anonymized information from about 5,700 patients on stable dosages of warfarin. The patients came from around the globe: Taiwan, Japan, Korea, Singapore, Sweden, Israel, Brazil, Britain and the United States.

This kind of study—one that includes people of different races, ethnicities and lifestyles—is essential to draw conclusions that are applicable to a wide range of people.

From this vast pool of data, the consortium members created a computer program to predict the ideal warfarin dosage for each patient based on his or her genetic variations and clinical information like age and body size.

Then the scientists checked their predictions against the actual dosage for each patient. (These stable dosages had been established the traditional way—they were initially based on standard clinical factors, then adjusted until they were optimal.)

Voila! The genetically based computational predictions were closer to the stable dosages than were the starting dosages obtained using the standard, best-guess method.

The computer program performed especially well for patients at the low or high ends of the dosing range. This got the scientists' attention, because nearly half of the people on warfarin are at the extremes of the range, and they are the ones most susceptible to dangerous bleeding or clotting.

The consortium published these discoveries last year in a major medical journal.



To make the broadest discoveries in pharmacogenetics, scientists have to include patients from around the globe.

As the consortium's research continues, its strategy is being tested in a large clinical trial to determine whether a gene-based approach to prescribing warfarin will improve the effectiveness and safety of the drug for new patients. The trial is called Clarification of Optimal Anticoagulation through Genetics (COAG).

Lowering the Pressure

Most of Johnson's work focuses on drugs that treat high blood pressure, or hypertension.

In the case of warfarin, genes influence *how much* of the drug a patient needs. For drugs that treat hypertension, genes influence *which* drug—there are dozens—would be best for each patient.

"If doctors randomly pick one of those medicines, there's only a 50 percent chance that it will work," Johnson says.

"We're trying to find out if there are genetic markers to use to pick the

right drug from the outset," she continues. "Right now, it's a trial-and-error process. It can be very frustrating for patients, especially for young people."

Too often, people get fed up when doctors repeatedly change the medicines, she says. The patients feel fine—hypertension has no obvious symptoms—and they may not understand the importance of finding an effective medicine.

"So they go untreated for an extended period. And that's bad," Johnson says.

Even though they can't feel it, the extra force of blood smashing against artery walls can seriously damage internal organs. Long-term consequences include kidney failure, strokes, heart attacks, heart failure and death. Because of this, hypertension is sometimes called the "silent killer."

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FIND MORE @

Check out an online tool for estimating warfarin doses at <http://www.warfarindosing.org>

