CHANGING THE DNA OF CLINICAL CARE

Genomics will transform medicine—but not until HIT translates data into knowledge

By Elizabeth Gardner

The most hyped scientific achievement of our time—the complete sequencing of the human genome in 2003—has taken awhile to make its utility obvious in clinical care. But consider:

•Nicholas Volker of Monona, Wis., has made it past the age of 5 because a full sequencing of his genome at the Medical College of Wisconsin revealed the rare genetic variant underlying the disease that was making holes in his intestines—an answer that had eluded all standard genetic testing. The research team also confirmed that his particular genetic profile made a bone marrow transplant the right treatment choice. Nicholas hasn't had an intestinal surgery since then—after enduring 100 of them before the diagnosis—and can eat real food. The medical college now reviews a steady stream of requests to sequence the genomes of children with mysterious diseases.

• Lukas Wartman, M.D., of Washington University in St. Louis, developed the leukemia that he had been studying as a researcher. His prognosis was grim until a sequencing of both his genome and his cancer's genome suggested that a drug hitherto approved only for kidney cancer might be effective. He's now in remission and doing well, and his physician, John DiPersio, M.D., says he can't keep up with the thousands of e-mail inquiries generated by a recent front-page article in *The New York Times*.

•The Mayo Clinic is now assuming that eventually it will sequence the genomes of every patient who walks through the door. Its Center for Individualized Medicine will officially open a clinic later this month, and the center's "Clinomics" program is specifically intended to develop ways to translate the genome's unwieldy mass of data into information that physicians can use to diagnose and treat. Clinomics co-director Eric Wieben says Mayo has been using sequencing techniques to guide therapy for cancer patients, and the new clinic will begin by focusing on cancer and "diagnostic odysseys"—cases where the patient hasn't been able to get a definitive diagnosis on a disease that might have genetic origins.

Now that the science of genomics has been refined to the point it can have widespread impact on clinical care, it's up to health I.T. to push it to the front lines. To that end, there's still a lot of work to be done, but experts predict it's going to happen a lot sooner than most HIT leaders think.

Endless questions

Sequencing the genome has generated an endless series of questions. Which gene does what? How do they interact with one another? Why does one gene affect health while another lies dormant? What's the significance of the million tiny variants—deviations from the "standard" genome—that each person's genome contains? Which diseases are the result of different combinations of 15 or 20 or 100 variants—or even more? Which variants are clinically significant, and which are just so much noise? Every answer is a potential clinical tool, and they're coming thick and fast.

The cost of sequencing is dropping sharply. When Nicholas Volker had his genome sequenced in 2009, it was a million-dollar affair. Now, it's more like $10,000, and new technologies hold the promise of a $1,000 sequencing within the next few years. But Wieben says sequencing itself may turn out to be a minor cost compared with analyzing and using the data. "The size of the processing capability is significant," he says, noting that the high-performance computing built for Mayo's research is now being enhanced to support the use

Photo Illustration by Engine Collective

of genome data in clinical care.

Millions of gene variants have been identified—some significant, most not. It will fall to medical informaticists to boil down a given patient's data to the few hundred variants that might be connected to the correct diagnosis or choice of treatment for the medical problem at hand. Jim Buntrock, who serves as the center's I.T. director in addition to several other roles at Mayo, says he's been told to expect to be able to sequence, analyze and store up to 200,000 complete human genomes over the next five years.

That's far beyond his capacity at the moment (though he says the time to sequence a genome is down to about 27 hours), but Mayo partners with several supercomputing centers and will also be expanding its in-house processing and storage capacity. It's also working with its major EHR vendors, Cerner and GE, to figure out how to build genomics information into clinical decision support, and Buntrock hopes to be able to supply that capability to other providers. "Now we have to start thinking architecturally, figuring out the number of variants that we might be managing as an extension to the patient's medical record."

A new standard

Whole genome sequencing and its relatives, like exome sequencing (see glossary, page 28) build on the single-gene and gene panel testing in use since the 1990s, and may eventually render them obsolete. They're likely to become the standard of care within the next decade, for purposes such as:

•Diagnosing patients like Nicholas Volker whose complex illnesses point to a genetic source but resist diagnosis by more common genetic tests.

•Identifying the best strategies to fight a certain cancer based on its genomic profile.

•Identifying drug sensitivities (both good and bad—some gene variants suggest that a drug will work beautifully, while others warn of severe adverse reactions).

•Differentiating between variants of diseases such as cardiomyopathy, to target the best treatments and to start preventive steps in patients whose family histories suggest that they're at risk.

