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Can we ever fully trust personal gene tests?

Kits sold to consumers that predict health risks from our genes have been hit by major concerns over their reliability. Nic Fleming investigates why.

By Nic Fleming
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"Neurological conditions, 60% probability," a nurse in green scrubs reads in a monotone voice. A young woman cradles her newborn while an anxious new father looks on. "Manic depression, 42% probability. Attention hyper-deficit disorder, 89% probability. Heart disorder, 99% probability... life expectancy 30.2 years."

The scene is from the 1997 sci-fi classic Gattaca, in which a man refuses to accept the rules of a future society condemning him to an underclass only fit for menial work because of his less-than-perfect genetic inheritance. Back in early 21st Century reality, gene tests don't yet feature in job interviews, thankfully. Yet the idea that the code of life within us – DNA – can predict our long-term health prospects from the moment of birth is a powerful and persuasive one.

Since the mid-2000s several companies have launched tests for the general public,

offering consumers cheap, simple genetic screening for a wide range of health conditions. Spit into a tube or take a sample with a cheek swab, send it off for testing and for as little as $99 you could receive in return information ranging from ancestral links to risks of specific diseases, according to the manufacturers.

But all has not been plain sailing for this nascent personal gene testing industry. In 2012, two of the three big players, decodeMe and Navigenics, pulled out of the market after being acquired by other companies. And in November last year, the third and arguably most high-profile company, 23andMe, which says it has **more than half a million customers**, stopped offering new tests after the **US Food and Drug Administration (FDA) said** it had failed to show its health predictions were accurate.

"That evidence is simply not available, so I would not be surprised if this marks the end of direct-to-consumer genetic testing for most common diseases," says epidemiologist Cecile Janssens, of Emory University, in Atlanta, Georgia.

If this is the case, then why do DNA tests sold to consumers appear to be as unreliable as US regulators say? And if these tests can't be trusted, where does that leave the broader hopes that our newfound ability to read our individual genetic code can help us live longer, healthier lives?

Screen test

Doubts about whether the industry could deliver what it promised surfaced early. In 2008, for example, I submitted samples of my DNA to three companies as part of an investigation for the **Sunday Times newspaper**. While deCODEme informed me my risk of developing exfoliation glaucoma, which causes loss of vision, was 91% below average, 23andMe said I was 3.6 times more likely than average to get it. British company GeneticHealth said I had four times the average risk of developing Alzheimer's disease by my late 80s, while deCODEme described the risk as 74% above average. I was given conflicting predictions for other conditions including age-related macular degeneration, Crohn's disease and hypertension.

I wasn’t the only one. In 2009, pioneering

human genome sequencer Craig Venter and several colleagues sent samples to 23andMe and Navigenics, and also received similarly **contradictory results**.

Critics have argued that without guidance people are liable to misinterpret their results, potentially leading to them feeling either unnecessarily alarmed or falsely reassured.

"What if a woman who learns she does not have the BRCA1 or 2 mutations that make her at high risk of breast cancer decides she will no longer go for her mammograms, even though for the average American woman not having them only cuts the risk from around 12% to 11.95%?" says Hank Greely, Director of Stanford University's Center for Law and the Biosciences.

Others respond that people have the right to their genetic data, and that access to it can improve health prospects and even save lives. Last year, Robert Green and colleagues from Harvard Medical School completed a survey of 1,800 customers who had bought direct-to-consumer genetic tests. Although the results haven't yet been published, he says preliminary findings suggest that around four in 10 claim the

tests motivated them to make changes such as improving their diet and doing more exercise, while only 1% reported altering prescription treatment without consulting a doctor.

"It's certainly an industry that should be carefully examined and potentially regulated," says Green, who set out his case against the FDA's decision **in the journal Nature** earlier this month. "But the emerging evidence suggests that sometimes people use their results to motivate lifestyle changes," he says. "In a very few cases individuals and their relatives have learnt that they were at increased breast and ovarian cancer, and arguably in some of these lives have been saved."

It's an interesting clash of perspectives, but one which may be beside the point now that the FDA has slapped a large question mark over the basic accuracy of the test predictions. After being ordered by the FDA to halt its testing service, 23andMe said customers would have access only to its results from ancestry and traits like hair colour, instead of disease risks, while it seeks FDA approval for health-related results.

Complex influence

One simple reason genetic tests are limited in their predictive powers is that many common conditions are influenced as much, if not more, by environmental and lifestyle factors than genetic ones. A **summary of twin studies** published by Emory's Janssens in 2010 identified that some conditions direct-to-consumer tests offer predictions for are highly heritable, such as type 1 diabetes at 88%, schizophrenia at 81% and Alzheimer's disease at 79%, but that most have low-to-moderate heritability, such as prostate cancer at 42%, depression 37% and type 2 diabetes 26%. "There is no utility at all in doing a genetic test for a disease with low heritability," says Janssens.

