Pharmacogenomics advocates make case for wider use

William Check, PhD

May 2018—Use of pharmacogenomic testing is still limited, despite ample research, the existence of guidelines, and the emerging evidence it can help patients. Panels can be costly and insurance coverage variable, and providers need guidance—from pharmacists, the lab, decision support alerts—in knowing what and when to order and in understanding the results. Plus, patients move.

“We have to have the information readily available when a patient needs it. It can be challenging to have our EHR provide results as patients move,” says Ann M. Moyer, MD, PhD, assistant professor of laboratory medicine and pathology and co-director, Personalized Genomics Laboratory, Mayo Clinic, Rochester, Minn.

She and Larisa H. Cavallari, PharmD, of the University of Florida, spoke on pharmacogenomics at the Association for Molecular Pathology meeting last year and with CAP TODAY recently. “Right now,” Dr. Moyer says, “the best thing about pharmacogenomics is that there is a lot of evidence that a number of genes impact drug response and have the ability and the potential to help our patients.”

Among the barriers, reimbursement is a big one, Dr. Cavallari says, but so is the demand for data from randomized clinical trials. “In my opinion, genotyping is a variable that can assist us in prescribing safer and more effective therapy,” she says. “We never required randomized trial data for analytes such as creatinine, which we routinely use in practice, so to me this demand is not realistic.”

Another obstacle is the variability of panels among labs. A Mayo Clinic patient had *CYP2C9* testing at two institutions. One laboratory detected the *2/*8 alleles and the other the *1/*2 alleles. Closer analysis found that the second laboratory did not include *8 on its panel, a major concern because *8 is the most common reduced-function *CYP2C9* variant in African Americans.

In 2003 Mayo Clinic began by testing *CYP2D6*. Its menu expanded one gene at a time until it offered more than 20 single-gene tests, which meant many separate workflows.

Dr. Moyer

With high-throughput SNP genotyping technology now available and more affordable, Mayo laboratories combined more than 14 workflows into one streamlined workflow. This has reduced the costs of testing and freed up technologists for other work. “Panels are justified by the fact that many patients are taking multiple medications and some drugs are impacted by variants in multiple genes,” Dr. Moyer says. “We might as well test for all available genes when we need the first one. The cost of running the test and resulting out an entire panel is about the same as for a single gene.” For panel-based preemptive testing (performed before the patient needs a medication) to become a reality, however, insurers would need to be willing to pay for a whole panel even if only one gene is needed at that time, she says.

“Pharmacogenomics is a bit different than many other genetic tests. We are not going to be uncovering something that the patient would not want to know. Although we can test multiple genes simultaneously, some providers or patients do not want information on all of the genes offered. Therefore, we continue to offer single-gene tests

where unneeded results are masked." She and colleagues collaborated with their IT staff to build in-house software for that purpose.

They also worked to enhance reporting capabilities. "Providers expect a visually appealing, user-friendly report," Dr. Moyer says. Most laboratory information systems are limited in their ability to generate attractive reports, and genotyping results need to be integrated into discrete fields for EHR functionality.

Mayo established clinical decision support rules for 10 genes and 21 drugs between 2013 and 2017. For example, a *CYP2D6* alert may say, "Metabolizer *CYP2D6* ultra rapid" in the center of the screen in large red type. The *CYP2D6* alerts apply to codeine, tramadol, tamoxifen, and several antidepressants.

Dr. Moyer and colleagues are now involved in a data-gathering project to explore stretching the boundaries of pharmacogenomics, from reactive testing—performed when the patient needs a medication—to preemptive testing. "It's time to try it," she says.

The information has to be preserved so it is available to future providers, implying long-term data storage. And future providers must know the data exist, which means easy EHR retrieval, and understand the results. The expectation is one-time testing, so broad testing is required.

An expectation to perform preemptive testing only once is challenged by the fact that most current tests are done by genotyping, but full-gene sequencing is becoming more powerful and less expensive. What happens when sequencing becomes more common for this application? Re-testing may be indicated when sequencing replaces genotyping, Dr. Moyer said.

There is also the question of when preemptive testing should be done. At birth? Adulthood? Age 40? At first prescription?

Despite the challenges of preemptive testing, Mayo is forging ahead with the Mayo RIGHT 10k project, a preemptive genotyping study that Dr. Moyer calls "research with clinical return of results." Its goal is to assess the impact of pharmacogenomic testing in clinical practice, including on provider workflows and patient outcomes. Implementing this study will allow the practice to establish the systems and processes needed for preemptive testing to be effective.

Subjects are 10,000 participants in the Mayo Clinic Biobank. "Biobank participants consist of healthy people and people with diseases, all of whom get care at Mayo," Dr. Moyer explains. Patients in the Biobank, many of whom are in their 50s and 60s but some of whom are younger, are followed and have consented to have their medical data used for research.

For RIGHT, 77 genes will be sequenced at Baylor, 13 of which will be clinically interpreted at Mayo. Variant information and interpretations will be entered into the EHR. At the outset, all of the clinical decision alerts currently in place will be available for providers. To enhance use of alerts, a broad educational campaign is being conducted among Mayo clinicians. Pharmacists will provide "e-consults"; in-person consults may be available as needed.

