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Genomic medicine is deeply biased towards white people

Lack of diversity in genome studies means that treatments derived from them are leaving people of colour behind. Changing that isn't only about justice – it could also lead to new therapies that would otherwise go undiscovered

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By **Layal Liverpool**

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IF YOUR doctor suspects you might have type 2 diabetes, they will want to know your average blood sugar level, which typically means taking a glycated haemoglobin test. This method of diagnosis is recommended by the World Health Organization and used pretty much everywhere. The problem, as Deepti Gurdasani discovered in 2019, is that the test may not work for everyone.

Gurdasani and her colleagues found that a gene variant present in almost a quarter of people with sub-Saharan African ancestry alters the levels of glycated haemoglobin in

their blood independent of blood sugar. This suggests they will be more likely to be falsely diagnosed with diabetes, she says.

Gurdasani's discovery is just the latest in a growing list of medical injustices resulting from the fact that the vast majority of people who have had their DNA sequenced are of European descent. Again and again, people from under-represented backgrounds find that drugs and diagnostics based on research that makes connections between DNA and disease don't work for them. The dearth of diversity in these studies also means that people in overlooked populations are more likely to get inaccurate results from tests that look at an individual's genetic risk of developing a condition, excluding them from the much-vaunted promise of personalised medicine.

All of which explains why researchers like Gurdasani, a geneticist at Queen Mary, University of London, are sequencing the DNA of thousands of people from under-represented populations around the world. This isn't just about justice: increasing the diversity of genetic studies could also uncover novel genetic variants associated with disease, providing targets for treatments that would otherwise go undiscovered.

"There's this treasure trove of human genetic variation that could lead to a new understanding of human biology," says Keolu Fox, an anthropologist and genome scientist at the University of California, San Diego. The challenge now is to make sure that in the rush to harness it, geneticists don't exploit the very people they seek to include.

Medical revolution

Genetics' transformation of medicine started with the Human Genome Project. Completed in 2003, it gave us the entire genetic blueprint of a human for the first time. As whole genome sequencing got faster and cheaper, ventures like the 100,000 Genomes Project sprang up, improving our understanding of human DNA. These days, we can pore over tens of thousands of whole human genome sequences, comparing them in forensic detail to make connections between genetic variants – the tiny portions of the genome that differ between individuals – and disease.

These genome-wide association studies (GWAS) have identified gene variants behind all manner of conditions and even led to the development of new treatments for several, including rheumatoid arthritis and inflammatory bowel disease. The growing catalogue of human genomes that makes GWAS possible also underpins the promise of genetic testing in medicine, where it is being used to predict which conditions a person is susceptible to and, in some cases, to suggest preventative treatments.

But as things stand, it is mainly people with European ancestry who stand to benefit – as they make up the vast majority of those whose genomes we have sequenced. According to an analysis by Sarah Tishkoff at the University of Pennsylvania in Philadelphia and her colleagues, 78 per cent of individuals included in genomic studies of disease up to 2018 were of European descent, 10 per cent had Asian backgrounds and just 2 per cent were of

African descent. That means that gene-disease associations based on these studies are unlikely to capture the full diversity of the human population. That's a major problem. "The lack of ethnic diversity in human genomic studies means that our ability to translate genetic research into clinical practice or public health policy may be dangerously incomplete or, worse, mistaken," the authors concluded.

Blood samples at the UK Biobank project, which holds genetic and health data
Christopher Furlong/Getty Images

Gurdasani's discovery that the test for diabetes is anything but universal shows this lack of diversity is already having an effect on people's lives. A similar issue is seen with cystic fibrosis, which often goes undiagnosed in people of African descent. Tests for the condition frequently look for known mutations within the *CFTR* gene, such as the deltaF508 mutation that is found in 70 per cent of people of European descent with the condition. But in people with African ancestry, that particular mutation only accounts for 29 per cent of cystic fibrosis cases. Instead, the cause is often one of a number of other mutations in the same gene – markers that may be less likely to be detected as most investigations undertaken to identify mutations in the *CFTR* gene have been conducted in European ancestry populations.

Similar bias may also influence the effectiveness of medicines, such as the breast cancer drug tamoxifen. The way our bodies process drugs like tamoxifen is strongly influenced by a gene called *CYP2D6*. There are more than 100 different versions of this gene, all of which occur at different frequencies in different populations – and various studies have shown that people of Asian or African ancestry are more likely than people of European descent

to have a version that means they metabolise tamoxifen less well, meaning they may benefit less from it.

These kinds of genomic inequities are starting to be challenged in court. In 2014, the anti-blood clotting drug clopidogrel, sold under the trade name Plavix, became the subject of a lawsuit, for instance, when studies suggested that a genetic predisposition common in people of East Asian or Pacific Island descent results in poor metabolism of the drug, potentially leading to negative effects. The state of Hawaii sued the manufacturers of Plavix, Bristol-Myers Squibb and Sanofi, over their marketing of the drug in the state, claiming the companies failed to properly warn consumers about the drug's potential risks. (The two companies counter-sued, arguing that the demand for what they consider unnecessary warning labels breaches their rights to free speech. But the counter-suit was dismissed in October last year.)

