PHARMACY PRACTICE NEWS

PGx Helps Pharmacists Match Right Rx to Right Patient

More and more health systems today are playing the pharmacogenomics match game.

With the growth of evidence linking drug response to genetic variants and costs dropping for an expanding array of genomic tests, it's not surprising the discipline is gaining traction. Involved clinicians are uploading patient genotypes into electronic health records and using drug–gene matchups to improve dosing or to select safer, more effective therapeutic alternatives.

Technology and collaboration are the key drivers of these advances in precision medicine. At the 2016 American Heart Association's Scientific Sessions, Larisa H. Cavallari, PharmD, FCCP, BCPS, presented a preliminary analysis of outcomes data from seven major health systems that have been testing for the cytochrome P450 2C19 (*CYP2C19*) genotype in patients undergoing percutaneous coronary intervention (PCI) and using the findings to help guide antiplatelet therapy.

Larisa H. Cavallari, PharmD, the director of the Center for Pharmacogenomics at the University of Florida College of Pharmacy, in Gainesville.

She reported the findings on behalf of the National Human Genome Research Institute–funded IGNITE (Implementing Genomics in Practice) Pharmacogenetics Working Group investigators, part of a consortium of 16 health systems that have implemented various pharmacogenomics tests to enhance therapeutic decision making.

The team found that about 31% of patients had a loss-of-function [LOF] variant, which reduces clopidogrel [Plavix, Bristol-Myers Squibb] activation and effectiveness. Of those, "about 60% were placed on an alternative to clopidogrel," said Dr. Cavallari, an associate professor and the director of the Center for Pharmacogenomics at the University of Florida (UF) College of Pharmacy, in Gainesville.

Additionally, "the LOF patients who were treated with a different antiplatelet therapy had a lower incidence of major cardiovascular events compared with those treated with clopidogrel."

The PCI analysis "is the initial example of how institutions in the Pharmacogenetics Working Group pooled data to examine [pharmacogenetic] outcomes in clinical practice," Dr. Cavallari said. "We [developed] a common patient data collection form they filled out and sent to the University of Florida to aggregate with patient data from other sites. We are now working on the manuscript."

Pharmacists at the Center

James M. Hoffman, PharmD, MS, the chief patient safety officer at St. Jude Children's Research Hospital, in Memphis, Tenn., told *Pharmacy Practice News* that pharmacogenetic information is being used to improve drug therapy at many different centers of innovation. "We're at a very different place than we were, say, five years ago. Now we have many more models of practice, with resources like CPIC [Clinical Pharmacogenetics Implementation Consortium; https://cpicpgx.org]. And, of course, pharmacists are right at the center of that effort."

At St. Jude, said Dr. Hoffman, who is the co-chair of the CPIC Informatics Working Group, "every patient is approached about getting a panel of genes tested. We're able to load the results into our electronic health record and use that genetic information to improve drug therapy over the course of their entire care."

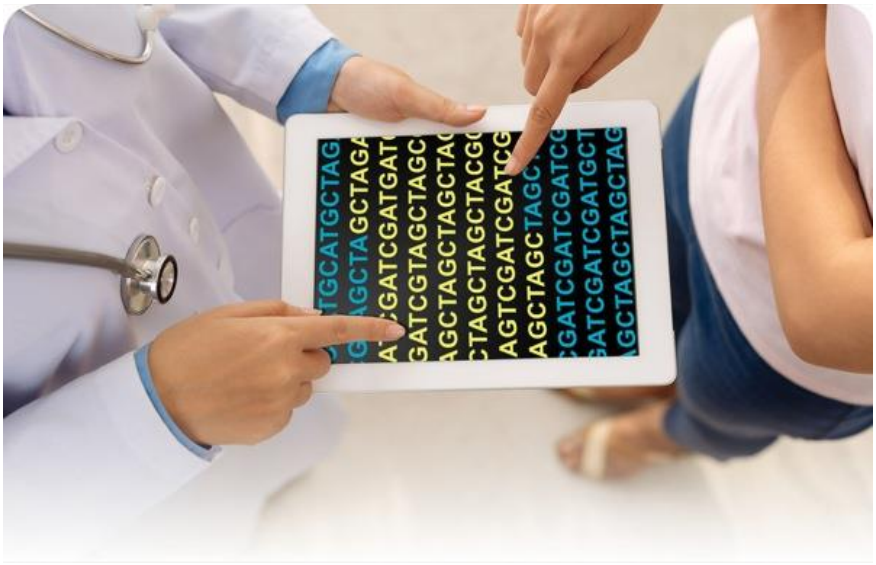
The approach has worked. "With just a small number of genes included," he said, "nearly 80% of the patients have had an actionable result—that is, a result that would change drug therapy."

