

POLYGENIC RISK: WHAT'S THE SCORE?

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RESEARCHERS ARE IMPROVING RISK PREDICTION for common chronic diseases using genetic data. These 'polygenic risk scores' can help personalize preventive measures and could soon become part of routine healthcare practice, once some limitations are overcome.

The concept of a polygenic risk score (PRS) had been circulating among researchers for several years. It wasn't until 2018, however, that these scores were shown to have potential for broad-scale clinical use. A study by Amit V. Khera and colleagues at the Cardiovascular Disease Initiative of the Broad Institute in Cambridge, Massachusetts, identified people at high risk for five common diseases, based on their genome¹.

The team used genome-wide genetic data and

imputation methods to assess millions of common genetic variations associated with coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease and breast cancer. For each disease, they applied a computational algorithm that combines information from all of the variants into a number, or PRS, that reflects a person's inherited susceptibility to these diseases.

When the team tested their polygenic predictor for heart disease on 290,000

participants in the UK Biobank, they found that 8% of the population had 3-times the normal risk of a heart attack. "Those people are totally flying under the radar right now within our clinical practice," says Khera, who is also a cardiologist and human geneticist at Massachusetts General Hospital. "We can't find them without doing genetic testing."

Using the same approach for inflammatory bowel disease and breast cancer, the team found that their PRSs were consistently able

to identify a group (between 2-10% of the population) at particularly high risk¹. Khera's results feed into a growing body of evidence supporting wider use of PRSs.

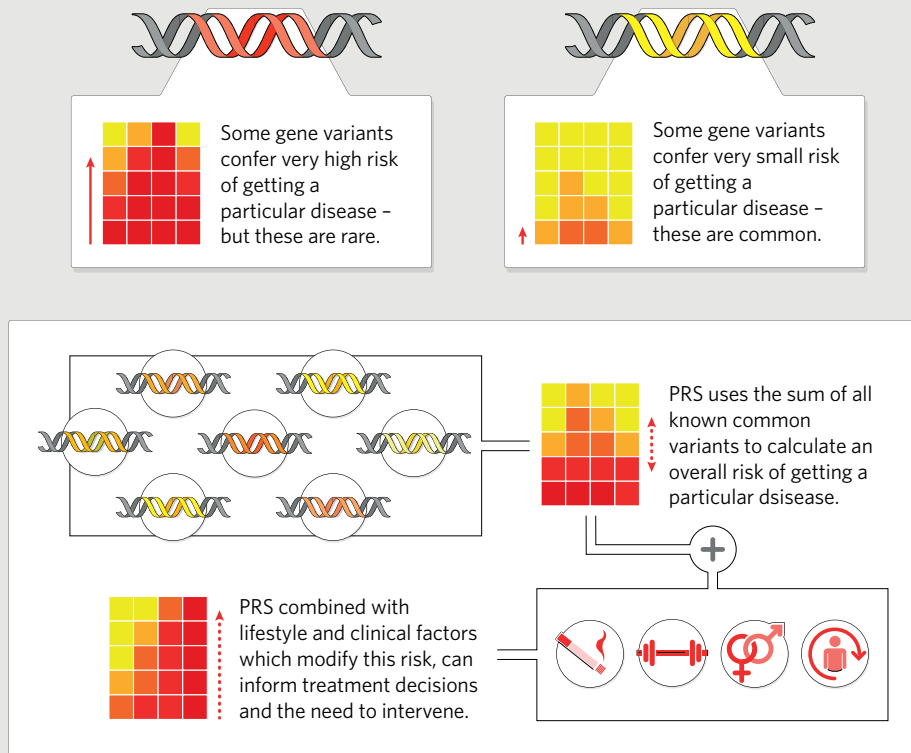
Given the benefits of early detection and treatment of these diseases, some researchers are asking what is needed to increase the adoption of PRS in healthcare settings. This article explores the development of PRS and how researchers are addressing some of the challenges surrounding their personal and clinical use.



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CLINICAL APPLICATION OF PRS

A polygenic risk score (PRS) is calculated from many small genetic variants, and can often be modified by lifestyle factors.



From single gene to whole genome variations

Genetic testing is widely used to diagnose monogenic diseases, such as cystic fibrosis or sickle cell disease, caused by mutations in a single gene. These tests can also identify unaffected carriers of disease-associated genes, allowing them to make informed family planning decisions or, in cases like Huntington's disease, to make plans in case they develop the condition in the future.

However, common diseases, such as type 2 diabetes and many neurodegenerative diseases, tend to be polygenic — influenced by a large number

of genetic variants scattered throughout the genome, as well as environmental and lifestyle factors.

New genomic technologies allow researchers to rapidly and inexpensively sequence large gene panels, all protein coding genes (exome) or the entire genome (whole genome sequencing, WGS), providing a complete survey of a person's genetic make-up. For nearly two decades, geneticists have been comparing genomes, searching for the differences that might explain why only some people develop a particular disease.

A genome-wide association study (GWAS) can identify such variation, generally in

the form of DNA letter-swaps known as single nucleotide polymorphisms (SNPs). Through GWAS, researchers found a greater number of disease-associated variants than they initially expected, but these variants' individual contribution to disease was negligible. Several years on, they have developed tools to accurately determine the cumulative effect of millions of small genetic variations on disease risk².

