POLYGENIC POWER

A new test can calculate hereditary risk for sudden heart attack and other common diseases—and it may redefine the parameters of preventive health care.

CHALLENGE: How do we forecast hidden hereditary disease risk?

SOLUTION: Innovating an approach that captures how tiny changes across the genome can affect patient health.

Erin Colman never expected to go from planning a wedding with the man she loved to planning his funeral, but that nightmare became a reality. Colman met John Waskiewicz in Boston eight years ago and the two were friends for six years before finally dating. Things got serious quickly and they were set for a 2018 summer wedding in Vermont, near where they loved to ski.

Waskiewicz was also a runner and a swimmer. He worked out every day, ate healthily, and went to doctors regularly after his mother died at age 39 from a brain aneurysm. His blood pressure and cholesterol levels were normal. There was no sign anything was wrong.

One Saturday afternoon last April, when he was just 44, Waskiewicz came home from a bike ride, lay down in bed, and died in his sleep from a heart attack.

"I looked at the data from his Garmin watch and realized what time he went to bed and that his heart had stopped very quickly," Colman said. "It just didn't make sense. He was the healthiest one of all of us. He knew about his mom and did everything he could to prevent it."

In August, Colman—who was a longtime donor to the Broad Institute's BroadIgnite program—read an email from the Broad that piqued her interest.

Researchers led by Sek Kathiresan—formerly a Massachusetts General Hospital (MGH) cardiologist and Broad institute member—had come up with a way to integrate information from 6.6 million spots in the human genome to forecast hidden risk for five common diseases, including coronary artery disease and atrial fibrillation. Rather than identifying a single rare genetic mutation, their new algorithm was the first to look across all genetic variants to predict risk.

Colman contacted the Broad and met with cardiologist Amit V. Khera, associate director of the Broad's Cardiovascular Disease Initiative and past BroadIgnite awardee, to talk about this approach—called polygenic risk scores. Khera and Colman agreed to test Waskiewicz's polygenic risk score for both coronary artery disease and atrial fibrillation to see if he was genetically inclined for what happened to him.

A paper co-authored by Khera and others, published in *Nature Genetics* last summer, illustrates how polygenic risk scores can, with much greater accuracy, determine hidden genetic risk not just for coronary artery disease and atrial fibrillation but for Type 2 diabetes, inflammatory bowel disease, and breast cancer. The researchers have also developed a polygenic risk score for obesity, as reported in *Cell*.

Their algorithm captures in a single measurement how thousands of changes across the entire genome—each with a tiny increase or decrease in odds—can add up to affect one patient's health. In quantifying the long-known risk of inheriting disease, the tool holds the potential to make an incredible impact on clinical care. "Once validated, it could be used by anyone who wants to understand how their DNA puts them at risk for common diseases, particularly for people who have a strong family history of disease," said Khera.

From left: Patrick Ellinor and Amit Khera.

Kathiresan, who recently became co-founder and CEO of Verve Therapeutics, foresees scores being used soon—starting with coronary artery disease—in primary care, along with routine blood pressure and cholesterol tests. In fact, thanks to the *Nature Genetics* paper, the Broad is now partnering with IBM to help bring these scores into the clinic. Leading this project is Anthony Philippakis, the Broad's Chief Data Officer, who trained at Brigham and Women's Hospital with a focus on rare genetic cardiovascular diseases. Also deeply involved in this collaboration is Patrick Ellinor, an institute scientist at the Broad and cardiologist at MGH. Khera, who recently launched his own laboratory at MGH, started this work thanks to a seed grant from BroadIgnite.

The scores are generated by an algorithm that runs a patient's genetic analysis against established genetic combinations and mutations most strongly associated with the diseases. These associations are based on an accumulation of individual analyses from genome-wide association studies (GWAS) and the U.K. Biobank—a government-backed resource of health records, genetic information, blood

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Opposite:
John Waskiewicz and Erin Colman.

“IT COULD BE USED BY ANYONE WHO WANTS TO UNDERSTAND HOW THEIR DNA PUTS THEM AT RISK FOR COMMON DISEASES.”

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measurements, and lifestyle choices from 500,000 willing individuals across the U.K. A key next step is an even more sophisticated predictive tool that takes into account both genetic information and patient data from the medical record. Developing this tool would not be possible without the continued support of IBM, noted Khera.

In addition, Broad computational biologist Mark Chaffin is constantly refining the algorithm by analyzing how each gene variant for sudden cardiac death connects to the measurable data from thousands of patients for things like high cholesterol, heart pumping function, and electrical tracing from heart intervals. Collaborating with Partners HealthCare Personalized Medicine, he’s using bioinformatics to narrow down the initial list of variants.

“The power of polygenic scores is largely driven by how accurately you can assess the contribution of each variant to the risk of disease,” he said. “The number of genetic studies doing that continues to grow every year, helping us get more sophisticated about how to assign the weights of each variant.”

One challenge Chaffin has encountered is finding diverse samples, since most of the individuals catalogued by the U.K. Biobank were white Europeans. The researchers are now working with colleagues in the Broad’s Medical and Population Genetics Program to conduct additional GWAS studies that capture more globally diverse groups to more accurately predict polygenic risk scores for all populations. What’s more, the additional data will also lead to the development of stronger predictive models for all patients.

Polygenic risk scores also have the potential to help scientists understand the molecular processes that play key roles in diseases prior to their onset.

For example, let’s say a researcher wants to learn more about a complex, neurodegenerative disease like Alzheimer’s. Calculating the polygenic risk scores of younger, asymptomatic people with a family history of Alzheimer’s—and seeing how they compare with those without a family history—could provide insight into the disease’s early biomarkers, as well as the pathways by which symptoms develop.

“If you can see meaningful differences between high and low polygenic risk individuals, then then you can more comfortably draw an arrow as to what causes less common diseases very early in life,” said Kathiresan. “I think this is going to be very powerful in understanding the biology of Alzheimer’s.”

Of course, a caveat bears repeating: a high score isn’t a guarantee you’ll get the disease. It’s a wake-up call. “Like cholesterol levels, just because you have a high polygenic risk score doesn’t mean you’re going to have a heart attack, and vice versa if you have a low score,” Kathiresan said. “It’s about being educated and proactive about your health.”

DNA is not destiny. “When I went to medical school, we were basically taught how to take care of sick patients,” he said. “Here we have an opportunity to profile people before they have a problem—and tailor their care based on their genetic risk profile.” —*Anna Fiorentino* ■