For pain care and more, PGx testing at Avera Health

Elizabeth Silverman

July 2018—Putting pharmacogenetic testing into play at Avera Health was years in the making. It took time to operationalize it at an affordable cost. Today, it has wide physician acceptance and is seen as a strong benefit for patients. “Pharmacogenetics is what will differentiate Avera in a new era of ACOs and personalized medicine, and will ultimately lead to a model for transforming health care,” says Trisha Lauterbach, MS, MLS(ASCP)^{CM}, laboratory operations manager at Avera Institute for Human Genetics (AIHG), Sioux Falls, SD.

Genetics and molecular testing are the paths down which laboratories are heading, notes Mike Black, MBA, MT(ASCP), DLM, Avera Health’s laboratory service line administrator. “Traditional testing—hematology, coagulation, urinalysis, microbiology, and the blood bank—is always going to be a part of the patient testing platform. But, as an added value, if research and the clinical side work together, pharmacogenetic tests will be of great benefit to physicians,” Black says, in their ability to reduce the number of medication-related office visits and see more patients.

Avera’s physicians knew the era of genetics had arrived with the sequencing of the human genome and that pharmacogenetics was important, says Erik Ehli, PhD, scientific director of the AIHG, the laboratory that performs the testing. They wanted a laboratory on the cutting edge of it. “In conjunction with our pharmacists,” Dr. Ehli says, “the [AIHG] laboratory took the ball and started running with it.” The AIHG isn’t aiming to do the basic research, he adds, but instead to leverage the existing knowledge and apply it to improving outcomes.

Avera is a nonprofit integrated health care system based in Sioux Falls and operates in more than 300 locations across South Dakota, Minnesota, Iowa, Nebraska, and North Dakota. Its pharmacogenetics program had its origin in 2006 with the building of Avera’s Behavioral Health Center. Timothy Soundy, MD, chair of the Department of Psychiatry at the University of South Dakota School of Medicine and a psychiatrist at the Avera Behavioral Health Center, proposed that a genetics laboratory be established to use pharmacogenomics to improve behavioral health outcomes. The laboratory, now called Avera Institute for Human Genetics, principally studied two genes, *CYP2D6* and *CYP2C19*, and their use in guiding prescribing decisions.

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In 2010, a real-world pharmacogenetics opportunity presented itself in the form of the South Dakota Developmental Center in Redfield, whose developmentally disabled patients with co-occurring psychiatric disorders were typically taking a large number of medications. “At that time,” Dr. Ehli says, “Dr. Soundy proposed a research

study to answer the question whether an analysis of the genes involved in medication metabolism could decrease the burden of the number of medications these patients were taking." The state of South Dakota funded the pilot project, and a first-generation microarray platform was used. "Based on the results," Dr. Ehli says, "we were able to reduce the medication burden for some patients."

The AIHG's success in the behavioral health setting led to a study of clopidogrel in 2012 in conjunction with the cardiologists at Avera Heart Hospital, and in 2013 to the clinical use of pharmacogenetics for pain management in Avera's surgical population. Lauterbach says 65 percent of the surgical patients had medication adjustment recommendations based on a genetic variant. The pain panel soon caught the attention of the then-president and CEO of Avera McKennan Hospital and University Health Center after a personal experience, and he became a source of high-level buy-in. "The buy-in has to start from the top," Lauterbach notes.

Physician champions arose out of the pilots conducted throughout the Avera Health system. "What we found," Lauterbach says, "was that if a physician had a positive outcome with a patient, they would begin to order the test consistently, and as they shared their experiences and spread the word, their colleagues would try it on a few patients as well. It has been a kind of snowball effect. After we were featured on 'NBC Nightly News,' we had patients from all over the world calling to have testing done."

But the Avera team had hurdles to overcome before pharmacogenomics could be integrated into the Avera Health system, including preanalytic hurdles. "How do we operationalize the preanalytic side across a five-state, six-region health care system?" Lauterbach asks. "How do we get the test there? How do we ensure the providers know about it and know how to order it?" At first the physicians were apprehensive. "It became clear we needed to make pharmacogenetic testing orderable in the same way as a CBC," she says.

Also important was a clear reporting format. "Pharmacogenetic testing has to fit into the existing physician workflow, and if it's exceptionally difficult to find the order, to order the test, or to find and interpret the results, you're not going to have a product that succeeds," Lauterbach says. "We started working with our electronic medical record and laboratory information system experts to look at how do we order this test, how do we report results, and how do we treat this like any other laboratory test that we offer in our health system."

In the end, the most efficient use of resources was to tap the expertise of the pharmacists, nurses, and laboratory personnel and to use them as the link in order entry and result reporting. Now, physicians from all over the health system order pharmacogenomic testing in Avera's EMR, and the sample is electronically tracked and processed like all other laboratory samples. Once the sample has arrived at the AIHG, laboratory personnel enter the genetic variants as structured laboratory results in the EMR's laboratory module, and the pharmacist pulls the results and the patient's medications and demographics from the EMR to create a personalized report. For the final report, the pharmacists evaluate the patient's genetics and current medications and offer recommendations in an easy-to-interpret stoplight format: A medication with a yellow or red indicator signals a moderate to significant drug-drug-gene interaction, and a medication with a green indicator signals minimal interaction. Even for physicians who had been reluctant, Lauterbach says, it was powerful to be able to offer tangible data demonstrating their drug of choice may not have the desired effect.

