

# From human genome to global genome – why precision medicine must address genetic diversity

The publication of the first human genome sequence more than 15 years ago marked the start of a new era in medicine. In the years since then, researchers have greatly expanded knowledge of gene-disease links and gained a better understanding of the underlying molecular pathways.

**T**he first precision therapies, targeted to specific molecular alterations, are already available. Despite this progress, the lack of diversity in genetic databases limits the potential benefits and markets for these advances. To further grow the field of precision medicine, much more knowledge is needed of the global diversity found in the human genome.

## **Incomplete genetic knowledge limits the advancement of precision medicine**

It is a well-known fact that most drugs do not make it past the early stages of clinical trials. Even those that do reach the clinic often do not perform as well as hoped – for example, a recent study found that more than half of cancer drugs entered the market without evidence that they improved survival or quality of life<sup>1</sup>. And when drugs do work, they do not always work equally well in everyone.

Precision medicine aims to improve the odds of success, getting the right drugs to the right patients in the right dose, saving time and money and ensuring that more people are likely to receive effective treatment<sup>2</sup>. These promises are starting to

be realised for certain patients where there is a clear link between a genetic variant and the effectiveness of a certain drug. For example, ovarian cancer patients can be helped by the cancer growth blocker olaparib (Lynparza), but this drug only works if the cancer is caused by a pathogenic variant of one of the BRCA genes<sup>3</sup>, as revealed by a simple genetic test.

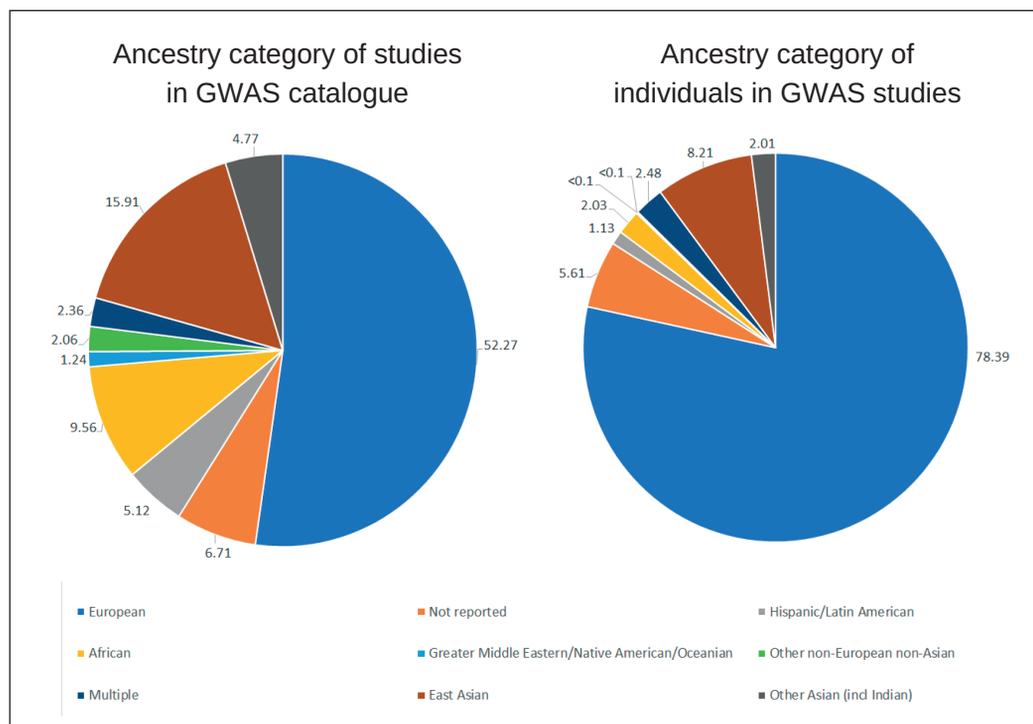
However, there are still many missed opportunities. Precision medicine requires knowledge about specific genetic variants and how they relate to disease. The more common variants – the ones that are studied the most – are the ones most likely to become targets for new drug development. But a common variant in one part of the population is not necessarily common everywhere, and this approach will only be effective if there is a fuller understanding of the different genetic variants across the entire global population.