"This is a fun space to be working in right now," Dr. Moyer says. "It has the potential to benefit patients. We just have to figure out the logistics to make that happen."

Shands Hospital, part of the University of Florida Health System, instituted *CYP2C19* testing for clopidogrel in 2012. Three years later it began to offer *CYP2D6* for opioids, and in 2016 *CYP2C19* testing was expanded to the UF Health hospital in Jacksonville.

Clopidogrel testing checked all of the required boxes for pharmacogenomic testing at UF Health: evidence that genotype influences drug response, existence of a Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline, availability of an alternative drug, and payer reimbursement. Clinical trial data on clinical utility were

lacking, but for implementation at UF, this is not a requirement. Several approaches were taken to help fill the gap in evidence on outcomes.

A meta-analysis published in 2010 found that major adverse cardiovascular events and stent thrombosis during clopidogrel treatment were significantly higher in patients with a loss-of-function *2 or *3 allele. This did not prove, however, that genotype-guided dosing would reduce the incidence of adverse events.

To help address this, Dr. Cavallari, associate professor and director of the Center for Pharmacogenomics at UF, and colleagues did an observational trial at UF Health including patients tested for *CYP2C19* at the time of coronary intervention as part of routine clinical practice, with alternative therapy—prasugrel or ticagrelor—recommended for patients with a loss-of-function allele. In the first two years of the program, 408 patients were tested. Of these, 126 (31 percent) had a LOF allele and were poor or intermediate metabolizers. Of the patients with a LOF allele, 68 (54 percent) were prescribed alternative therapy. “It ended up that all of the poor metabolizers were put on alternative therapy,” Dr. Cavallari says. For the intermediate metabolizers, providers were a bit more skeptical about switching from clopidogrel to alternative therapy.

Does switching a patient to alternative therapy make a difference clinically? The data showed that it does: Patients with a LOF allele who were switched to alternative therapy had a much lower incidence of major cardiovascular events than those who remained on clopidogrel. In fact, switching LOF allele patients to alternative therapy reduced the incidence of such events to the same level as patients without a LOF allele who were mostly treated with clopidogrel.

Encouraged by these findings, Dr. Cavallari and colleagues at six other academic centers in IGNITE (Implementing Genomics in Practice), a network funded by the National Human Genome Research Institute, pooled data from patients genotyped across sites to examine outcomes with genotype-guided antiplatelet therapy. Of 1,815 subjects, 572 (31.5 percent) were found to have a *CYP2C19* LOF allele. Of those, 346 (60.5 percent) were prescribed alternative therapy. Outcomes were the same as in the University of Florida observational study: Patients with a LOF allele who were switched to alternative therapy had a significantly lower incidence of major cardiovascular events, a rate equivalent to that of patients without a LOF allele. This was true for intermediate metabolizers as well as poor metabolizers.

Dr. Cavallari

In genotyping of *CYP2D6* alleles for opioid prescribing, intermediate or poor metabolizers do not get the analgesic effect of the opioid whereas ultra-rapid metabolizers may experience toxicity. As with *CYP2C19*, there was evidence that genotype influences drug response, existence of a CPIC guideline, and availability of alternative drug or dosing, but data on clinical utility of genotype-guided opioid prescribing were lacking.

When primary care physicians requested implementation of genotyping of *CYP2D6* for codeine and tramadol in 2015, Dr. Cavallari and colleagues set up a prospective cluster design pragmatic trial to evaluate the effect of genotype-guided therapy on patient-reported pain outcomes. They enrolled 480 patients with chronic pain of more than three months duration. Genotyping showed that 10 percent were intermediate or poor metabolizers. After considering concomitant use of CYP2D6 inhibitors, 30 percent were intermediate or poor metabolizers. For those patients, alternative therapy was recommended in the EHR.

Changes in therapy within three months were made only 31 percent of the time they were recommended. “This was lower than what we’d like,” Dr. Cavallari says. She and colleagues understood why. “We collected genetic

samples in the clinic and it took a week for the genotyping results to come back. The patients might not be returning to the clinic within the study period. So the availability of the genotyping result at the time of the practitioner and patient encounter was crucial." This finding was the same for private practice sites.

Preliminary clinical outcomes data from this study were presented in March at the meeting of the American Society for Clinical Pharmacology and Therapeutics. Outcomes among intermediate and poor metabolizers in the implementation group taking codeine or tramadol at baseline were compared with those of similar patients in the control group. More patients in the implementation group had a clinically significant reduction in pain intensity compared with those in the control group—16 percent versus two percent—even though compliance with the recommendation to change was only 31 percent.

Based on these positive data from chronic pain patients, Dr. Cavallari and colleagues are about to start a trial in acute pain from hip or knee arthroplasty. "Patients have two visits prior to surgery. We will get a genetic sample at the first visit. The surgeon prescribes pain medication at the second visit. At that time genotyping data will be available," she explains.

Dr. Cavallari has joined in gathering rigorous data for two gene-drug pairs. "I personally don't think randomized controlled trial data are needed," she says. "But some level of evidence of benefit is needed for clinicians and payers. We can't afford to do clinical trials for every gene-drug pair."

In some cases, she adds, such as *HLA-B*1502* allele screening for risk of carbamazepine-induced Stevens-Johnson syndrome, "It would even be unethical."
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