Even if a disease is highly heritable, that does not necessarily mean DNA tests can make an accurate prediction of risks. For many conditions, scientists have found that large numbers of genes may have small effects, and the way these interact with each other and non-genetic causes such as smoking, diet and physical activity levels is far too complicated for the simple models used by the tests to untangle. "In most common diseases such as type 2 diabetes

or heart disease, there are many risk factors, both genetic and non-genetic, that play a role," says Janssens. "These can interact in unique and complex ways in different people, and it's difficult to capture this complexity in a model."

This view is supported by **research carried out by John Burn**, Professor of Clinical Genetics at Newcastle University, who looked into the effects of six genes on the risks of babies born with spina bifida. "The effects of these variants didn't just add together in a simple way," says Burn. "There were some situations where a variant was a disadvantage unless it was in the presence of another variant when it became an advantage. Companies that have been offering genetic tests for common diseases imply they understand these relationships but in fact they grossly underestimate their immense complexity."

On top of these problems many cases of the disease-associated markers (or SNPs as they are known) discovered so far only account for a small part of the known heritability of those conditions, and there is little consensus about why this might be. "The case of the missing heritability is the

biggest issue right now in human genetics," says Greely.

In research **published last summer**, Janssens and colleagues found variations in the predictions produced by 23andMe, deCODEme and Navigenics were due in part to them using widely different numbers of SNPs for the same conditions, and sometimes using drastically different average disease risks. For coeliac disease, for example, deCODEme had an average population risk of 1% – eight times higher than that used by 23andMe and 16 times higher than Navigenics. Variations in the disease predictions provided for individuals therefore might be more to do with which company they decide to do their tests with than their genes.

The health risk reports 23andMe provides for its users do acknowledge the role of environmental factors in disease susceptibility and also state the information provided "is intended for research and educational purposes only, and is not for diagnostic use". However in its **November letter to the company**, the FDA made it clear it is now among those who see this disclaimer as disingenuous when sitting

alongside statements such as the health reports being a "first step in prevention" enabling users to "take steps toward mitigating serious diseases".

Risk assessment

The question is whether more advanced genetic tests will provide a clearer picture. Direct-to-consumer genetic tests, and other types of DNA analysis, use "SNP chips" which can identify up to one million genetic variants. New techniques mean that reading all six billion bases of the human genome – known as whole genome sequencing (WGS) – is getting cheaper and quicker. The current cost is around $5,000. Some predict that once this drops to around $1,000, it won't be long before everyone has their genomes sequenced. In December British Health Secretary Jeremy Hunt called for the country to become the first in the world to **routinely sequence everyone's genomes at birth**.

"I think we're moving from a SNP world where the associations are weak and questionable, to a whole genome world where there will be more strong and clinically valid associations," says Greely.

"For the common diseases for which the known genetic contribution to heritability is limited, whole genome sequencing isn't going to make any difference, but it could do for the thousands of rare monogenic diseases as well as in other non-rare conditions for which there are strong associations like Alzheimer's. That may mean the medical implications are not enormous for most of us, he says, “but if it gets cheap enough I suspect that good healthcare systems will get whole genome sequences on their patients in another 10 years or so."

Sequencing everyone's genomes could improve existing disease screening programmes such as those for breast and bowel cancer. Those identified as being at a greater genetic risk could be tested more frequently and at an earlier age, while those at lower risk could be tested less often, making it possible to pick up illness sooner and save money. "We might, for example, give all women a cancer predisposition test at the age of 30," says Burn.

Another benefit of universal DNA analysis is likely to be significant reductions in children born with rare "recessive" disorders, which

only occur when a child inherits malfunctioning genetic variants from both their mother and father. These illnesses often come as a complete surprise to the families concerned because those who carry just one copy of the genetic abnormality are "carriers" but do not show any sign of ill health. About one in 25 Caucasians of northern European descent carries the gene variant for cystic fibrosis and around one in 12 African-Americans is a carrier of sickle cell anemia, for instance. In a world in which we all know our carrier status, couples who know their unborn offspring are at risk could undergo IVF and select embryos without these conditions.

With more and more people seeking to find information about their reproductive risks before or during pregnancy, many are deciding not to wait for the advent of widespread genome sequencing. The market for "carrier screening" has been growing rapidly in recent years, especially in the US. San Francisco-based company **Counsyl**, for example, sells tests that look for some 400 mutations and that cause around 100 genetic disorders for $599.

Non-invasive prenatal DNA tests involving

obtaining foetal DNA from pregnant women's blood are also gaining in popularity. These are safer and do not carry the risk of miscarriage that come with traditional screening methods such as amniocentesis. They are currently being used for detecting Down's syndrome and for early sex detection of X-linked diseases like Duchenne Muscular Dystrophy and haemophilia, however they have the potential to be used for many more conditions in future.

Both science fiction such as the film Gattaca and current problems faced by 23andMe et al provide important warnings about the dangers of overly simplistic approaches to genetics. These are valuable lessons, however they shouldn't detract from the dramatic impact this is already having on the quality and length of many human lives, and its potential to power improvements for even more of us in the future.

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