Decoding Your DNA: Can Polygenic Risk Scores Reveal Your Disease Risk?

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Tiny gene variations can add up to big insights. Here’s how polygenic risk scores use AI and genomics to predict health risks.

Certain genes can make you more susceptible to certain diseases, and the increase in your risk can be *huge*. Women **with harmful changes to Breast Cancer Gene 1 or 2 (BRCA1 or BRCA2)**, for example, have a 60% chance of developing breast cancer in their lifetime, compared to just 13% for women without these genes.

But not every risk is so massive. Teeny-tiny genetic variations can increase your susceptibility to certain diseases or disease states by teeny-tiny amounts. Each one of your little gene changes could elevate risk for heart attack, stroke, certain cancers, diabetes, or other conditions. Alone, each of these increases are infinitesimal… a proverbial drop in your bucket of risk of that disease.

What Polygenic Risk Scores Actually Measure

“For many common disorders, there’s a contribution of tens, hundreds, or sometimes even thousands of those genetic changes,” says **Elizabeth McNally, M.D., PhD**, director of the Center for Genetic Medicine at Northwestern University’s Feinberg School of Medicine. “We take the information from genome-wide association studies, and we add them together.”

The result of that addition is a “polygenic risk score,” a measure that determines whether all your genetic drops are accumulating into a significant area of your risk bucket. It’s possible thanks to machine learning technology… because humans (and previous computers) couldn’t comb through and add together such huge reams of data.

“Our genetic code is often described as a book with a string of 3 billion letters, and we differ from each other, or groups of us differ from other groups, because some of those letters have been changed in our genetic code,” notes **Jonathan Mosley, M.D., PhD**, associate professor of internal medicine at the University of Tennessee Southwestern. The differences in our code can be massive: Two people sitting next to each other might have 5 million differences in these genetic letters.

Adding them together in a polygenic risk score and combining that score with other testing and your family history, McNally says, these scores can be a powerful, bonus predictor of potential disease. The effect size, though, won’t be as large as with single, riskier gene changes, monogenic risks, like BRCA1 or BRCA2.

While those genes can increase your risk of breast cancer by 20 to 50 times, “if I do a polygenic risk for breast cancer and sum up all the different changes, sometimes the level of change is only a two-to-threefold increased risk of developing breast cancer,” McNally offers.

From Data to Action: What Your Score Can Tell You

Armed with this type of information about increased risk from polygenic factors, she notes, your doctor could tailor your health recommendations and management to your specific genetic risk. In the example of a polygenic risk of breast cancer, your physician might do more testing and monitoring for the disease than if you didn’t have these genetic risks.

And the scores aren't just for breast cancer: A large cohort of scientists, including McNally, conducted a study on polygenic risk scores **for 10 different conditions**, including asthma, obesity, Type 1 and 2 diabetes, coronary heart disease, kidney disease, and prostate cancer. The scores are also being studied not just for tailoring medical treatment based on disease risk, but **on how different pharmaceuticals might work for specific genotypes**: These scores could help tell if a person is more or less likely to experience certain side effects from a new drug.

The Best Uses for Polygenic Risk Scores

Their most useful cases, McNally says, could include:

• **Situations where family history isn't accurate or available:** "A lot of people don't know their family history, or their family doesn't like to talk about it, or they're adopted or came from a really small family," adds McNally. "Rather than having to dredge up what is often an inaccurate family history, polygenic risk scores… can help let you know if you are at an exceptionally high risk for some things."

• **Rarer cancers and diseases that aren't always tested for:** Some diseases, like colorectal cancer, don't have symptoms or warning signs we can see when they're in the early stages of development. But for younger patients, they're comparably rare. If you have an increased polygenic risk score for it, though, your doctor would know to start screening for it earlier than "normal."

• **Actionable conditions:** If you've got an increased genetic risk of a disease or condition, but there's nothing you can do to help prevent it, the score isn't particularly useful. But for actionable conditions like obesity, heart disease, or hypertension, knowing you're at risk can change what you (and your doctor) do. For example,

McNally mentions that if you're at an elevated polygenic risk for certain coronary conditions, having stage 1 hypertension — elevated blood pressure that's usually monitored, but not treated — would be a condition she'd consider treating.