Dr. Cavallari said the IGNITE investigators have implemented a number of drug–gene tests in addition to the most common one—clopidogrel and *CYP2C19*. They include opioids and *CYP2D6*; thiopurines and thiopurine methyltransferase (*TPMT*); and simvastatin and *SLCO1B1*. Dr. Cavallari described some of the consortium's work at the 2016 annual meeting of the American College of Clinical Pharmacy (ACCP), in Hollywood, Fla.

At UF—one of three original IGNITE sites, along with Duke University in Durham, N.C., and Mount Sinai in New York City—every patient who undergoes PCI is genotyped for *CYP2C19*, "unless the physician chooses to deselect the test from the standard PCI order set," Dr. Cavallari said.

In addition, she added, "we also offer *TPMT* testing for thiopurine dosing, and we've implemented *CYP2D6* testing, mostly in our primary care setting, for patients taking opioids. We just started genotyping *CYP2D6* to assist with pain management in our cancer clinics as well.

And then we also genotype for *CYP2D6* and *CYP2C19* in our child psychiatric clinics for antidepressant selection."



At St. Jude Children's Research Hospital, every patient is approached about testing a panel of genes. If they agree, the results are loaded into the hospital's electronic health record and used to improve drug therapy over the course of their entire care.

Credit: Darryl Leja, National Human Genome Research Institute.

Improved Proton Pump Inhibitor Dosing

UF Health also has implemented *CYP2C19* testing for proton pump inhibitor dosing. "Given the number of patients who take proton pump inhibitors, this could have a big impact," Dr. Cavallari said, adding that "we're planning to study the effect of genotyping on patient outcomes, including relief of symptoms of dyspepsia and gastroesophageal reflux disease."

UF Health has taken a data-driven approach to pharmacogenomics testing. "As the evidence for each gene–drug pair builds to a level that we feel supports implementation, we're moving forward," she explained. "The clinicians who are treating the patients have worked very closely with us in implementation."

Dr. Cavallari said UF Health was also looking forward to genotyping a panel of genes for patients who may not need a drug immediately, but whose genetic information would be stored in the medical record to guide dosing if they needed a particular drug. "It just gets to the point where there are so many gene–drug pairs that it makes sense to test for many genetic variants at once rather than testing relevant variants each time a particular drug is prescribed," she said.

Epigenetics Gains Traction

Advances also are occurring in a secondary branch of pharmacogenomics, called epigenetics, which focuses on changes in gene expression caused by environmental challenges, aging or other, often unknown, factors. Over a lifetime, these variances can have a profound influence on the risk for cancer, neurologic disorders, cardiovascular disease and other life-threatening conditions.

Joseph L. McClay, PhD, an assistant professor in the Department of Pharmacogenomics and Outcomes Science at Virginia Commonwealth University (VCU), in Richmond, noted that the changes are often reversible. “That’s why there has been so much emphasis on trying to create drugs that can target those epigenetic biomarkers and change gene expression.”

At the ACCP meeting, Dr. McClay described the half dozen drugs currently available for targeting the underlying mechanisms of epigenetic alteration. But he also offered a glimpse of what’s in store for this rapidly expanding area of drug research and development.

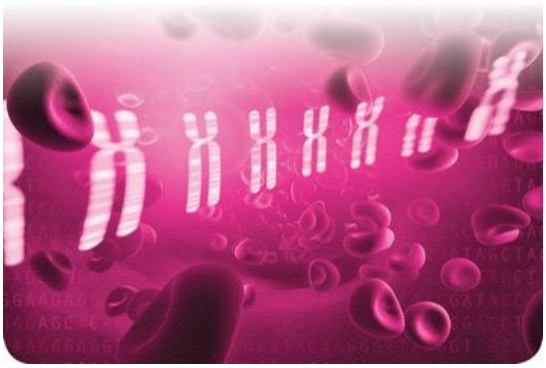
“My graduate student looked at all currently active clinical trials to see how many drugs had epigenetic modes of action,” he said. “There are dozens. There is an extraordinary amount of interest in understanding how these epigenetic biomarkers contribute to disease and how you can treat them.”

Each of the six currently approved epigenetic drugs is indicated for some form of blood cancer. The earliest was azacitidine (Vidaza, Celgene), a DNA methyltransferase inhibitor approved in 2004 for treating several subtypes of myelodysplastic syndrome, including refractory anemia and chronic myelomonocytic leukemia. The newest, belinostat (Beleodaq, Topotarget/Spectrum), was cleared two years ago for the treatment of relapsed or refractory T-cell lymphoma.

Dr. McClay’s laboratory at VCU has been engaged in several areas of pharmacogenetic research. “At the moment,” he said, “we’re looking at genes associated with psychiatric disorders and seeing how some of them are genetic regulators. We’re trying to figure out the patterns of regulation across the genome in the hope of understanding how that increases risk for the disease and then potentially finding new drug targets.”