Not for everyone

While predicting a person's risk of developing a condition based on their genome sequence remains an imperfect science, there is mounting evidence that it works far less well in people of non-European descent. In 2019, a team led by Alicia Martin at Massachusetts General Hospital in Boston found that the accuracy of such disease prediction is about twofold lower in populations of Asian descent than those with European ancestry, and roughly fivefold lower in populations of African descent. Other research has found that genetic tests vastly overestimate the risk of schizophrenia in people of African descent.

"If we continue to sample Europeans and extend our findings to other populations then that certainly is not going to work for everyone," says Gurdasani. If anything, it is going to exacerbate existing inequalities related to health.

That's the scenario many in the field are now working to avoid. Several large-scale efforts to sequence more people from under-represented backgrounds are under way. The GenomeAsia 100K project has sequenced the genomes of nearly 2000 people from 64 countries across Asia so far. The H3Africa initiative consists of 51 projects around the continent led by local researchers, including population-based genomic studies of disease. And the US National Institutes of Health is almost three years into a programme called All of Us, designed to create a database of genetic information and other health records from more than a million people with diverse ancestry across the country. Even commercial genetic testing companies like 23andMe are actively seeking more samples from people of under-represented backgrounds.

In some cases, belated efforts to chart the fullness of human genomic diversity are already beginning to bear fruit, as previously overlooked sequences reveal novel gene variants. Nowhere is that more apparent than in Africa, where genetic diversity far exceeds that in any other part of the world. That's because all humans originated there, and those who migrated outwards only took a fraction of that original diversity with them.

Gurdasani and her colleagues collected DNA sequences from more than 6000 people across 25 villages in south-west Uganda, including almost 2000 complete genomes, alongside information from participants about their health. When they analysed it alongside similar data from 8000 people from across Africa, they found various gene variants associated with cardiovascular and metabolic disease, 23 of which hadn't been discovered before.

One of those is a variant that offers protection against malaria – the same variant that renders the most common test for diabetes useless for many people of African ancestry. Several gene variants Gurdasani identified during subsequent sequencing efforts are equally intriguing, including one that could be a potential target for HIV treatments. That work isn't yet published.

Tishkoff, too, has found previously unknown gene variants by sequencing volunteers in Ethiopia, Tanzania and Botswana. One newly identified variant associated with skin pigmentation could play a role in skin cancer. And in November 2020, a study from the H3Africa initiative reported the discovery of more than 3 million novel genetic variants.

This is just the start. Despite people of non-European descent accounting for a smaller proportion of participants in GWAS studies, they already contribute more in terms of genetic discoveries, says Gurdasani. "The more diverse populations you study, the more opportunities you have to identify associations with disease, which is what leads us to targets for drugs and new therapies," she says. What's more, those therapies will be more likely to work for everyone.

There is also a push to sequence smaller, more isolated populations, including Indigenous peoples, on the basis that many of these populations have adapted to extreme environments. Greenlandic Inuits, for example, have relatively low levels of heart disease even though they have traditionally eaten a diet rich in fat, so biologists have begun to study gene variants within these populations in the hope it could improve our understanding of heart health and inform the development of new treatments. By sequencing the genomes of a group of Melanesian individuals, researchers were able to discover new variation in several genes associated with metabolism.

"There's this new modality of treating Indigenous people's genomes like coal or cobalt"

Genomic justice

"We're starting to see the true value of this data," says Fox. But as the possibilities for enhancing our understanding of disease and developing new treatments become clear, Fox warns that researchers must properly reckon with the ethical considerations involved in sequencing the DNA of people from under-represented groups – not least the very real danger that efforts to increase diversity end up exploiting the populations they set out to include.

“There’s this new modality of treating Indigenous people’s genomes like coal, cobalt, diamonds or oil,” says Fox. “Because you can’t tell me these sequencing experiments are actually going to result in an improvement in brown people’s lives. The real issues have to do with access to clean water, malaria and so on.”

Gurdasani also emphasises the need to tread carefully. “There is a long history of samples and data [taken from under-represented groups] being used, without consent, for other purposes,” she says. One notorious case dates to the 1950s, when cancer cells were taken from an African-American woman called Henrietta Lacks without her or her family’s consent. They went on to provide the first immortalised human cell line, meaning they are cultivated and reproduce indefinitely. The cells are still widely used for medical research today. This is far from the only example. In 2019, the Wellcome Sanger Institute in the UK was accused of commercialising a genetic testing product without the consent of the hundreds of African people whose donated DNA was used to develop it.

The genomes of Greenlandic Inuits could tell us more about heart health
Justin Lewis/Getty Images

Tishkoff says researchers must prioritise ethical considerations. “You can’t just go there, grab blood and leave,” she says. Instead, you have to engage with the communities involved, building trust and collaborations – and accept that there is no one-size-fits-all strategy. “It takes time if you’re doing it the proper way,” she says.