A recent analysis estimates that 78% of the people whose DNA is included in genome-wide association studies (GWAS) are of European descent, with a similar picture emerging when looking at the overall catalogue of studies carried out to date<sup>4</sup>. A further 8% are East Asian, 6% have no

**By Sumit Jamuar,  
Dr Jonathan Picker,  
Dr Saumya Jamuar  
and Dr Yaron Turpaz**

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**Figure 1**  
Distribution of ancestry in the overall catalogue of GWAS studies (left) and individuals within studies (right), adapted from Sirugo et al 2019<sup>4</sup>



reported ethnicity and the remaining 8% represents everyone else – including all of Africa, Latin America, Pacific island nations, the Middle East, Central and South Asia and various indigenous tribes across the world (see Figure 1).

Despite early efforts to capture a wider range of human genetic diversity, such as the HapMap<sup>5</sup> and 1,000 Genomes Project<sup>6</sup>, there are major gaps in our understanding of the genomic variants in populations around the world. One particularly striking example comes from the recent pan-genome analysis of more than 900 individuals of African ancestry, which identified hundreds of millions of bases that are not represented in the current human reference genome<sup>7</sup>.

The conclusion is stark: the vast majority of the world’s population is not represented in genetic databases. In turn, this means that they cannot benefit from, nor contribute to, advances in genetic medicine to the same extent as people of white European ancestry.

**Pharmacogenetics can explain variations in drug response**

The biomedical research community is slowly becoming more aware of the limitations that come with the lack of diversity in genetic databases, but the problem has persisted for years. Almost two decades of genetic research have consistently been carried out on DNA from people that only repre-

sent a small part of the global population, leading to healthcare inequalities where people are misdiagnosed or receive the wrong treatment and ignoring potentially huge sectors of the global pharmaceutical market.

One example is in the treatment of asthma patients. In the United States, asthma is most prevalent among people of Puerto Rican or African descent, but the commonly-available asthma medication albuterol does not work as effectively in these populations as it does in people of European descent. Recently, a study looking at the genomes of asthma patients appears to have found a genetic factor that explains the variations in response to albuterol, but without further data from people of non-European backgrounds, it has not been possible to repeat the study and come to a definitive conclusion<sup>8</sup>.

Cardiovascular disease is another area where different parts of the population do not respond in the same way to available treatments. Since the 1980s, clinicians have been aware that certain antihypertensive drugs are more likely to work in people of European background and others are more successful in people of African descent<sup>9</sup>. In general, it appeared that white people responded well to all types of antihypertensive drugs, while black people benefited more from diuretics or calcium channel blockers than from ACE inhibitors or beta-blockers.

A trial of heart failure treatments among people of different ethnic backgrounds even led to the development of BiDil, a heart disease drug aimed specifically at people who self-identified as black<sup>10</sup>. However, BiDil has not been as popular as hoped<sup>11</sup>. Physicians were sceptical of the benefits and some raised concerns that a drug was being marketed using the unscientific concept of perceived race rather than underlying genetic make-up<sup>12</sup>.

For some drugs, the observed differences in efficacies between ethnicities can be explained by pharmacogenetics. People with an Asian background often require a lower dose of the blood thinner warfarin, for example, resulting from common polymorphisms in two genes related to warfarin metabolism<sup>13</sup>.

For example, our knowledge of the genetic basis of cystic fibrosis is mostly based on the genetic variants that are commonly found in people of European background. This disease is often underdiagnosed in African Americans because the genetic variant that accounts for 70% of cystic fibrosis cases in people of European descent only occurs in 29% of African American patients<sup>14</sup>. As a result, cystic fibrosis is underdiagnosed in this population, disenfranchising them from access to specialty care and targeted treatments.

Incomplete knowledge of genetic diversity also leads to miscategorisation of pathological variants: a 2016 study showed that out of 192 genetic variations that were supposed to be linked to a disease in western populations, just nine were genuinely disease-causing in South Asians<sup>15</sup>. Our own unpublished analysis of public genomic data has revealed that a supposedly pathological variant linked to epilepsy in those with European ancestry is present in 96% of Indians without causing any signs of the disease.

The lack of information about the underlying genetics of disease and drug response across different sections of the global population means that currently-available precision medicine treatments mainly benefit people who have a genetic profile that most resembles that of the most commonly studied genomes – those of a white European background.

Instead of developing solutions based on a small proportion of the global population, the industry should be looking at disease profiles and genetics from a much more diverse set of individuals to identify drug targets and understand their effects in the body.

Several groups and organisations are trying to broaden participation in genetic studies by includ-

ing groups that thus far have been under-represented. But in order to do this, they have to address the issues that have led to the imbalance in genetic representation in the first place.

