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Preemptive pharmacogenomics

Working toward bringing timely, individually tailored, precision health care to patients

When it comes to health care, the right prescriptions not only improve patients’ lives—they sometimes save them. So, when a patient requires a medication, a clinician prefers to prescribe it immediately. But that’s not always possible. About 200 of the drugs approved by the U.S. Food and Drug Administration (FDA) note pharmacogenomic (PGx) information—interactions between a patient’s genes and the medicine they need—that should be considered before prescribing that medication. An example is the cancer drug tamoxifen, the efficacy of which depends on an individual’s liver enzyme activity as determined by their particular genetic makeup. Using preemptive pharmacogenomics (PGx), clinicians can obtain a patient’s genetic information—on all potential markers, or only those that are informative when prescribing medications—in preparation for future pharmaceutical needs. More important, early genetic testing can support potentially life-threatening decisions about the best drug treatment for a patient. The Clinical Pharmacogenetics Implementation Consortium, in providing guidelines to clinicians on using genetic test results in prescribing, assumes that PGx implementation will grow. Collecting and analyzing that genetic information requires technology designed for the job, and Thermo Fisher Scientific (Waltham, Massachusetts) and some of its partners are looking forward to fulfilling those needs.

Better and safer

“Genetics can cause a person to respond to a drug in a way that was not intended,” says Scott Megill, president and CEO at Coriell Life Sciences, in Philadelphia, Pennsylvania—a company that partners with Thermo Fisher to provide reporting and interpretation of molecular diagnostics tests. Depending on a patient’s genetic makeup, a drug could provide no therapeutic effect at all or even be unsafe.

Ulrich Broeckel, founder and CEO of RPRD Diagnostics, in Wauwatosa, Wisconsin—another Thermo Fisher partner—explains that PGx testing can be done essentially two ways: when requested, on an as-needed basis; or preemptively, so that if a need arises, the patient’s genetic information is already on file. His company focuses on making PGx testing more widely available so that physicians have information readily at hand to make the best decision for each patient. PPGx could benefit many—maybe most—patients. About 50 human genes show a high degree of variation that is correlated with responses to medications, but just knowing that a gene varies does not provide meaningful information. “You can’t say that someone who has a variant will always have a problem with a medicine,” says Philip Empey, associate director for pharmacogenomics at the Institute of Precision Medicine, a collaboration between the University of Pittsburgh and the University of Pittsburgh Medical Center. And it’s more complicated than simply identifying whether a gene varies or not. “With some targets, the number of the genetic variant—the number of copies of that gene—is important,” adds Empey. With the cholesterol drug simvastatin, for example, having more copies of a specific allele increases the odds of an adverse event (1).

As in any area of medicine, more data is better. Making more PPGx data available will improve its overall value to health care. For PPGx purposes, genomic data collected from the individual is stored as an electronic health record. When enough data is collected, it can be utilized to improve health outcomes. For this reason, the University of Pittsburgh plans to do PPGx testing on more than 100,000 patients and track the results. “Only with a large study of preemptive genotyping can we determine its clinical and economic value,” says Empey, who is leading this study.

Easier data acquisition

PPGx data collection and analysis starts with a sample, such as blood, buccal swab, or saliva. Then, the genes from that sample must be analyzed. “When focusing on analyzing a targeted set of pharmacogenomic markers, where a rapid turnaround is important, qPCR—real-time [quantitative] polymerase chain reaction—is the better choice,” says Peter Norster, associate director, global market development, applied healthcare solutions at Thermo Fisher. For example, Megill says his colleagues “build specialized panels, such as for cardiac medications, mood disorders, and even a presurgery test” based on qPCR. This technology also makes it easy to add a gene or a section of a gene to a panel, he notes. Thermo Fisher provides a qPCR research solution for PPGx in their OpenArray platform, although other companies are also in that market space.
However, qPCR is not the best method for analyzing large numbers of genes. "When covering all markers—ones that are relevant today and ones that might be useful in the future—a microarray method works better," says Norster. Working together, RPRD Diagnostics and Thermo Fisher developed the Pharmacogenomics Solution, which includes the microarray plates and reagents needed for PPGx genotyping. "It covers all of the genes that should be tested," says Broeckel. Pharmacogenomics is fully verified and includes highly predictive markers in critical genes such as CYP2D6, CYP2C9, and CYP4F2 as well as copy number variation calling. It allows clinical researchers to gain valuable insight into an individual's ability to process drugs based upon high, moderate, low, or preliminary scientific evidence.