As genetic studies have the potential to reveal underlying genetic conditions that participants may be unaware of, Gurdasani says it is crucial that researchers build medical

infrastructure when working in regions with limited healthcare services. During her study in Uganda, for example, Gurdasani and her team, including scientists based at the UK Medical Research Council's Uganda Medical Informatics Centre, worked to develop infrastructure so that study participants had access to treatment and genetic counselling. "You can't diagnose people with disease and then not have a pathway of care," she says.

Fox is particularly concerned about the pharmaceutical industry recruiting people from under-represented backgrounds to identify mutations that lead to the development of profitable drugs, without giving anything back to the people themselves. "It's extractive," says Fox. "It's colonial. But there's this illusion of inclusion." He has the same concern about consumer genetics companies, some of which have started to partner with drug manufacturers – as a collaboration between GlaxoSmithKline and 23andMe shows.

Fox argues that all genetic studies should be led by people from the groups being studied and provide direct benefit to them. In 2018, he and his colleagues published a framework for enhancing ethical genomic research within Indigenous communities, and he hopes to set up a network of labs dedicated to genetic research led by Indigenous people. He also points to existing examples, such as LunaDNA, a community-owned platform for biomedical research that distributes proceeds to people who share their DNA.

Tishkoff is optimistic that we can do this in the right way. "I think we're going in the right direction," she says. "But at the same time, there's a long way to go."

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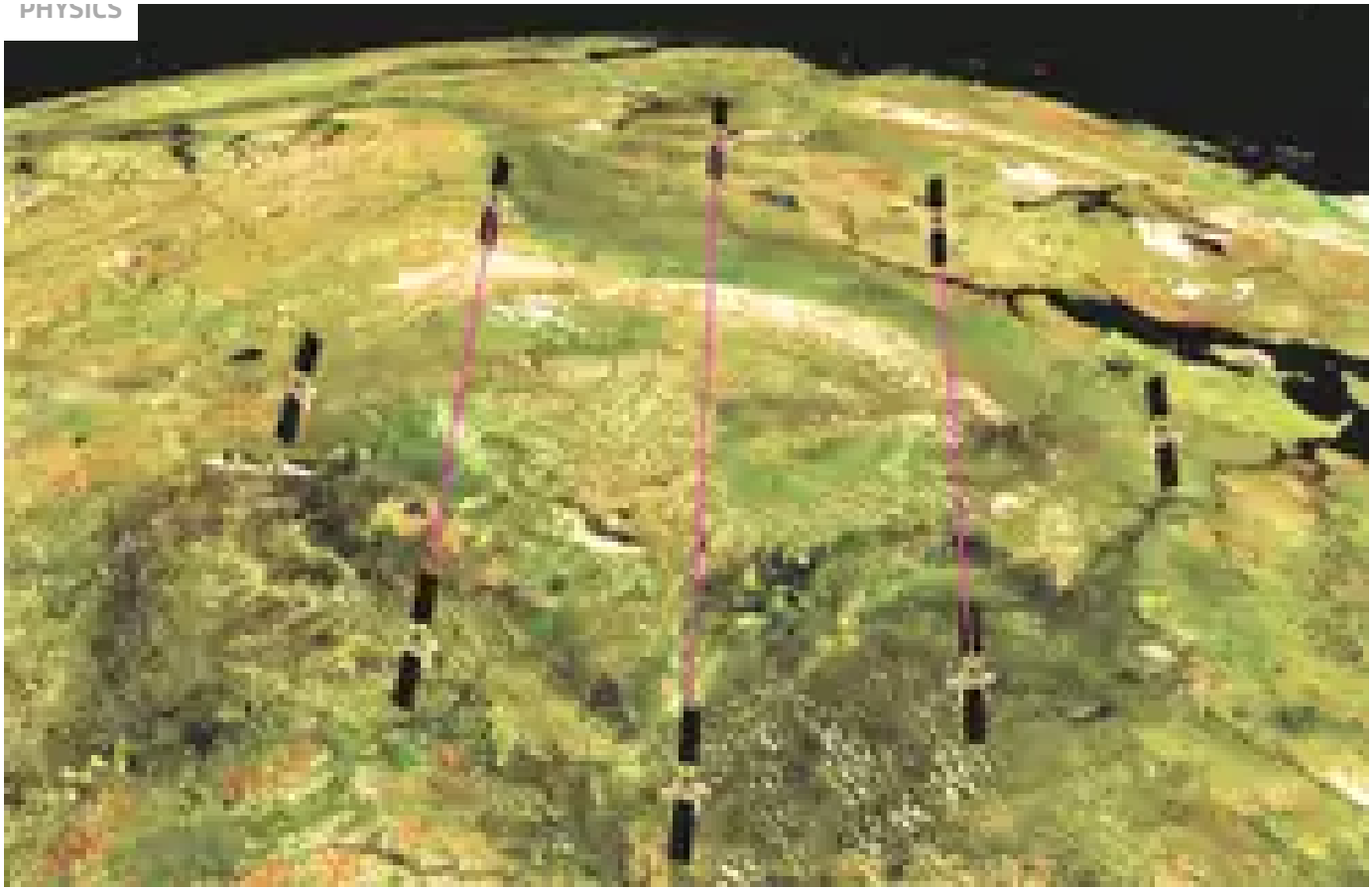

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