### Reasons for the lack of global genome coverage

One of the causes for the existing unequal distribution of genomic data has been that many GWAS studies and other research projects have taken place in countries where the majority of the population has white European/Caucasian ancestry. Furthermore, a desire for statistical rigour has encouraged researchers to largely focus on well-controlled, homogenous cohorts, rather than risk including smaller segments which might not provide the same statistical power<sup>16</sup>.

Another reason for the lack of diversity is that trial recruiters are finding it difficult to engage and involve under-represented groups. In the UK, researchers from the 100,000 Genomes Project noticed that cancer patients from Black and Caribbean communities were less likely to volunteer to have their genome sequences researched than white patients. An internal report found several reasons for this, including pressure on medical staff to recruit patients in a timely manner, which discouraged them from putting additional time and effort in reaching communities with possible language or cultural barriers<sup>17</sup>.

The same study also looked at reasons why these communities were reluctant to take part and found a persistent culture of distrust around genetic research. In recent years, the UK police force has been widely criticised for a biased method of DNA collecting, leading to black people being overrepresented in the police DNA database. This meant that the members of the black community were reluctant to share their DNA, even for a health cause. In the United States, meanwhile, the African American community has traditionally been less likely to trust doctors, partly as a result of the Tuskegee Syphilis Study<sup>18</sup>.

### Increasing diversity in genetic databases

Several new initiatives are now taking steps to include communities that have been reluctant to participate in genetic research and counter the lack of early recruitment of these groups.

The NIH programme All Of Us has a specific goal to build a research cohort of a million or more people representing the diverse backgrounds of the US population in order to advance precision medicine. It is encouraging anyone in the country

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to sign up, share health records on a secure site and volunteer to provide blood and urine samples. This will provide All Of Us with a collection of information that links genetics to health. To ensure that it is reaching a wider cross section of the population than previous genetic studies, the NIH is actively engaging with minority groups, such as churches and community associations that bring together African American or Hispanic ancestry groups. As of May 2019, 143,000 people have already taken part in All Of Us and more than half of them are from ethnic minority groups<sup>19</sup>.

But All Of Us is still not reaching everyone in the US. Native Americans have expressed concern that the NIH had not consulted them before launching the programme<sup>20</sup>. They worried that people could be identified based on their DNA if they are from a very small tribe, or that findings from Native American individuals could lead to new treatments that would benefit companies more than the tribes that provided the information. In response to the concerns, All Of Us is now holding formal meetings with tribal leaders.

Involving communities directly and early in the process is thought to be an effective method to engage under-represented groups with genetic research. This community-driven approach is adopted by several other initiatives that are also trying to bring more diversity to genetic databases. Organisations such as Human Heredity & Health in Africa (H3Africa) and Global Gene Corp are expanding genetic knowledge of global populations by working directly with researchers in countries where people are most affected by the current gap in genomic data and insights.

The African Society of Human Genetics launched H3Africa in 2010 to increase participation in genetic research on the African continent. Funded by Wellcome and the NIH, it provides support to African researchers to carry out genetics research within the continent, rather than relying on studies from Europe or North America. Since launch it has processed samples of more than 70,000 research participants across different countries in Africa, for studies that are directly relevant to the health of these populations<sup>21</sup>. For example, a recent H3Africa project uncovered that certain variants of the gene *APOL1*, normally associated with chronic kidney disease, are linked to an increased incidence of stroke among indigenous West Africans<sup>22</sup>.

Studying African genetics benefits people outside of the continent as well, such as the 75 million African Americans in the United States. In addition, because all humans ultimately originated

from Africa, genomes from this continent may hold valuable information for everyone.

As part of their mission to democratise healthcare through genomics, Global Gene Corp has launched India's largest DNA sequencing programme<sup>23</sup>. Currently, the 1.3 billion people living in India make up 20% of the global population but represent less than 2% of genetic studies. The Indian diaspora also makes up a significant part of the global population, with an estimated 30 million people of Indian origin living in other countries. By matching de-identified medical records to genomic sequencing data, this project is expanding the genetic dataset of people of Indian descent and providing vital insights for the pharmaceutical industry. The company is also using the data to build an evolving personalised pharmacogenomics app (ggcMETM) that is tailored to the Indian population.

Another initiative is the collaboration between Global Gene Corp, the University of Namibia and the Namibian Ministry of Higher Education, Training and Innovation. In November 2018 it announced a new national genomic initiative in the country<sup>24</sup>, aiming to build a framework for genomic research and improve precision medicine. Future plans also include setting up a Centre of Excellence in Genomics in Namibia, providing training programmes to build local capacity and expertise in this fast-growing field. The two million people in this country represent several ethnic groups and tribes that are currently underserved by available genetic medicine.

