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The flip side of personal genomics: When a mutation doesn't spell disease

Researchers worry about misinforming people about the risk of disease.

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The same genetic mutation may affect some people more severely than others.

What started as a summer science project soon turned into a family medical crisis for geneticist Heidi Rehm. In July, she ordered a test to sequence her 14-year-old daughter's DNA, hoping to find a genetic explanation for why one of the girl's adult teeth hadn't emerged. Instead, mother and daughter found that they both carried a genetic mutation linked to dilated cardiomyopathy — a heart-muscle abnormality that can lead to sudden death, especially in adults.

After consulting a cardiologist and investigating her family's mutation — which had been seen only in people with diagnosed cardiomyopathy — Rehm found that it might not be as lethal as it had first seemed. Her story shows how far genetic sequencing still has to go before it becomes a routine part of medical care. Although scientists are using sequencing to save sick people's lives, many still question whether it helps those without a diagnosis.

Because most genes linked to disease were discovered in ill people and their families, geneticists don't have an accurate understanding of how mutations behave in people who are not obviously sick. "This is a fascinating flashpoint in the field right now," says Robert Green, a geneticist at Brigham and Women's Hospital in Boston, Massachusetts. "Many people are deeply concerned that widespread screening of ostensibly healthy people could actually lead to harm."

Green is an organizer of the Understand Your Genome conference, due to take place on 15 November in Boston, which will bring together scientists and physicians to debate such issues. About 40 of the 140 attendees paid US$2,900 to have the protein-coding portions of their genomes sequenced by Illumina of San Diego, California — giving them a personal connection to concerns about misdiagnoses.

Perfect storm

Concerns about the potential harm in sequencing the genomes of healthy people come as new companies vie to provide such services for the general public.

In August, researchers reported that the average person carries about 54 genetic mutations that are considered lethal, but that don't seem to harm their health. As a result, physicians don't know what to tell healthy people who harbour these variants.

Some people have received erroneous information as a result, says physician and bioinformaticist Isaac Kohane at Harvard Medical School in Boston. He led a team that reported in August that some African American people had wrongly been told a decade ago that they harboured genetic mutations that increased their risk of developing hypertrophic cardiomopathy, a potentially fatal thickening of the heart muscle. Geneticists later sequenced many more African Americans, and realized that the genetic variants were too common in this population to be harmful[1].

"We really have a perfect storm of insufficient data and insufficient competence," says Kohane, who adds that physicians aren't yet prepared to handle genetic test results of this type.

Green and other researchers are trying to remedy the information deficit. In a study published on 9 November in *Science Translational Medicine*, for instance, Green's team found that people who carry genetic variants linked to heart disease and cancer are four to six times more likely to develop those conditions, regardless of their family history of the diseases. Green says the study is important because it's one of the first times that scientists know how much a mutation might increase the risk of a disease in a family with no known history of it[2].

"I'm often in a position of sitting with a family, and they say, 'How much does this increase my risk?'," Green says. "It's something we have virtually no data on in the general population."

Insurance concerns

Rehm faced precisely that situation when she found out about her family's mutation. It involves a switch of one DNA base for another in the *MYH7* gene, which encodes a heart-muscle protein, and had only ever been seen in patients with the disease.

When Rehm hunted down reports of people with the same variant, she found that it does run in families with cardiomyopathy. But she also discovered that her own mother also carries the variant, and has normal heart function, as does Rehm. This suggests that the variant has what geneticists call incomplete penetrance: it is capable of causing severe disease in some families, yet is harmless in others.

It's not clear what Rehm and her daughter should do with the information. Rehm hasn't had her daughter's heart tested yet, because symptoms of cardiomyopathy usually don't appear until adulthood. But she is concerned about the girl's future.

If her daughter's medical record states that she carries a potentially fatal genetic mutation, she may not be able to buy life, health or long-term disability insurance, because she might be considered a high-risk customer. The election of Donald Trump as US president also concerns Rehm, because Trump has pledged to repeal 'Obamacare', the US health law that compels insurers to offer coverage to people with diagnosed medical conditions.

"It's very likely to be used against her if Trump repeals Obamacare," Rehm says.

Rehm adds, though, that she and her daughter are not concerned about their own health. Rehm says that she will probably check in with a cardiologist every few years, but doesn't expect the discovery of the mutation to change the way she lives her life. "People deal with uncertainty all the time, and they usually deal with it quite well," she says.

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References

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2. Natarajan, P. *et al. Sci. Transl. Med.* **8**, 364ra151 (2016).