At St. Jude, preemptive PGx tests guide prescribing

Karen Titus

April 2015—St. Jude Children's Research Hospital, Memphis, brings a razor-sharp focus to its mission: the 78-bed institution cares for children with catastrophic illnesses, including leukemias and lymphomas, solid tumors, hematology disorders (including sickle cell disease), and infectious diseases. It doesn't have an emergency department. Consistent with its goal of advancing cures, all its patients are enrolled in research protocols.

It makes sense, then, that St. Jude would bring a similarly sharp focus to its laboratory testing, in the form of therapeutic drug monitoring and pharmacogenetics testing.

Dr. Molinelli

It does so with a twist: Before TDM and genotype results are entered into patients' medical records, a clinical pharmacist tells clinicians what the results mean. "We don't release results into the record until the pharmacist has entered an interpretive consultation note for that result," says Alejandro Molinelli, PhD, director of the clinical pharmacokinetics laboratory at St. Jude.

The laboratory also pages the pharmacist once a result is ready. It's different from the usual routine, Dr. Molinelli says, "where basically results are posted to the medical record just by themselves, with no interpretive consult. If the ordering physician has a question, they usually call the lab and get any clarification." At St. Jude, "We're pushing an interpretation together with the results."

Among the tests: thiopurine methyltransferase *(TPMT)*, which is critical to managing thiopurine medications used to treat pediatric leukemia; and *CYP2D6*, which is involved in metabolizing a variety of common medications, including codeine.

"We have a fairly limited number of clinical genotypes that we are testing," says Dr. Molinelli. These tests are done at reference labs, an approach that works "because we have a manageable number of patients," he says.

Dr. Haidar

In 2011, St. Jude began a clinical research protocol called PG4KDS. The goal is to enroll every new patient at the institution and preemptively genotype each one, says Cyrine Haidar, PharmD, clinical pharmacogenetics coordinator at St. Jude. The testing, which is done at the Medical College of Wisconsin in Milwaukee, uses the Affymetrix Drug Metabolizing Enzymes and Transporters (DMET) Plus array supplemented by a *CYP2D6* copy number assay to look at 230 genes. "But we only report and result the ones in the medical record that have clinical

actionability," she says.

Dr. Haidar and colleagues (Hoffman JM, et al. *Am J Med Genet C Semin Med Genet.* 2014;166C:45–55) reported that through August 2013, 1,559 patients had been enrolled, with four gene tests released into the electronic health record for clinical use: *TPMT, CYP2D6, SLCO1B1,* and *CYP2C19*, which are coupled to a dozen high-risk drugs. Of 1,016 patients, 78 percent had at least one actionable genotype.

For all their promise, pharmacogenetics testing and therapeutic drug monitoring have moved into clinical practice somewhat awkwardly. The story is a familiar one: A new approach to testing comes along; promises about its potential fill the air; the orders roll in and results are delivered—then, crickets.

Dr. Haidar suggests that one reason pharmacogenetics has been relatively slow to ratchet up, at least in the United States, is that despite all the initial excitement at its promise, "Once they [clinicians] got the results, nobody had the training to interpret the results." Call it an early case of information overload. Says Dr. Haidar: "I know colleagues who work in cardiology institutions who used to tell me that cardiologists used to order certain genotypes—and they don't anymore, because they don't know how to interpret these results."

Making the pharmacist consults de rigueur probably helped to create strong physician buy-in from the start at St. Jude, Dr. Haidar says.

Dr. Molinelli says that acceptance of pharmacogenetics does seem to have come more easily at St. Jude than at other institutions. "Probably because of the value-added consult that the pharmacist gives to the physicians," he agrees. "A lot of times, if you are an ordering physician and you get a level, *What do I do with it? If it's low, maybe I can bump it up a little. If it's high, maybe lower it.* But having the consult guides them and gives them a pretty definitive recommendation as to what to do."

The success has also been a result of, and fostered by, what Dr. Molinelli calls an extremely close relationship between the laboratory and the pharmacists. In another twist, the laboratory is overseen by the Department of Pharmaceutical Sciences. "That makes the relationship a whole lot closer," he says—though such a setup would by no means be a prerequisite to successful pharmaceutical consults at other institutions, he adds.