Acting on the score

Several companies claim that they can calculate PRSs for multiple disorders, yet the scores are not routinely used. "We are still figuring out how

to use PRS in practice, and in which cases they can lead to actionable and cost-effective measures," says Alicia Martin, a population and statistical geneticist at Massachusetts General Hospital.

Determining a person's susceptibility to diseases has clear benefits. For example, Khera's findings suggest that in women with a high risk of breast cancer, starting the screening regimen earlier could improve outcomes. "Our goal is to empower people to overcome whatever [disease] predisposition is in their DNA," says Khera.

For conditions that lack proven preventive measures, a PRS might seem to offer little immediate benefit. Some people, however, still wish to know their risk of developing a fatal disease. One such person was Rahul Desikan, co-director of the Laboratory for Precision Neuroimaging at the University of California, San Francisco, who died earlier this year from an aggressive form of amyotrophic lateral sclerosis (ALS). He wrote in April in *Stat* that polygenic analysis would probably have revealed his condition and allowed him to "start preparing for it and make every hour count". What's more, even if

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some diseases are currently incurable, PRSs can be used to match drugs in clinical trials to individuals who are most likely benefit from them. "A trial of an immunotherapy drug, for example, might give

more bang for the buck by focusing on individuals who have high immune polygenic scores,” Desikan explained.

Sharpening the score

An important concern surrounding the clinical implementation of PRS is that, so far, the scores have largely been calculated from European DNA sequences³. “The frequency, and the degree of correlation with disease, of common genetic variants in African Americans, are distinct from European Americans — and this reduces the accuracy of PRS,” says Martin.

Martin is involved in various global projects that aim to characterize genomic variation in diverse populations and develop statistical methods to analyse multi-ethnic data and improve the accuracy of PRS. One of these projects is Neuropsychiatric Genetics in African Populations (NeuroGap). “The early human migrations out of Africa took a subset of genetic diversity into Europe, East Asia and eventually into the Americas,” she says. “Conducting large genetic studies in African populations will rapidly improve the accuracy of PRSs for all populations.”

Other efforts to bring the promise of genomic research to more people include All of Us, funded by the US National Institutes of Health, which is building a large-scale biomedical data resource that reflects the diversity of the US population. The population genetics company, Color, recently announced a plan to enrol 100,000 volunteers from underrepresented groups to better assess the risk of heart attack from

low coverage WGS. It will take many such initiatives to improve universal disease-risk predictions.

Because many health-related conditions involve environmental and lifestyle factors as well as genetic susceptibility, combining PRS with other known risk factors will further improve risk prediction and help define clinical action thresholds⁴. According to Ali Torkamani, a geneticist at the Scripps Research Institute in La Jolla, California, there is enough evidence to support the use of PRS in decisions around statin treatment. For patients identified as having a moderate clinical risk of developing coronary artery disease (from commonly measured clinical risk factors such as smoking, high blood pressure, and cholesterol levels), adding polygenic risk information can help physicians make the decision to prescribe statins as an additional preventive measure.

Handling the score

The other uncertainty around PRS implementation is how it should be explained. Torkamani and his team have developed MyGeneRank, an app that can calculate an individual's PRS for coronary artery disease from their 23andMe genetic data, health data collected on mobile devices, and a series of questionnaires. Their goal is to understand how people react to receiving the score, and to monitor any changes in health-related behaviours afterwards.

“There are some concerns about the psychological impact of knowing your genetic risk of disease,” says Torkamani. “For instance, it might cause anxiety in people

who are at the high risk end or it may make low-risk individuals more prone to unhealthy behaviours. But so far, we haven't seen much evidence of this.”

If anything, genetic risk knowledge may actually encourage the adoption of healthy lifestyle changes more broadly. The GeneRisk study in Finland, presented at the ASHG conference in 2018, showed that providing personalized cardiovascular disease risk information, based on a combination of traditional risk data and PRS, motivated healthy behaviours. Even participants at lower

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risk seemed inspired to lose weight, stop smoking or visit a doctor. Similar initiatives in Estonia, where the government is funding a programme to genotype more than 10% of the country's population, are investigating the use of a PRS for type 2 diabetes⁵. Individuals are given the option to learn their score, and those at highest risk are encouraged to make lifestyle changes, such as reducing sugar intake and increase exercise, to prevent or delay the onset of diabetes.

Torkamani emphasizes that the way a PRS is communicated, and transparency on score performance, are important determinants of uptake. “Effectively communicating that a high-risk score does not mean that someone will

definitely develop a condition, and that a low score does not mean that they will remain disease free, is key to driving the adoption of healthy behaviours,” he says.

To help physicians and patients handle genetic risk information, Massachusetts General Hospital is launching a new Preventive Genomics Clinic this year in which specialists will interpret patients' genetic risk scores and advise on the steps they should take to minimize their risk. “Initially it will focus on monogenic mutations, but we expect it to move rapidly into the polygenic space as these tests go mainstream in the next year or two,” says Khera.

As long as the baseline genetic data is representative of the whole population, there is no reason why PRS will not soon be available to help everyone stay healthy for longer. “The wonderful thing about DNA is that it is stable throughout the lifespan,” says Khera. “You can envisage a not-too-distant future in which, for 50 dollars, you get a genetic susceptibility report card that identifies what diseases you may be at risk of from an early age, so you could take steps to prevent them.” ■

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