Experts caution, however, that it's going to take awhile before genome sequencing is a routine part of clinical practice for most physicians.

"For those of us who study rare diseases, genome sequencing is nothing short of revolutionary," says James Evans, M.D., who directs the Clinical Adult and Cancer Genetics Services at the University of North Carolina and also edits the journal *Genetics in Medicine*. "But as someone who also practices general medicine, I wouldn't yet call it revolutionary in a real-world sense." Evans thinks all providers should be aware of situations where genome sequencing and related testing would be useful, and identify an appropriate lab to do those tests, even if the volume is fairly low at the moment.

Ten years out, though, Evans can envision using genome sequencing even for preventive medicine, such as flagging people who have clear dispositions to develop a given disease. For example, a patient with the genomic variant for Lynch syndrome, which radically increases the risk of colon cancer, could be scheduled for a yearly colonoscopy and routine removal of precancerous polyps.

DiPersio, who cares for Lukas Wartman at Washington University, is cautious—not about the science itself, but about the snake oil purveyors who inevitably spring up around such a major scientific advance. He recalls the craze about 20 years ago for testing tumor tissues to create individualized chemotherapy regimens. A cottage industry of charlatans with shaky science—or none—gave false hope to cancer sufferers. "These tests are going to be cheap enough that you'll start seeing that approach," he says. "There will be the same army of guys delivering information that's either idiotic or confusing." He expects a significant time lag between research discoveries and the ability to use them to help patients.

Marc Williams, M.D., director of the Genomic Medicine Institute at Geisinger Health System, agrees that there's such a thing as too much, too soon. He points to a case where a patient used a direct-to-consumer genomic test to discover that he had an increased risk for prostate cancer, and then circulated among physicians until he found one willing to do a biopsy that showed a cancerous prostate. "He went around saying, 'This test saved my life!'" Williams says. "But if everyone did that, a lot of people would be treated for indolent cancers that would never have become a threat, and they'd be incontinent and im-

When Will Insurers Cover Genetic Testing?

Though insurers don't routinely cover genome sequencing, at least not yet, it's not the cost as such that makes them shy away, says Susan Pisano, spokeswoman for American's Health Insurance Plans. She points out that insurers cover all kinds of expensive services—if they're medically necessary and proven to be effective. The industry uses the following criteria for covering tests:

•Is there a clinical basis for suspecting that the patient has the disease being tested for?

•Is the test validated and reviewed by peers?

•Is there a treatment if the test is positive?

•For genetic testing, will the patient undergo genetic counseling afterwards?

Pisano says that for the most part, insurers are waiting for government and professional organizations to evaluate the evidence for genome sequencing and related tests and treatments, and for solid practice guidelines to be developed. The exception is testing for the BRCA1 and BRCA2 genes that are associated with a high risk of breast cancer. Patients don't have to be exhibiting symptoms of the disease in order to be covered for the test as long as their family history suggests that the genes might be involved.

potent for nothing. We have to understand how to use this information effectively."

In many ways, genomic information is no different from any other personal health information, like a lab result or a family history. Its privacy needs to be protected, it has to be translated into a useful form for clinicians, it has to be stored, and it has to be shared.

The difference is primarily one of degree. An unusually large pile of data contains a few useful and potentially life-saving nuggets of information. And unlike most health information, the same pile of data can be mined for additional nuggets for at least the next several decades, as the genomic knowledge base grows.

Most providers will farm out genomic sequencing to independent labs or to large academic medical centers that may also handle the initial translation of the results into actionable information.

Baylor College of Medicine in Houston does exactly that for genomic tests, says Jeffrey Reid, assistant professor in its Human Genome Sequencing Center. The center reports what he calls "very digested data objects" that address only the issues that prompted the physician to order the sequencing. "Genetics does not yet do well with 'healthy people' testing, where there's nothing wrong with you or your genome, but there are signals that you have higher risk for breast cancer," he says. "Currently I think you can do that better with a very detailed family history. But that type of data will get better and better as more databases are built."

Looking ahead

Health information technologists should be planning for a huge change within the next three to seven years, says Sandy Aronson, executive director of I.T. at the Partners HealthCare Center for Personalized Genetic Medicine. "This switch is going to happen very quickly when it happens, and it's important to start the process of planning how additional genetic support is going to be built into your electronic health record," he says. "Start planning now." Aronson and his team developed software called GeneInsight to provide exactly that type of support and have integrated it into EHRs used at both Partners and its research collaborator Intermountain Health Care.

Here are some things to look at in planning for EHRs for the genomics age:

Better family histories. "Family history has not been well represented in many EHRs," says Greg Feero, M.D., special advisor to the director for genomic medicine at the National Institutes of Health. He also practices family medicine in Maine, and his job is to help figure out how genomics will fit into everyday practice.

