Data can be dangerous, especially when it comes to drugs, and the numbers do not always tell the whole story. Consider the cytochrome P450 superfamily of enzymes that metabolizes a wide range of drugs. The PharmVar database lists nearly 200 missense variants for the gene coding for a single enzyme, CYP2C19—CYP2C19 is one of 13 genes in the CYP2 family. However, only a relatively small number of these variants have been functionally validated.

While enzymes such as CYPs play important roles in breaking down and inactivating drugs, they are also responsible for activating others. For example, clopidogrel is an antiplatelet medication that is bioactivated through cleavage of the precursor prodrug by CYP2C19. A patient with a loss-of-function mutation in CYP2C19 won’t get “the antiplatelet effect you want in order to prevent in-stent thrombosis and other catastrophic events after somebody has a coronary stent,” says Dan Roden, Sam Clark Professor of Experimental Therapeutics at Vanderbilt University in Nashville, Tennessee. “It’s a manifestation of what I’m fond of saying: The most common adverse drug event is failure of the drug to do what you want it to do.”

Just as the genome can influence height or eye color, it can influence drug response phenotypes as well. The result can be altered drug efficacy, an adverse reaction, death, or a new pharmaceutical target. Finding the connections between genetic variants and drugs, understanding their mechanisms of action, and learning how to mitigate, manipulate, circumvent, and perhaps harness those differences is what pharmacogenetics and its successor pharmacogenomics (PGx) are all about. Despite a few clear, well-established examples, the need to demonstrate these connections by establishing the evidence base, and to educate stakeholders such as patients, providers, regulatory agencies, and payers, remains an obstacle to PGx’s progress.

Paving the way to better drug labeling
Most of the early and best-known examples of pharmacogenetics involved the way genetic variation altered a drug’s pharmacokinetics (PK). PK factors—absorption, distribution, metabolism, and excretion, (ADME)—influence how much active drug reaches its target.

Take the case of 6-mercaptopurine (6-MP), a drug that revolutionized both transplant medicine and the treatment of childhood acute lymphoblastic leukemia (ALL). It acts by interfering with rapid cell turnover and DNA replication; but in about one of 300 children, 6-MP wipes out the bone marrow, with potentially fatal consequences. “So my lab said, ‘let’s look at the enzyme that catalyzes a major step in the biotransformation of 6-MP, thiopurine methyltransferase (TPMT),’” says Richard Weinshilboum, professor of medicine at Mayo Clinic in Rochester, Minnesota.

Two TPMT variants were found that caused the proteins to be rapidly degraded, preventing them from adequately metabolizing 6-MP, “which means that a standard dose was, in their case, about 10 to 15 times too much, because their body couldn’t get rid of it,” explains Weinshilboum.

The work was published around 1980. By 1990, it was standard practice at Mayo Clinic to test for the variants before administering chemotherapy. Around 2002, the U.S. cont.>
**Casting a wider net**

With the Human Genome Project, scientists had a reference map for the entire human genetic sequence and could cast a wider net in their search for genetic variants that impact drug metabolism. They could look beyond known drug metabolizing genes to “genes having to do with disease pathophysiology and the mechanisms of drug response, that also show genetic variation,” says Weinshilboum. Recognizing this, the National Institute of General Medical Sciences at the U.S. National Institutes of Health in Bethesda, Maryland, established the Pharmacogenomics Research Network (PGRN). “That was a key in terms of opening the door for PGx to begin to take genome-wide approaches, which allow you to agnostically identify genes that we weren’t teaching about to the medical students,” he says.

Many of the pharmacogenes found had to do with pharmacodynamics—defined as everything involved with a disease’s biology and how a drug does its job if PK is held constant, says Roden.

One example involves the human leukocyte antigen (HLA) complex of the immune system. For instance, more than half of patients with the HLA-B*57:01 allele who are given the anti-HIV drug abacavir will get a potentially fatal hypersensitivity reaction known as Stevens-Johnson syndrome. But this has “virtually disappeared from clinical practice because every patient who comes to an HIV clinic who was going to receive abacavir has an HLA test done, and if they [test positive for HLA-B*57:01], they get a different drug,” says Munir Pirmohamed, director of the MRC Centre for Drug Safety Sciences and Wolfson Centre for Personalized Medicine at the University of Liverpool in the United Kingdom.

“Now we’re in an era where we are rapidly identifying, through the techniques of genome-wide association studies [GWAS] and then next-generation sequencing, variants that indicate why the drugs we use today show different responses, and are potential targets into drugs of tomorrow,” says Weinshilboum.

**Thermo Fisher Scientific**’s PharmacoScan GWAS platform, for example, “pretty much comprehensively covers all known [pharmacogenes], including those where the evidence is not as strong yet,” says Ulrich Broeckel, founder and CEO of RPRD Diagnostics and professor of pediatrics at the Medical College of Wisconsin, Milwaukee, who uses this technology. “It is a clinical and diagnostic platform, but it’s also a research platform.”

**Sorting out the evidence**

While some of the variation being picked up in the postgenome sequence era is shared by appreciable portions of the population, 30% to 40% of all variability in drug response is due to rare mutations found in less than 1% of the population, says Magnus Ingelman-Sundberg, vice chairman and section head of the Department of Physiology and Pharmacology at Karolinska Institutet in Stockholm.

Pharmacogenomic findings far outpace the field’s ability to make sense of them, whether they involve rare variants, common variants that don’t always lead to a phenotype, or variants of unknown significance. In addition, compliance, drug-drug interactions, and other environmental factors may play a role as well, leading Ingelman-Sundberg to estimate that only “25%–35% of the variability in drug response is caused by genetic factors in the clinic.”

