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A Very Personal Problem

Now personalized genetic medicine offers tests to avoid dangerous drug reactions—yet doctors are reluctant to use them.

By Dina Fine Maron on **May 17, 2016**

IN BRIEF

- About half of all medical patients get a drug, in any given year that could interact with their genes and cause serious side effects.
- Inexpensive gene tests, as yet only available in a few hospitals, could avoid these life-threatening problems.
- Yet lack of insurance reimbursement and confusion over when and how to alter drug prescriptions hold back tests' widespread use.

Korei Parker is a boisterous seven-year-old with an infectious smile who improvises her own songs and loves to share them out loud. On an April day two years ago in Memphis, Tenn., where she lives, Korei came home from school with strange bruises. She had bumped into some things, she said—maybe a desk—but not hard enough to cause deep marks. Her mother, Rhonda, called their pediatrician and set up an appointment for later that week. But the next morning Korei woke up with new splotches across her arm and forehead. And when Korei brushed her teeth, her gums started to bleed.

Mother and daughter rushed to nearby St. Jude Children's Research Hospital. Doctors there figured out Korei was not producing enough new blood cells, which causes uncontrolled bleeding, bruising and infections. The illness is called severe acquired aplastic anemia.

The girl was quickly put on several drugs to boost her blood cells and fight infections. St. Jude doctors also did something unusual: They tested Korei for some 230 genes that affect which drugs—and what doses—would work best in her body. Certain gene variants can trigger the body to break down medications very quickly. In such cases, even high drug doses may fail.

Because of her particular genetics, the tests showed, Korei broke down voriconazole—a drug doctors had initially prescribed to stave off fungal infections—too fast. "She took adult dosages, and it didn't seem to do anything for her," Rhonda says. Her daughter had not contracted a dangerous fungus yet, but she was vulnerable, and her body would not be able to fight back. So physicians switched to another drug that interacts with bodily enzymes made by different genes. Korei's body processed that drug normally, and she remained infection-free.

Tailoring treatments to genetic makeup is part of the futuristic vision of personalized medicine, where all care is custom-fit to an individual's DNA. Remarkably, part of that vision—genetic drug matching, called pharmacogenomics—is already here. Korei Parker benefited from it. Although total human genome sequencing costs $1,000, getting drug-gene results on a few hundred genes at St. Jude costs about half that much for each patient. ***"The era of precision medicine is upon us," says Dan Roden, assistant vice chancellor for personalized medicine at Vanderbilt University Medical Center. "The low-hanging fruit here is pharmacogenomics."***

Unfortunately this fruit is being plucked by only a handful of hospitals. Lack of insurance coverage for the tests, along with confusion among doctors about what to do with the genetic data, is preventing the exams from being widely used.

The sad result, advocates say, is that people are getting sick needlessly. Between 5 and 30 percent of the global population is estimated to have the same troublesome gene variant as Korei, for example, and it affects how well people respond to multiple medications, not just voriconazole. ***Roughly 50 percent of hospital patients get a drug in any one-year period that could cause serious side effects because of that person's genetic makeup, according to analyses from St. Jude and Vanderbilt.*** One study at Vanderbilt, which examined only six drugs, estimated that drug-gene tests could eliminate some 400 adverse events in a patient population of 52,942. ***If tests were performed for more than six drugs across the U.S. population, that number of avoided ailments would likely climb into the hundreds of thousands.***

SHOTS IN THE DARK

Doctors are not accustomed to making medication choices using genetics. What they have done, for decades, is to look at easily observed factors such as a patient's age and weight and kidney or liver functions. They also considered what other medications a patient is taking and any personal preferences.

If clinicians would consider genetics, here is what they could learn about prescribing the common painkiller codeine. Typically the body produces an enzyme called CYP2D6 that breaks down the drug into its active ingredient, morphine, which provides pain relief. Yet as many as 10 percent of patients have genetic variants that produce too little of the enzyme, so almost no codeine gets turned into morphine. These people get little or no help for their pain. About 2 percent of the population has the reverse problem. They have too many copies of the gene that produces the enzyme, leading to overproduction. For them, a little codeine can quickly turn into too much morphine, which can lead to a fatal overdose.

These types of drug-gene interactions explain some long-standing medical mysteries. As early as 510 B.C. Greek mathematician Pythagoras (of geometry-class fame) found that when some people ate a particular type of bean they would get hemolytic anemia, a potentially deadly condition in which red blood cells are destroyed and removed from the bloodstream. Some 2,500 years later researchers discovered why that reaction occurred: these people inherit genetic variants that lead to a deficiency in the production of an enzyme called glucose-6-phosphate dehydrogenase (G6PD). That substance normally prevents red blood cell destruction. That very same genetic variant—which can be spotted with today's gene tests—also predisposes patients to hemolytic anemia if they take several drugs now on the market, including rasburicase, a medication often given to patients with leukemia.

Many such drug-gene interactions—both severe and subtle—could be avoided by taking different doses of the drugs or turning to substitutes. ***Researchers concluded in October 2015 in Nature that there are 80 medications—affected by about two dozen genes—with known alternative treatments.***

Some of the major recent research milestones about drugs and genes have been reached at St. Jude by Mary Relling, chair of the pharmaceutical sciences department. St. Jude sees a lot of pediatric cancer patients, and because many potential problem drugs are chemotherapy medications, the hospital was worried these children could be hurt by genetic interactions. Relling and her colleagues conducted years of drug-gene tests on a small scale. **Then, in May 2011, she spearheaded the effort to start testing all new St. Jude patients.**

The hospital also has a major advantage over others: it does not have to worry about insurance companies paying the institution back for these gene tests or denying the claims and making patients themselves pay. Patient care is paid for primarily by donations and grants. Thanks to that financial certainty, whenever a new patient starts care, St. Jude tests a blood sample for more than 200 genes.