He says a more robust, structured family history could end up as a Stage 2 meaningful use requirement, specifically so that EHRs will be genome-ready.

Intermountain Health Care's Clinical Genetics Institute is developing an elaborate, Web-based family history tool that patients can use to build elaborate pedigrees, with each ancestors' diseases, date of onset, and cause of death. Grant Wood, the institute's senior information technology strategist, says all that information will go into the EHR, to help clinicians choose appropriate genetic and genomic tests and make sense of the results.

Enhanced clinical decision support. David Dimmock, M.D., the pediatric geneticist who identified the gene variant that plagued little Nicholas Volker, believes very little genomic information, as such, will end up in the EHR. Instead, he wants a built-in risk calculator that signals the physician when a pattern of family history and physical symptoms indicates that a genomic test might provide useful answers. Once a patient's genome is on file, its information should be available as needed.

"Our providers say they don't want a lot

Genome Glossary

Base pair: Two amino acids whose bond forms one of the "rungs" of the ladder-like structure of genetic material.
Exome: A subset of the genome that makes up about one percent of the total genetic material but contains about 85 percent of the gene variants that cause disease. The exome includes only the exons, or the parts of the genes that provide the blueprint for the production of proteins. There are about 180,000 exons in the human genome. Sequencing the exome is quicker and less expensive than sequencing the whole genome.
Gene: A section of a chromosome that's active. The human genome has an estimated 20,000 to 25,000 genes, which compose only about 2 percent of the genetic material.
Genome: All the DNA, or genetic material, in the nucleus of a cell. The human genome has 23 pairs of chromosomes with about three billion base pairs of amino acids in all.
Microbiome: The genomes of microorganisms. The human microbiome includes the genomes of all the microorganisms found in the human body.
Pharmacogenetics: The science of using gene information to identify which drugs will work well for a given patient and which may cause adverse reactions.
Proteome: The set of proteins expressed by a genome, cell, tissue or organism. Unlike the genome, the proteome changes frequently in response to changes in the environment.
Single Nucleotide Polymorphism (SNP): A change in a single base pair that distinguishes one person's genome from another's. Millions of these variants have been identified by comparing genomes from many individuals. Everyone has a million or more SNPs. Some SNPs have no apparent effect; others are associated with diseases or drug sensitivities, either by themselves or in combination with other SNPs.
Transcriptome: The set of all RNA molecules, also called "transcripts," that carry out the instructions coded into DNA.
Variome: The set of all possible variants from a standard reference genome. The Human Variome Project, based in Australia, and the International HapMap, a collaboration among several countries, are two efforts to catalog all the variants in humans.
Whole Genome Sequencing: Determining the precise order of the three billion amino acid pairs that make up the genome, and identifying single pairs or sequences of pairs that distinguish one person's genome from another's.

of data," he says. "They want just-in-time reminders. If they put in a diagnosis of depression, they want a flag that this or that drug would be better, given the person's genomic information."

Storage. Each genome takes up the equivalent of a terabyte drive. Though the medically relevant variations may eventually boil down to a much smaller file, it's still a lot of data. One strategy would be to store genomes the way a PACS stores images. But Intermountain's Grant Wood hopes to keep genome data from becoming one more silo.

"If we're going to assume patient-centered care, then we have to consider a repository that's outside of any particular health care system," he says. "No matter where you go, any doctor's EHR should be able to link into that repository and get your information. That information is valuable for your whole lifetime, and a whole genome test with no access by other providers doesn't help anyone."

Standardized knowledge. Cracking the human genome is perhaps the first major medical advance ever that could lead to a single knowledge base shared by all providers, and quell the wild variations in practice patterns that have been a contributing factor in the inefficiency of U.S. health care.

NIH's Feero says the Department of Health and Human Services is looking at how to create a "gold standard" reference interpretation of all genomic variations.

"The question still looms about how to interpret [genomic] information over time, and how to ensure that the interpretation is the same in Seattle as in central Iowa," he says.

Ultimately, genomic testing will transform all of medicine the way it has already started to transform cancer treatment. The most common medical problems, like type 2 diabetes and cardiovascular disease, may turn out to be multiple diseases that respond to targeted treatments.

"We have at least a decade of hard work teasing apart this mass of data," says Marc Overhage, M.D., chief medical informatics officer for Siemens Healthcare. "It will be a slow evolution—almost invisible—but then suddenly we'll look back and wonder how we could ever have seen coronary disease as just one thing." ■