But even if it’s all driven by genetics, for some drugs a single common genetic variant has a large effect size, while for others there can be “100 different variants, and the combination of variants together will determine whether you respond to a drug or not. And if you have 100 different variants in the same or different gene, proving that it’s a certain combination of variants that drive responses in one direction or the other is much, much more difficult—I would even say impossible,” says Roden.

Thus, discerning the importance of a pharmacogenetic finding and putting it into action is not a trivial task. “There are thousands of scientific articles linking a gene with a drug,” says Mary Relling, chair of pharmaceutical sciences at St. Jude Children’s Research Hospital in Memphis, Tennessee. “But getting to the point where you could actually use that genetic information to make a prescribing decision requires an extremely high level of evidence, replication, validation, and mechanistic studies—and importantly, all of that information needs to be present for the alternative therapeutic recommendations one is going to make.”

There are criticisms that many studies have failed to demonstrate efficacy in a clinical setting. “That is correct to some extent, because some studies haven’t been big enough,” says Pirmohamed. But the problem is compounded by the fact that many critics use randomized control trials as their standard. He encourages the use of other types of study design, perhaps taking advantage of
**Featured participants**

- Karolinska Institutet  
  www.ki.se  
- Mayo Clinic  
  www.mayoclinic.org  
- Medical College of Wisconsin  
  www.mccw.edu  
- Myriad Genetics  
  myriad.com  
- RPRD Diagnostics  
  www.rprdx.com

**Additional resources**

- Clinical Pharmacogenetics Implementation Consortium (CPIC)  
  cpcpgx.org  
- PharmGKB  
  www.pharmgkb.org  
- PharmVar  
  www.pharmvar.org  
- Pharmacogenomics Research Network (PGRN)  
  www.pgrn.org

There are nearly 200 FDA-approved drugs with pharmacogenomic information on their labels, seven of which have strict warnings, says Broeckel.

“In terms of clinical application of PGx, we’re at the very early stages. I think we have examples where we have some really solid evidence that it makes a difference in the lives of patients. But we must continue to build that evidence base,” says Johnson.

The Clinical Pharmacogenetics Implementation Consortium (CPIC)—a joint effort of PGRN and the PharmGKB knowledge base—puts together a “freely available, nonprofit, evidence-based, expert-driven resource of very specific guidelines for the very, very few genes and drugs for which the evidence was already strong enough that if you had genetic variation information on a patient, it would be wrong not to use it to inform prescribing,” says Relling. To date, CPIC has 20 guidelines affecting 15 genes and 37 drugs.

Even so, says Relling, a recent survey of a major academic health care system found that only in about 1.5% of prescriptions for which the label requires or recommends a PGx test would be that test performed (even for well-established drug-gene pairs), and that seems to be the norm in both academic and mainstream medicine. There are many reasons for this, from issues of education, technology, and infrastructure to the economics of health care.

**Breaking the bottleneck**

In some ways, PGx faces a classic Catch-22 scenario: Evidence is needed to convince regulators, professional societies, providers, and payers alike that using genetic information makes a difference to patient outcomes and the bottom line, but that evidence has first to be generated. And most patients and clinicians simply aren’t aware of when and where PGx testing should be used, if they are aware of it at all, says Relling.

Some major academic medical centers “are really trying to move the field forward” by actively translating discoveries into clinical practice, says Julie Johnson, dean and distinguished professor at the University of Florida College of Pharmacy in Gainesville. The University of Florida, she says, has published “pretty compelling evidence not only that cardiologists across a multitude of different institutions will use [genetic] information to guide therapy, but that when they do use it, those patients have better clinical outcomes.” This finding was followed by a chronic pain management study in primary care settings—some in medically underserved, minority communities—leading to genotype-guided outcomes significantly better than the standard of care, and in most cases with a reduction or even elimination of opioid use.

Several institutions and consortia are studying the efficacy and best practices of preemptively sequencing or genotyping patients for a host of pharmacogenes—most often as panels—and embedding that data into their electronic health records (EHRs). Rather than the alert firing when there is a test available, Mayo Clinic is experimenting with it firing only when genetic information in the EHR counterindicates the prescription.

Either way, sometimes you need the medication immediately and can’t wait a week or two for genetic tests to come back, says Timothy Curry, education director of the Center for Individualized Medicine at Mayo Clinic. But he cautions that “just putting it into the medical record wouldn’t have been useful if we didn’t also accompany that with education—teaching people how to use that information.”

Preemptive or reactive, PGx panels are also useful when a combination of variants is implicated in drug choice. It is becoming more commonplace to look at a panel of mutations in the somatic tumor genome to assess how to treat the cancer, for example. Similarly, for variations in the germline genome for fields such as psychiatry, “the goal is to end traditional trial-and-error prescribing, which has largely been dictated by the single-gene approach,” says Bryan Dechairo, executive vice president of Myriad Genetics, a molecular diagnostics company based in Salt Lake City, Utah.

There are already some drug-gene combinations for which the PGx evidence is considered incontrovertible, in terms of both patient outcome and the cost benefit of testing. Drug labels are calling for testing, and EHRs are altering prescribers. Links between other drugs and other genes are constantly being uncovered. The future of PGx will likely be built on a critical mass of stakeholders—including patients and providers informed enough to ask for it.

Josh P. Roberts is a freelance writer based in Minneapolis, Minnesota.