Previously, he said, the lab had identified one target via genome-wide studies of DNA from patients enrolled in clinical trials. “Now we are trying to functionally characterize its role in drug response through genome-modification studies.”

PGx and Blood Cancer



Each of the six currently approved epigenetic drugs is indicated for some form of blood cancer.

In 2014, blood cancer accounted for approximately

9.4%

of the estimated

1.7 million

new cancer cases diagnosed across the country.

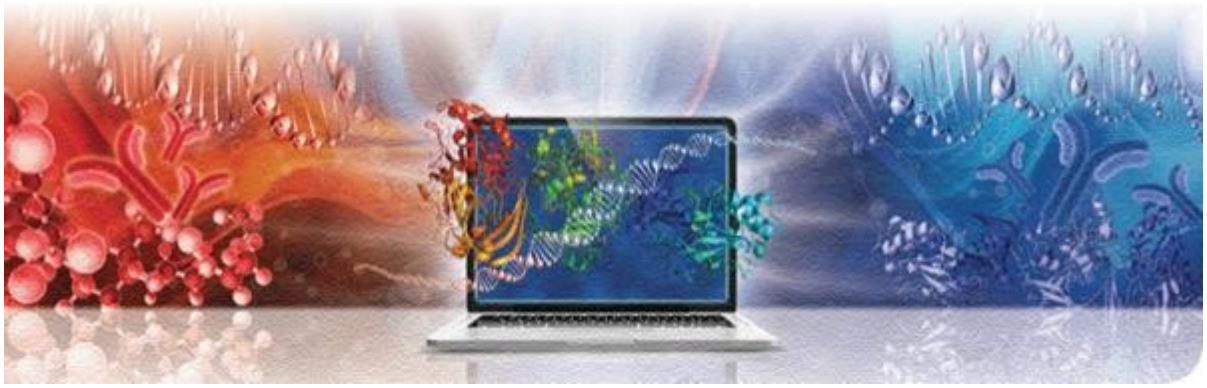
Credit: Ernesto del Aguila III, National Human Genome Research Institute.

Application in Geriatrics

Another area of investigation involves the effect of aging on changes in drug response. "We're interested in trying to identify epigenetic biomarkers of change in drug metabolism in older adults," Dr. McClay said. "Quite often older patients have a substantial decline in their rate of drug metabolism, and this can be associated with a higher risk for adverse events. So we started looking into potential changes in epigenetic regulation at some of the cytochrome P450 and other drug-metabolizing enzymes to see if there are any that are associated with age."

He cited, as an example, his colleague's efforts to develop targeted assays that measure DNA methylation at the cytochrome P450 2E1 (*CYP2E1*) gene promoter. "This gene shows some of the most consistent evidence for epigenetic changes with age among those involved in drug metabolism," Dr. McClay explained. "Further down the line, the aim is to see if we can develop epigenetic biomarkers of decline in drug response with age—and essentially assist in guiding clinical decisions in terms of dosing for older patients."

DMET Test Proves Valuable



St. Jude Children's Research Hospital, in Memphis, Tenn., has been a leading proponent of using personalized medicine to improve the safety and efficacy of drug therapy.

As part of the facility's PG4KDS protocol, the hospital preemptively genotypes patients for more than 200 genes using the Affymetrix Drug Metabolizing Enzymes and Transporters (DMET) Plus array (goo.gl/Acp7Oe), supplemented with a cytochrome P450 2D6 (*CYP2D6*) copy number assay. "The PG4KDS protocol provides a rational, stepwise process for implementing gene/drug pairs, organizing data, and obtaining consent from patients and families," the team reported in a paper describing the initiative, co-authored by Chief Patient Safety Officer James M. Hoffman, PharmD, MS.

Through August 2013, 1,559 patients were enrolled in the study, and four gene tests were released into the electronic health record (EHR) for clinical implementation: thiopurine methyltransferase (*TPMT*), *CYP2D6*, *SLCO1B1* and *CYP2C19*. These genes are coupled to 12 high-risk drugs. Of the 1,016 patients with genotype test results available, 78% had at least one high-risk (i.e., actionable) genotype result placed in their EHR, the investigators reported.

To maximize the clinical utility of the genetic screening protocol, test results were coupled with a standardized interpretive consult, the team noted. Moreover, to support gene-based prescribing at the point of care, 55 interruptive clinical decision support (CDS) alerts were developed. Patients are informed of their genotyping result and its relevance to their medication use through a letter.

"Key elements necessary for our successful implementation have included strong institutional support, a knowledgeable clinical laboratory, a process to manage any incidental findings, a strategy to educate clinicians and patients, a process to return results and extensive use of informatics, especially CDS," Dr. Hoffman and his team reported. "Our approach to preemptive clinical pharmacogenetics has proven feasible, clinically useful and scalable."

—PPN News Staff