Usable reporting

Collecting the genomic data is only the first step—interpreting the genetic data in a relevant way is also crucial. "You’re looking at targets and placing patients in different categories, such as their ability to metabolize a drug," says Empey. Most physicians were never taught to interpret a patient’s genetics to predict a drug response. To get the most from existing medicines, genomic data must be combined with medical information, and that need is likely to increase with precision medicine, which aims to find drugs for specific genetic targets.

This information can save lives. Megill relates the example of the blood-thinner Plavix (clopidogrel), which is often prescribed after a heart attack or stroke, and is even incorporated into some stents. Nonetheless, 27% of Caucasians and about 50% of Asians cannot metabolize this drug, which makes it worthless to them—all based on variation in one gene that encodes cytochrome P450, a liver enzyme involved in breaking down molecules in the body. With global sales of USD 1.7 billion in 2017, that would be about USD 450 million wasted without PGx testing—and that’s assuming it would fail for only 27% of the general population.

Addressing hurdles to PPGx

Given the value of PPGx, it seems likely that it would be frequently applied if more widely available. When asked how often PPGx is used, however, Shannon Manzi, director of the Clinical Pharmacogenomics Service at Boston Children's Hospital, says, “not often enough.” In fact, preemptive testing is mostly used in very limited circumstances. "Currently, our experience is that outside of a research study or a well-defined standard of care, the vast majority of testing is done after a patient either experiences adverse effects or has a history of nonresponse to a drug," says Manzi. So, the first hurdle is that the standard of care isn’t well defined.

The second challenge is that clinicians can’t always access the information as soon as it’s needed. "If the prescriber cannot access the data at the time of prescribing—or in less than 30 minutes—it is not useful," Manzi explains. "This also applies to the pharmacist at the time of dispensing." Manzi sees two possible solutions: Either universal preemptive testing, such as newborn screening—or something real-time—is needed. Real-time or near-real-time PGx testing is unfortunately not yet possible.

Furthermore, to get the full benefits of PPGx, says Norster, “the information must go into a person’s electronic health record, and that data must be accessible and follow you around," and be integrated into clinician workflows.

The last challenge is that the entire health care system—including clinicians, patients, and payers—must see the value of PPGx. Experts in the field already see its benefits and envision more in the future. “The key is to raise awareness about the value of preemptive pharmacogenomics,” says Broeckel. In addition, the methods of testing must be easy to use, widely available, and covered by payers. Once all of that is accomplished, every patient’s health record could include the crucial genetic information that would allow faster access to many medications—some of which could be needed at a moment’s notice.


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“Our Cancer Protocol is aimed at moving genomics into direct patient care. We designed it to better understand the genomics of a patient’s tumor and to make some tests available to patients prior to clinical availability,” says Julie Gastier-Foster, PhD, senior director, IGM Clinical Laboratory. “It’s not a pure research or a pure clinical protocol — it’s a blend.”

The Cancer Protocol reviews patient nominations from hospital oncologists for genomic profiling. In most cases, the nominees have tumors that did not respond to prior rounds of therapy or have recurred. Selected patients are invited to have a full genomic analysis performed.

“We study for tumor and normal DNA and compare the sequences of all known genes. We look for cancer susceptibility genes by testing the normal cells’ DNA, and we examine both the cancer DNA and RNA for clues to what is driving their cancer and might help guide therapy,” says Elaine Mardis, PhD, co-executive director, IGM and president-elect of the American Association for Cancer Research. “That level of comprehensive study is quite uncommon.”

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While it’s commonplace to test for liver and kidney function before prescribing certain drugs, that’s not so much the case when it comes to testing for how drugs might interact with our genes—even though a variant gene can pose as much risk as compromised hepatic or renal function.

By Josh P. Roberts

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.

Upcoming features

“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.”

Food and Drug Administration (FDA) held first-of-their-kind public hearings on incorporating that information into drug labeling, recalls Weinshilboum.

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...
collective experience, and “using real-world evidence from that
to show that it is having a clinical benefit in our populations.”