By March of this year the hospital had data in almost 3,000 patients' electronic medical records corresponding to seven genes and 23 drugs that are well understood and affect its patients. One record belongs to Eden Brewer, a five-year-old girl who was diagnosed with acute lymphoblastic leukemia at the hospital last year. Fortunately, her gene test results did not reveal any mutations that would require the doctors to change their treatment plan. But they did reveal she might have trouble with other drugs later on in life. One is called simvastatin, used to manage high cholesterol. Eden, it turns out, has a variant form of a gene, known as *SLC01B1*, that would keep her body from effectively processing the drug. For reasons that are not yet fully understood, that problem sometimes leads to life-threatening muscle damage. Simvastatin is a frequently prescribed drug, but Eden needs to stay away from it.

"It's exciting to have that kind of knowledge," says her mother, Nicole Brewer. "We have this new tool in our belt not just for while we're here at St. Jude but for her whole life—forever." If a doctor at St. Jude ever tries to prescribe this medication, a warning box will pop up on her electronic record.

FAIR WARNING

Vanderbilt University Medical Center is one of the few other institutions in the country that is using pharmacogenomics to help its patients. Roden, the personalized medicine head, likes to tell the story of the center's first patient to benefit back in 2010. The 68-year-old woman had been coming to Vanderbilt for care after a heart transplant, and her doctor had inserted a stent to prop open one of her blood vessels. Then he tried to prescribe clopidogrel, a drug typically used to prevent in-stent blood clots. When he typed the medication name into her electronic medical record, however, an alert popped onto the screen stating the patient's gene tests indicated she would metabolize the drug poorly. The alert was part of Vanderbilt's then new effort to experiment with pharmacogenomics. It suggested another drug, prasurgrel, which would not run afoul of these genes.

Six years later Vanderbilt continues to focus on heart patients because it has been able to document several genetic effects on cardiac medications. ***One hospital analysis, looking at more than 9,500 of its patients, found that 91 percent had at least one gene version that would prompt doctors to recommend a change in dose or medication.*** A subset of those patients—roughly 5 percent—had two copies of genes that would boost their chances of conditions such as stroke or heart attack from a clot if they took those medications at standard doses.

Vanderbilt, like St. Jude, has mostly shouldered the costs of these tests because of the insurance problem. The insurance companies say they will cover only some tests because not all have been definitively shown to improve clinical outcomes. "Coverage does vary for these tests as a result of limited clinical evidence around their effectiveness for patients," says Clare Krusing, a spokesperson for America's Health Insurance Plans, the national trade association for the health insurance industry.

There are signs that this skepticism is beginning to soften. Vanderbilt officials say that in the past few years reimbursement policies from some insurers have evolved, and companies have started to cover a small percentage of the costs. Other hospitals are taking note. Several years

after Vanderbilt started offering tests, the University of Maryland Medical Center started offering them, too—though, like Vanderbilt, usually just to cardiovascular patients. That institution has used clinical research grants from the federal government to cover the testing costs for more than 600 patients. But Maryland hopes to change over to billing insurance companies soon, according to Amber Beitelshees, one of the people heading up the Maryland effort.

Still, fewer than 10 hospitals around the country—including Maryland, Vanderbilt and St. Jude—are offering pharmacogenomic tests to certain patients. The other main obstacle to wider use, besides reimbursement, is the lack of a prescribing road map. Many doctors were educated in an era before such testing was available so they do not even think to order them. And a lot of physicians would likely find they are not equipped to understand the results. “You need more than this raw information—you must build the informatics tools—decision-support systems,” Roden says. A busy doctor needs to be told the patient had genetic testing for certain variants, what the tests found and be given easy-to-understand guidance on what prescribing changes could be made, he notes.

St. Jude pharmacists work on alerting doctors about alternative medications. The hospital also has created fact sheets about the significance of particular genetic variants, and those sheets are given to patients with any test results.

What the FDA does not monitor are in-hospital tests such as the ones at St. Jude. In the 1970s, when regulations for hospital-developed tests were first crafted, such diagnostic probes were relatively simple, and it seemed adequate that tests were developed at federally certified laboratories. Now that complex genetics are involved, and the tests are being used more often, the FDA has proposed stepping up its oversight. So far, however, it has no timeline for putting changes into action.

The situation, like insurance acceptance, may be slowly changing. At the moment, Relling is co-directing a research group—supported by funds from the National Institutes of Health—to carefully document any new drug-gene relations solidified with new research. With that information the scientists set standards about what genes should typically be tested and spell out what prescribing changes should be made based on test results. The standards they develop are intended to be given to other labs at other hospitals.

As more of these tests are done and show patient benefits, experts hope the obstacles and resistance will shrink and eventually disappear. When more physicians learn about the problems with genetic interactions, Relling believes, they will be reluctant to prescribe drugs without the tests, and that will force more offerings from more institutions*. “If you knew about this genetic information and you did not act on it,” she says, “you would not be practicing good medicine.”*