THE NEW YORKER

THE PROBLEM WITH PRECISION MEDICINE

By Cynthia Graber February 5, 2015

The excitement surrounding personalized, genetics-based medicine has so far outpaced the science.

Photograph by Dilip Vishwanat/The New York Times/Redux

Last Friday, in a speech at the White House, President Obama unveiled what he called his Precision Medicine Initiative, a two-hundred-and-fifteen-million-dollar plan to collect genetic information from a million American volunteers in order to further the development of personalized, genetics-based medical treatments. Obama called precision medicine "one of the greatest opportunities for new medical breakthroughs that we have ever seen," saying that it promised to deliver "the right treatments at the right time, every time, to the right person." So far, however, the excitement surrounding personalized medicine has outpaced the science. DNA testing has become increasingly useful in the detection and treatment of various conditions, including cancer, intellectual developmental delays, birth defects, and diseases of unknown origin, and the cost of genetic analyses has dropped even as the speed with which their results are delivered has risen. Nevertheless, for most people, genetic medicine is not yet delivering customized care. As scientists continue to draw connections between DNA data and health outcomes, the problem of interpretability continues to grow. Many doctors are simply not qualified to make sense of genetic tests, or to communicate the results accurately to their patients.

David Miller, a geneticist at Boston Children's Hospital, ran into that problem last fall, when a couple brought their five-year-old daughter to see him. The girl had poor coördination and was short for her age, and she was prone to infections. Her previous physician had ordered a DNA test to determine whether her physical developmental delays were tied to a known genetic condition. If they were, perhaps the results could suggest a course of care. When the test came back, it showed a missing fragment of code on chromosome 22—the telltale marker for something called DiGeorge syndrome. The prognosis that the physician gave the girl's parents was dire: common symptoms of DiGeorge

include learning and growth delays and heart defects, and patients are at an increased risk of developing psychiatric disorders such as schizophrenia. There is no known cure. When Miller reëxamined the test results, however, he noticed that the deletion on chromosome 22 was not in the same location as the one that causes DiGeorge; it was likely an insignificant genetic blip. The girl did not have the syndrome, and, her parents were relieved to hear, there was no need to monitor her heart and mental health.

Mistakes such as the one that Miller caught are unfortunately common, according to the medical geneticists and genetic counselors with whom I've spoken. (Medical geneticists are physicians who have gone through medical school and then trained in genetics; genetic counselors have obtained a specialized master's degree.) And those mistakes can cause greater harm than merely stoking the anxieties of a sick person or her parents. A 2012 study in **The Cancer Journal**, for instance, describes the case of a woman who underwent extreme surgery, including the removal of her uterus, because of an incorrect reading of her genetic-test results. The risks of misinformation extend to maternity care, too. Noninvasive prenatal screenings, which analyze shreds of fetal DNA in a pregnant mother's blood, are not always as definitive as some doctors and parents like to imagine. Last month, Aleksandar Rajkovic, the director of reproductive genetics at Magee-Womens Research Institute, at the University of Pittsburgh, published a paper in which he documented another incorrect identification of DiGeorge syndrome that resulted from one such screening. As with Miller's patient, the test had determined that a chromosomal deletion existed, but it couldn't say precisely where.

Part of the dearth of genetics expertise among physicians stems from the fact that many of those currently practicing went to medical school before the

human genome was sequenced. Mary Norton, a clinical geneticist in the field of high-risk obstetrics at the University of California, San Francisco, told me that when she took her board exams, about twenty years ago, she had to memorize all of the genes that had been identified and associated with diseases. At the time, there were fewer than a dozen; now a single panel might test for a hundred. "It's very complicated, especially for generalists, who have a million other things on their minds besides genetics," she told me. Norton is a full-time geneticist, but she admits that the volume of new research remains daunting. When she's scheduled to give a talk, she reviews the literature a few days beforehand; otherwise, she says, she'll likely miss something new.

In theory, doctors could turn to specialists to fill in their gaps in knowledge, but, depending on where they live, they may be hard pressed to find someone qualified. According to the American College of Medical Genetics and Genomics (A.C.M.G.), there aren't enough trained medical geneticists to fill all the jobs currently on offer. As a result, according to Rajkovic, doctors in need of an education in genetic tests receive instruction from the testing companies themselves—the same companies that, as he notes in his DiGeorge case study, tend to push new products without sufficient evidence of their efficacy. "In this race to offer more value, they are jumping the gun, in my opinion," Rajkovic told me. Many geneticists also pointed out that companies' marketing materials make it seem as though the tests are infallible. As the testing firm Sequenom puts it in one advertisement: "Positive or negative results. Never maybe."

General-care physicians seem to understand that their lack of training is a hindrance. Last fall, a survey appeared in the journal **Genetics in Medicine** that examined data from thirty-eight other studies; a majority of respondents expressed reservations about not fully understanding test results or not being

able to devote the time necessary to discuss testing options and outcomes with patients. There are a number of initiatives under way to fill the breach, one of which is a project called MedSeq, which was launched by a medical geneticist named Robert Green, of Brigham and Women's Hospital and Harvard Medical School, in Boston. As part of MedSeq, interested physicians recruit patients to have their genomes sequenced. Each genome analysis gets summarized in a report, which the doctors are taught how to evaluate and explain to their patients. The doctors' patient interactions are recorded, and geneticists listen to the audio after the fact and inform the doctors when they've made a mistake. Martin Solomon, a MedSeq participant and a physician at Brigham and Women's, admits that he's made mistakes. (Solomon calls his patients to let them know.) "That's why the MedSeq study is so important," Solomon said. "The data is going to be there. We have to figure out how to make that data usable in a constructive way, and to make physicians comfortable with it."

For Solomon, genetics is simply a new tool with a learning curve, the same as any other. "When the electrocardiogram was first developed, about a hundred years ago, most physicians thought it was voodoo," Solomon said. "Now, if you don't understand it, then you shouldn't be practicing medicine." But Mary Norton sees that analogy as too simplistic. The pace of genetics research, the variability of test methods and results, and the aura of infallibility with which the tests are marketed, she told me, make this advance a more complicated one than the EKG. Norton believes that, as genetics becomes increasingly integrated into medical care, "over time everyone will come to have a better understanding of genetics." But, as the demand for DNA testing increases, she says, "it will probably be a bit worse before it gets better."

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