There are nearly 200 FDA-approved drugs with pharma-
cagnostic 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 Con-
sortium (CPIC)—a joint effort of PGRN and the PharmGKB
knowledge base—puts together a “freely available, nonprof-
it, 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 gen-
etic 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 prescrip-
tions for which the label requires or recommends a PGx test
was that test performed (even for well-established drug-
gene pairs), and that seems to be the norm in both academ-
ic 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.
Transfection Reagent
Fuse-It siRNA is a transfection reagent that enables rapid, efficient gene silencing without being distracted by side effects of the transfection method, such as cell stress and toxicity. The principle is simple: The Fuse-It liposomal carrier, which includes small interfering RNA (siRNA), fuses with the cell membrane and then releases the siRNA directly into the cytoplasm. Thus, siRNA is immediately incorporated into the RNA-induced silencing complex (RISC), leading to efficient gene knockdown without the interfering processes of endocytosis or lysosomal degradation. Because it is based on the charge of natural cell membranes, Fuse-It-siRNA can be used with most cell types. Researchers performing knockdown studies in sensitive primary cells will greatly benefit from its extremely low cytotoxicity.

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For info: +49-(0)-89-520-46-17-0
www.ibidi.de

ELISA Kit for Endotoxins
The EndoCAb ELISA has been developed for determination of endotoxin core antibodies in human plasma or serum in patients or healthy individuals. These antibodies play an important role in the clearance of pathogens in both disease and medical interventions. One hypothesis suggests that if patients’ preoperative endogenous endotoxin-core anti-body (EndoCAb) level is low or even moderately low, they may be unable to cope with the efflux of endotoxins, which may have mild to severe clinical consequences. The assay is of interest for various experimental conditions ranging from in vitro lipopolysaccharide neutralization by plasma components and in vivo studies on kinetics of antibodies to endotoxin levels in health and disease. The EndoCAb standard IgG, IgM, and IgA median units are arbitrary and are based on medians of ranges for 1,000 healthy adults in a particular locality. Users should establish appropriate local statistical controls for their studies.

HyCult Biotech
For info: 855-249-2858
www.hyculbiotech.com/hk504

Multiplex DNA Reference Standard
Horizon Discovery’s OncoSpan is a cell line-derived, multiplex DNA reference standard for validating NGS assays. It features 385 variants across 152 key cancer genes. OncoSpan uses bioinformatics and droplet digital PCR to help drive fast, easy, and more complete validation of oncology gene panels and exome sequencing assays. Horizon also offers OncoSpan customers an online companion NGS quality-control solution called OncoMatic, which enables them to upload OncoSpan NGS data after sequencing, automatically assessing the called variants, reporting on variant frequency data, and tracking several quality metrics per sample. The combination of OncoSpan and OncoMatic provides access to an accurate reference standard truth set for use during establishment and validation of critical NGS bioinformatics pipelines, saving costs and helping to maintain compliance with standards such as those set by the College of American Pathology and EuroGentest.

Horizon Discovery
For info: +44-(0)-1223-976-160
www.horizondiscovery.com

Real-Time PCR System
The AriaMx Real-Time PCR System combines a thermal cycler, an advanced optical system with an LED excitation source, and a complete data analysis software package. The instrument can hold up to six optics modules, and the scanning optics design delivers optimal separation between the dyes and between samples. It features a closed-tube PCR detection format compatible with a variety of fluorescence detection chemistries, such as SYBR Green and EvaGreen dyes, and fluorogenic probe systems including TaqMan probes. AriaMx amplifies your productivity with its unique modular and flexible design; intuitive touchscreen interface; advanced, easy-to-use reporting; and 120-plus attributes monitored via its onboard diagnostics, which pinpoint assay or instrument issues as they arise. Use AriaMx for a variety of research applications, including gene expression analysis, genotyping/high-resolution melt capability, mRNA quantification, NGS quantification (library prep, result validation), nucleic acid monitoring, and rare-allele detection.

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Gene Expression Panels
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Figure 1. SeqCap EZ Prime Exome provides better coverage of target regions with 27% less sequencing compared to Supplier I. For the Prime Exome samples, target-enriched libraries were prepared from 100 ng of Coriell DNA using the HyperCap Workflow, with the KAPA HyperPlus Kit and the SeqCap EZ Prime Exome Panel. The same workflow was followed for the other samples, using Supplier I’s probes in place of Prime Exome. Prime Exome required 4 Gb of sequencing vs 5.4 Gb required by Supplier I. Sequencing was performed using an Illumina® HiSeq® 2500 instrument with 2 x 101 read length using v4 chemistry. For each panel, 8 replicates were prepared; only 6 of the alternative supplier’s samples yielded sufficient reads.