The close partnership is apparent on a practical level. Like a journalist embedded with a military unit, for the laboratory that means "you basically go on the day-to-day operations," says Dr. Molinelli. He participates in weekly rounds, for example, which is a way for him to develop relationships with key pharmacists as well as glean feedback and learn their needs. Perhaps an assay isn't working as well as expected from a clinical standpoint, for example. Likewise, the laboratory can let the pharmacists and clinicians know if there will be delays in testing on a particular day.

From her perspective as one of the clinical pharmacists, Dr. Haidar also sees the upsides to having a strong relationship with those in the laboratory. "They're a huge asset," she says. Clinicians don't hesitate to contact the pharmacy with any questions related to TDM or genotyping, she says, because of the pharmacists' tight relationship with the laboratory. "We know who the people in the pharmacokinetics lab are. We see them all the time," she says. "We're in contact with them every day."

As if further proof is needed, Dr. Haidar notes that the laboratory is located on the fifth floor of the hospital, relatively close to one of the patient areas. "We're not in the basement—a lot of our lab has windows," Dr. Molinelli jokes.

St. Jude has moved smoothly through several chokepoints that can slow acceptance of pharmacogenetics testing. One is turnaround times. The preemptive approach virtually eliminates that problem, Dr. Haidar says. Once a patient has a St. Jude medical record number and will actively be treated at the institution, genotyping begins. "We have genotype results in the medical record before we ever anticipate [using] a certain drug," she says.

Nor is reimbursement a deciding factor for doing a test. The hope, of course, is that a patient's insurance will cover

the cost of testing. But if not, or if the patient is uninsured, the test is still done. Families never receive a bill from St. Jude for treatment, travel, housing, and food.

Doing pharmacokinetic and genotyping in the pediatric population does have some of its own challenges, however.

Dr. Haidar says she and her St. Jude colleagues have learned plenty from the adult pharmacogenetics/TDM world. In particular, she says, St. Jude has maintained a close relationship with those involved in pharmacogenetics testing at Vanderbilt University. The two institutions are part of the same consortiums and implementation groups. "We compare notes," she says. Despite the differences in patient populations, quite often the frequencies and actionability of genes are the same in both groups.

The recommendations for clinical care are often different, as is true for warfarin. The literature on warfarin genotyping targets exclusively—or nearly so—adult patients, Dr. Haidar says. When it comes to translating that to the pediatric population, the answer is simple if unhelpful: "We don't know how to do that yet," she says.

Since the laboratory literature in general skews toward adult patients, she continues, "We sometimes have issues with interpreting results. This has been one of our biggest hurdles. Extrapolation for pediatrics sometimes is easy, but sometimes it's not, depending on the drug and the gene."

The search for evidence continues to shape the program's growth. Call it a work in progress. Systematic pharmacogenetic testing for two genes began in 2007, with *TPMT* and *CYP2D6*, both of which were used for patients with acute leukemia—a tightly curated menu, to borrow from the aesthetically minded world.

The program's expansion has since evolved logically, step by step. Much of the guidance has come from the pharmacogenetics oversight committee. Members include pharmacists, clinicians, pathologists, and pharmacogenetics experts, as well as external advisory physicians, Dr. Molinelli says. The group is an effective check on clinicians' requests for new tests, he notes, since it scours the literature for evidence that will support their use. Members also review current clinical offerings regularly and change testing recommendations as new evidence emerges.

St. Jude also relies heavily on the Clinical Pharmacogenetics Implementation Consortium guidelines. When laboratory colleagues at other institutions ask for guidance in setting up a pharmacogenetics/TDM program, "I refer them to the guideline, always," Dr. Molinelli says.

Starting small, and moving at a deliberate pace, has been a conscious choice, says Dr. Molinelli, and has contributed to the program's success. "Start with several key genes for your patient population," Dr. Molinelli advises. At St. Jude, for example, it simply wouldn't make sense to make warfarin testing a cornerstone of a pharmacogenetics program. "You have to choose the tests you implement according to your patient population," he stresses. "You cannot just take a wholesale approach."
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