Whole genome sequencing improves diagnosis of rare diseases and shortens diagnostic journeys for patients

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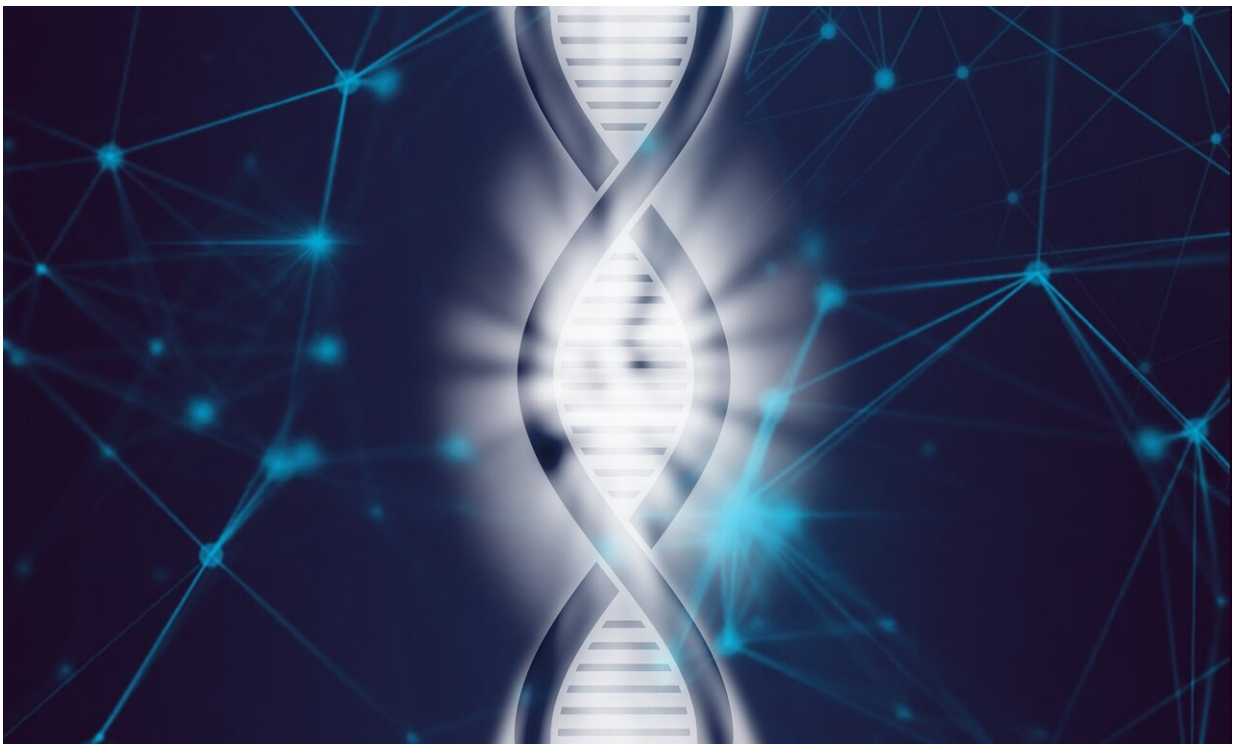

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A world-first scientific study, published in the *New England Journal of Medicine*, has shown that whole genome sequencing (WGS) can uncover new diagnoses for people across the broadest range of rare diseases

investigated to date and could deliver enormous benefits across the NHS.

The pilot study of rare undiagnosed diseases involved analysing the genes of 4,660 people from 2,183 families—all of whom were early participants in the 100,000 Genomes Project. The ground-breaking Project, led by Genomics England and NHS England, was established in 2013 to sequence 100,000 whole genomes from NHS patients and their families.

The pilot study, led by Genomics England and Queen Mary University of London and undertaken in partnership with the National Institute for Health Research (NIHR) BioResource, found that using WGS led to a new diagnosis for 25% of the participants. Of these new diagnoses, 14% were found in regions of the genome that would be missed by other conventional methods, including other types of non-whole genomic tests.

Many of the participants had gone through years of appointments, without getting any answers. By having their whole genome sequenced diagnoses were uncovered that would not have previously been detectable. The pilot study shows that WGS can effectively secure a diagnosis for patients, save the NHS vital resources and pave the way for other interventions.