However, implementing genetic testing and genomics research in healthcare systems around the world is not simply a matter of directly copying existing systems from European or North American countries. One recent example of this localisation comes from a project to establish such a system in Singapore, which took local cultures and attitudes to preventive healthcare into account and adapted the process accordingly<sup>25</sup>.

### Democratising healthcare can expand the reach of precision medicine

Merely increasing diversity in global genetic databases is not enough to close the healthcare inequality gap. Access to healthcare has long been a challenge in many countries, particularly in rural areas. How can people living in remote regions of Africa receive adequate healthcare if the only hospitals are in cities? This challenge must be met to ensure that the benefits of precision medicine are opened up to a truly global market, not just the minority with European ancestry.

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For years, gaps in communication networks formed part of the problem. With phone lines and cable internet only reaching more built-up communities in Africa, anyone living outside of a decent-sized town would be unable to use any web-based services to easily connect with clinicians. Establishing a phone cable network is a huge and costly undertaking, and these networks were never able to connect every person on Earth. But with the arrival of mobile technology, access rapidly improved<sup>26</sup>. Placing a mobile reception mast is far less costly than laying a cable network and this has allowed remote communities to ‘leapfrog’ past cable technology straight to wireless connectivity.

This brings new opportunities for creative solutions to bring healthcare to everyone. Any technology that can be delivered through a wireless network can reach far and wide. This could include healthcare apps, drone delivery or designs for 3D-printing medical materials. Some of this is already happening. In Rwanda, the local government worked with Babylon Health to launch a nationwide service that allowed people to access virtual consultations through an app on their phone, from anywhere in the country<sup>27</sup>.

With digital healthcare technology already democratising access to medical expertise around the world, more people than ever before are getting access to healthcare. This is all the more reason to make sure that future medical advances in precision medicine will be available to everyone. By democratising genomic research in the same way, hand in hand with new digital technology, countries whose populations are currently under-represented in genetic databases can make great strides in filling this gap in information by actively recruiting participants into research studies.

Increasing the diversity of genetic databases helps everyone, not only those people who are currently not well-represented. Investment in this area will increase the opportunities for finding new genetic links to disease, providing knowledge that can benefit all of us. With more diverse genomes being sequenced, formerly rare genetic variants may turn out to not be so rare after all, attracting industry investment in what might have seemed like relatively niche targets for new drug development. And with a broad collection of genetic variants from many different populations, we may better understand the pharmacogenetic reasons for adverse drug effects, which ultimately saves time and money in clinical testing.

There is enormous potential for the development of new precision medicine drugs to reach large, global markets, but that can only happen

with access to more genomic information and insights from different populations around the world. It is time to move from the concept of a gold-standard ‘human genome’ to ‘humanity’s genome’ – a globally-diverse set of reference genomes drawn from many populations – to ensure that the revolution in precision healthcare will bring benefits to everyone, wherever they come from and wherever they live. **DDW**

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*Sumit Januar is co-founder, Chairman and CEO of Global Gene Corp. He has held several senior leadership positions in start-ups, global client coverage, strategy & transformation and a turnaround unit in an FTSE 100 company in London.*

*Dr Jonathan Picker is co-founder and co-Chief Scientific Officer of Global Gene Corp. He is Assistant Professor of Paediatrics at Harvard Medical School and a clinical geneticist at Boston’s Children’s Hospital.*

*Dr Saumya Januar, MBBS, MRCPCH, is co-founder and co-Chief Scientific Officer of Global Gene Corp; Head, SingHealth Duke-NUS Genomic Medicine Center, Singapore; Attending, Genetics Service, KK Women’s and Children’s Hospital, Singapore; Assistant Professor, Paediatrics, Duke-NUS Medical School, Singapore; Clinical Director, SingHealth Duke-NUS Institute of Precision Medicine, Singapore; and PI, Singapore Undiagnosed Disease Programme*

*Dr Yaron Turpaz MBA is Chief Data and Technology Officer and Managing Director of Global Gene Corp. He was previously the Chief Information Officer at Human Longevity, Inc (HLI) and Managing Director of Human Longevity Singapore. He has previously worked at AstraZeneca as Vice-President, R&D IT, the Eli Lilly Singapore Centre for Drug Discovery as Director of Integrative Computational Sciences and Affymetrix, Inc.*

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