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THE TRANSFORMATIVE BENEFITS OF POPULATION-LEVEL GENOME SEQUENCING

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Geometric illustration of a crowd of human figures. | Photo Credit: Getty Images/iStockphoto

In the last decade, genomics has undergone a revolutionary shift with the advent of technologies that have significantly improved throughput and reduced the cost of whole-genome sequencing, giving rise to population-scale genome-sequencing programmes – where scientists decipher the complete genetic makeup of large populations, offering unprecedented insights into the intricate view and tapestry of human diversity.

This week, the UK announced the completion of half a million whole-genome sequences, almost 0.7% of its population. Such data-sets are transformative, with far-reaching implications for both immediate and long-term advancements in the biological sciences.

An early effort to use large-scale population genetic studies was initiated in Iceland by deCODE genomics in 1996, with most of the Icelandic population enrolling for genetic studies in around a decade's time. The initiative, along with the democratisation of sequencing technologies, provided the initial impetus for programmes that wished to use population-scale genomic data for precision medicine and public health.

The deCODE effort considerably improved our understanding of the genetics of diseases and the utility of such data in risk assessment. It also contributed significantly to the methods, infrastructure, and standards with which researchers handle large-scale genomic data and set up discussions on their bioethics. The project also laid the groundwork to integrate medical records and people's genealogies, resulting in new drugs and therapeutics.

deCODE's success plus the wider availability of sequencing technologies gave rise to a number of population-scale genome initiatives around the world, including many pilot programmes initiated in the last decade. At first, several projects worked with hundreds to thousands of genomes, but in the last half a decade, such endeavours have leapfrogged to lakhs of genomes.

Indeed, one of the first such was the UK's '100K Genome' project, which aimed to bring genomics into routine healthcare. We estimate more than a dozen countries today have genome programmes of a lakh genomes or more. A recent initiative by the pharmaceutical companies Regeneron Genetics Center, AstraZeneca, Novo Nordisk, and Roche, along with the Meharry Medical College, Tennessee, has even planned to sequence more than five lakh individuals of

African ancestry through the Diversity Human Genome Initiative.

Many large-scale genome programs are currently underway, including the AllofUS programme in the U.S., which will collect genetic information of a million people with funding from the National Institutes of Health. The European Union recently launched the '1+ Million Genomes' initiative. A 'Three Million African Genomes' is also currently in the works, as is the Emirati genome programme's scheme to sequence more than a million samples (more than 400,000 have already been completed).

Population-scale genome efforts have significantly diverse objectives. Many programmes take advantage of a unique population composition to understand disease prevalence and biomarkers for diseases, and use that to inform the discovery of novel therapeutic targets. Other efforts seek to build scalable public-health initiatives where genomic data is used in decision-making and medical care.

For example, according to one estimate, 18.5% of the UK's 100K initiative was actionable, translating to direct healthcare benefits to participants.

The cost of whole-genome sequencing is also falling in tandem. Together with a growing body of evidence as to the data's usefulness, it is entirely possible that a significantly large number of humans around the world will have their whole genome sequenced in their lifetimes in the coming decade as well as a similarly significantly large number of people being able to access information derived from sequencing data for routine diagnostic workups and to newborns for diseases.

Of course, just as population-scale programmes open new doors, they also confront new challenges, especially with regard to the ethics of and the access to these genomes, and the discoveries that build on them. There are also significant concerns regarding the equitable representation and access to the fruits of discoveries (e.g. over-representation of certain ethnic groups in population-scale data sets).

Countries like the U.S. have also proactively created regulatory frameworks to prevent the misuse of genetic data, such as to prevent insurance and employment discrimination, using the terms of the Genetic Information Non-discrimination Act.

Asia, and India, are not far off vis-à-vis population-level sequencing either. The GenomeAsia project, led by multiple partners across the continent, plans to sequence a lakh whole genomes from diverse populations. An initial pilot data set with whole genomes of 1,739 individuals belonging to 219 population groups in 64 countries was published in *Nature* in 2019.

A pilot programme for population genomes in India named IndiGen provided an early view of more than a thousand genomes of individuals from cosmopolitan areas in India. It also yielded some clues to the landscape of many treatable genetic diseases and variants of clinical significance, including the efficacy and toxicity of drugs and the prevalence of rare disorders. A larger programme to sequence 10,000 whole genomes from diverse population groups is in the works under the GenomeIndia initiative.

Looking to the horizon, the long-term impact of population-scale genomics extends beyond individual health, shaping our comprehension of human evolution, migration patterns, and adaptation to diverse environments. It will also contribute significantly to our knowledge of human biology. In essence, population-scale genomics stands at the forefront of a genomic revolution, poised to revolutionise healthcare, illuminate our evolutionary history, and propel us towards a future in which precise, personalised approaches will influence the landscape of

medical and biological understanding.

And just as the day when we will sequence a billion genomes in a single project isn't far off, the time for an individual acquiring a right to access and understand their own genome sequence is also at hand.

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