Which tests to offer was driven by Avera's physicians and what they were requesting. "Based on our research and our studies," Dr. Ehli says, "we started to see patterns with genes and SNPs and what medications our primary care and psychiatric physicians were ordering. So working hand in hand with the pharmacists, we were able to look at which ones were going to provide the maximum benefit to our patient population."

Turnaround time and price were challenging issues. "In 2014 we were using a microarray that had over 1,000 different genes on it," Lauterbach says, "but we were only using a handful. A patient would come to see a psychiatrist, who would order the psychiatric panel, and we had a turnaround time of two to three weeks and it cost $1,600 to $1,800, and insurance didn't cover it. That was a huge challenge. We knew we had a tool that could guide medication prescribing but couldn't get our physicians to order it—turnaround times were too long and it was too expensive."

At that time, the lab had nearly a decade of experience in molecular methods and tapped its expertise to move to a second-generation microarray in conjunction with PCR-based methods, which sped up the testing and lowered the cost of labor and reagents. The decrease in cost made it possible for the AIHG to offer the test to Avera patients for less than $200, a price with which patients and physicians were comfortable and that made it possible for Avera to cover the cost of the testing. (Insurers cover the test in certain cases, but not often.) The reduction in the time required for the second-generation microarray-based test meant Avera could offer results for genotyping panels for pain medication (*CYP2D6, CYP2C9, CYP3A4*) and clopidogrel (*CYP2C19*) in fewer than 10 to 14 days. In certain cases, when the physicians need rapid results, the AIHG has the capability to turn around results in one day by using PCR-based testing.

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Inpatient surgery has had great success with the pain genotyping panel, Lauterbach says. Surgical patients' blood is drawn when they arrive in the morning and is sent to the core laboratory, which then sends it to the AIHG. Testing and data analysis take about six hours. "By the afternoon, when the pain team rounds on a patient postsurgery, the pharmacogenetic results are in the patient's EMR," Lauterbach says. Clinical decision support alerts are used to educate physicians at the point of care.

Avera now also offers a preemptive pharmacogenetic test, GeneFolio, that is an integral part of primary care and for which the turnaround time is 10 days. The latest version of GeneFolio consists of 15 genes: *CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, VKOR1, SLCo1B1, OPRM1, COMT, SERT* (SLC6A4), *5-HTR2A, ADRA2A*, and *MTHFR*. In addition to genotyping, a pharmacist reviews each patient's medications and genetics, and a personalized pharmacogenomic report is provided to the physician in the EMR. "A patient may come in initially because of pain, but maybe in a year they experience depression or anxiety, so the results of the panel can be used again and again," Lauterbach says. "Just because a patient isn't going to be using a specific drug class at that very instant, at some point in their journey with Avera they are probably going to need at least one of the classes covered in GeneFolio, so it's in the patient's best interest to have testing done early."

Typically, GeneFolio is offered in an outpatient clinic setting—for example, presurgical—to patients taking several medications or to those not having success with their medications, especially in behavioral health. But it can be ordered in the hospital setting too.

Administrative buy-in was critical, Dr. Ehli says. The level and depth of the administrative support required became apparent in 2013 when the AIHG began to prepare for CLIA certification. Avera McKennan was the first hospital laboratory in the nation to become CAP ISO 15189 accredited, in 2008. "AIHG had the knowledge base of the latest

genetic tests," says lab service line administrator Mike Black, "and we had extensive knowledge in regulation and the standard protocols and policies and procedures. I think it was a perfect collaboration." The AIHG achieved its CLIA certification in 2014—a six-month process from application to certificate. CAP laboratory accreditation followed in January 2016.

Finding pharmacists with the requisite background to serve as the clinical intermediary is another challenge. Pharmacy and medical students rotate regularly through the AIHG's laboratory. "In pharmacy schools and medical schools throughout the U.S.," Dr. Ehli says, "there's going to have to be an increasing emphasis on pharmacogenetics," given the growing interest in how it can be used to help patients.

Dr. Ehli's area of expertise is also in next-generation sequencing, and while he is enthusiastic about the potential, he is realistic about the practical needs of his laboratory. "Additional information generated from sequencing could be an ethical concern, and based on how we are using evidence-based information to leverage scientific knowledge to create our panel, we see microarrays as the best solution at this time." Cost is also an important consideration because they don't want to exclude patients who are unable to pay. "However, we could leverage a lot more medical knowledge with sequencing, and as the price comes down, I firmly believe that next-gen sequencing will play a major role." At this time, however, "microarrays are what we see as a blend of cost and benefit. But in five or 10 years, who knows?"

It may become commonplace to sequence the genomes of all patients, Dr. Ehli says, and some Avera scientists and physicians would like to do so. "Then we could have all the information we need in terms of pharmacogenetics and risk for Mendelian disorders and so on, but right now microarrays are the best balance between cost, data, and turnaround time. But we always have our eye on sequencing for the future."

Also in the future are new tests to be added to GeneFolio. Among them may be genes that affect disease risk, wellness, and lifestyle traits. Ultimately, it is the needs of the patient that predominate. "We are always looking for ways we can help our patients and the community as a whole," Dr. Ehli says.

Elizabeth Silverman, of New York, NY, is a writer who covers genomics.