The Limitations You Need to Know

The big limitation with these scores is race and ethnicity: Most polygenic risk scores are based on statistics from "genome-wide association studies," which combine and analyze DNA from large groups of people. But those groups are **mostly people of white European ancestry**. As genetic "distance" from this group increases, the accuracy of the scores decreases. Scientists are working to incorporate more diverse genetic information in future models.

For the scores that are currently available, Mosley also worries that the risk of a disease can be deceiving to patients, especially at a younger age.

"You've got to think about diseases in terms of absolute risk… age is going to be the biggest explainer of risk," he says. "So your absolute risk of prostate cancer by the time you're in your late 70s is very high. But if you're 40 years old, and the average risk for a person [to get prostate cancer] is 1 in 1000, and the polygenic risk score tells you that you're doubling your risk, then your current risk is only 2 in 1000."

The scores, he explains, aren't always beating the "normal" way of assessing risk, either. In a study he co-authored **published in the *Journal of the American Medical Association***, a polygenic risk score was not better at predicting coronary heart disease events, like heart attack, than conventional predictors like blood pressure, cholesterol, and family history.

McNally disagrees here: "Family history and polygenic risk get at different things," she counters. "Adding them together is probably the best way to do that." An elevated

polygenic risk score also does not mean you'll necessarily get a disease, and a low one doesn't mean you won't get that disease. It's simply a measure of genetic risk, which is only part of the overall risk for a condition.

Should You Get a Polygenic Risk Score Yet?

"One of the biggest barriers that we have is a workforce that doesn't really know how to order the tests," McNally notes. "You often have to go outside your clinic and hospital to have it done."

And if you get a measure of polygenic risk from an outside DNA test, your doctor may not know what to do with it, Mosley adds.

"A polygenic score is a calculation. There are many different ways to calculate it. It depends on what data you use to determine the risk, or the variance, that also influences the score. So when you have a polygenic risk score, you'd really need to say, based on risk from *this* population, and according to *this* calculation, this is my score," he shares. Depending on the source of your score, it could be similar to getting a sleep score from your watch; it won't be clear to your doctor what's been measured, so they won't necessarily know how to act on the score.

This isn't true across the board, though, according to McNally. Some hospitals and medical systems are now making these scores available to patients directly. **At Mass General, for example**, polygenic risk scores are now being made available for coronary artery disease.

If it's available, McNally says, this type of measurement could be worth going beyond normal testing: "For people with the very highest polygenic risk, that [added] risk is

actually pretty high.” Knowing how many drops of risks are in your bucket could help direct your doctor’s testing and care, and shape your habits.

Can You Ask for a Polygenic Risk Score?

You can, but access depends on where you look. Most primary care physicians don’t yet offer polygenic risk testing, since interpreting these scores requires specialized training. But the field is changing quickly. So where can you get it?

- **Leading research hospitals** such as Mass General Brigham, Mayo Clinic, and Northwestern are already integrating polygenic scores into select patient programs.
- **Some online testing companies,** like **Function Health**, **Superpower**, and **Inside Tracker**, include advanced biomarker panels and DNA testing, but they aren’t calculating your polygenic risk score.

For now, the best way to start is by talking to a genetic counselor or precision medicine specialist about options suited to your health goals.

Remember: DNA Isn’t Destiny

Even if your genes point to elevated risk, your future is not written in code. As Harvard cardiologist **Dr. Pradeep Natarajan** notes, polygenic risk scores reveal *potential*, not prediction. Lifestyle, environment, and medical care still shape the outcome. In fact, research shows that even those in the highest genetic-risk categories for diseases like heart disease or diabetes can dramatically lower their real-world risk through consistent movement, sleep, stress management, and diet.

Dr. Eric Topol put it simply in our recent **Super Age Live conversation**: “We have a path to healthy aging right now: it doesn’t require expensive stuff. Move, sleep, eat real food, and connect with others.”

Your genes may load the gun, but your daily choices decide whether it fires.

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