Participants who received a diagnosis through the pilot include:

- a 10-year-old girl whose previous seven-year search for a diagnosis had multiple intensive care admissions over 307 hospital visits at a cost of £356,571. Genomic diagnosis enabled her to receive a curative bone marrow transplant (at a cost of £70,000). In addition, predictive testing of her siblings showed no further family members were at risk.
- a man in his 60s who had endured years of treatment for a

serious kidney disease, including two kidney transplants. Already knowing his daughter had inherited the same condition, a genomic diagnosis made by looking at the whole genome for him and his daughter enabled his 15-year-old granddaughter to be tested. This revealed she had not inherited the disease and could cease regular costly check-ups.

- a baby who became severely ill immediately after birth and sadly died at four months but with no diagnosis and healthcare costs of £80,000. Analysis of his whole genome uncovered a severe metabolic disorder due to inability to take vitamin B12 inside cells explaining his illness. This enabled a predictive test to be offered to his younger brother within one week of his birth. The younger child was diagnosed with the same disorder but was able to be treated with weekly vitamin B12 injections to prevent progression of the illness.

For around a quarter of study participants, their diagnosis meant they were able to receive more focused clinical care. This included further family screening, dietary change, provision of vitamins and / or minerals and other therapies.

The study is the first to analyse the diagnostic and clinical impact of WGS for a broad range of rare diseases within a national healthcare system. The findings support its widespread adoption in health systems worldwide.

The high performance of WGS for specific conditions observed in the pilot study—including intellectual disability, vision and hearing disorders of 40-55% diagnostic yield—has underpinned the case for the inclusion of WGS to diagnose specific rare diseases as part of the new NHS National Genomic Test Directory.

The pilot study was also conducted in partnership with the National

Institute for Health Research (NIHR) and Illumina who undertook the sequencing, and it was funded by the NIHR, the Wellcome Trust, the Medical Research Council, Cancer Research UK, the Department of Health and Social Care, and NHS England.

Professor Sir Mark Caulfield (lead author) from Queen Mary University of London, and former Chief Scientist at Genomics England, said: "We hope this major advance will enable rare disease patients worldwide to start receiving diagnostic whole genome sequencing where appropriate. Our findings show that deployment of this comprehensive and efficient genomic test at the first signs of symptoms, can improve diagnostic rates. This study has paved the way for clinical implementation of whole genome sequencing as part of the NHS Genomic Medicine Service."

Professor Damian Smedley (lead author) from Queen Mary University of London, said: "This is the first time that whole genome sequencing has been directly embedded into rare disease diagnostics in a healthcare system like the NHS and applied at scale across the full breadth of rare disease. Our novel software, together with collection of detailed clinical data, was key to us being able to solve the "needle in a haystack" challenge of finding the cause of a rare disease patient's condition amongst the millions of variants in every genome. A large proportion of the diagnoses we discovered were found outside the coding region and would not have been detected by existing approaches. This study makes the case for healthcare systems worldwide to adopt whole genome sequencing as the genetic test of choice for rare disease patients."

Jillian Hastings Ward, Chair of the Genomics England Participant Panel, said: "The people who signed up for whole genome sequencing in this pilot study were hoping to find new diagnoses for their loved ones, and were willing to share their precious data with Genomics England so that rare diseases could be better understood. The pilot has helped on both of these fronts and we are delighted that whole genome sequencing is now

being routinely offered by the NHS to more families across England as a result. This is the beginning of a great leap forward and it needs families, clinicians and researchers to continue to work together for its full potential to be realised."

Dr. Richard Scott, Chief Medical Officer at Genomics England, said: "Historically, diagnosis of rare diseases has often been reliant on clinicians doing multiple different targeted tests—an approach that can delay diagnosis and access to more tailored care. Improved knowledge of genomics and the whole genome sequencing and data infrastructure that the government and NHS have invested in now offers us the ability to radically transform the process. This paper provides evidence of that transformation and where it has most impact. We're proud at Genomics England to be working in partnership with the NHS to bring the benefits of whole genome sequencing to patients."

More information: 100,000 Genomes Pilot on Rare-Disease Diagnosis in Health Care—Preliminary Report, *New England Journal of Medicine* (2021).

Provided by Queen Mary, University of London

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