THE GENE GENIE

Professor Mark Caulfield, Chief Scientist at Genomics England, explains how advances in genomics research and big data are revolutionising treatments for cancer and rare diseases.

One child who participated in the 100,000 Genomes Project had exhibited developmental delay and suffered intractable seizures from the age of four months. By the time she was four years old, her parents had enrolled her in a number of research projects, but none were able to diagnose or treat her with any medicine.

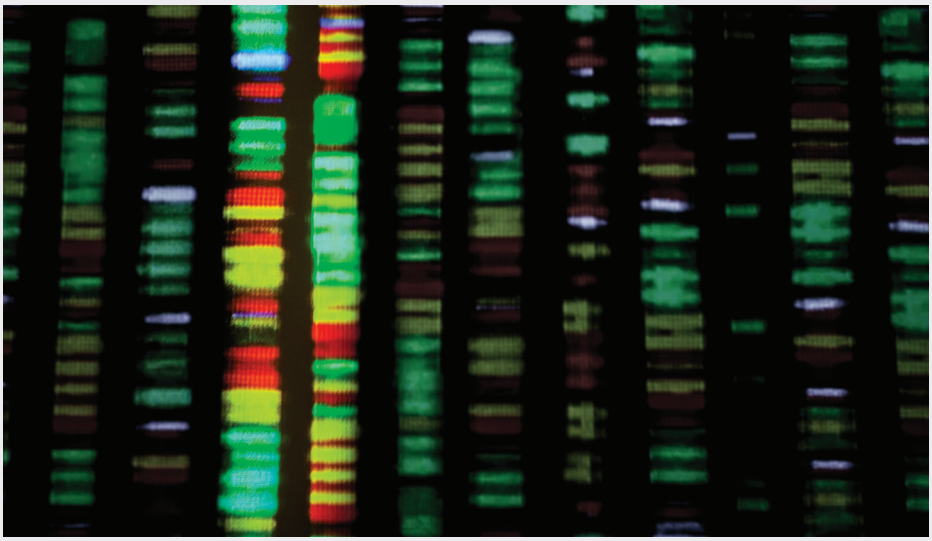
"We searched through the genome and found there was a mutation in a sugar transporter, and she was unable to take sugar into the brain. This triggered seizures because her sugar level was dropping," says Professor Mark Caulfield.

"The girl started to receive a high-fat diet – the brain has a mechanism to make sugar out of fat. Her seizures reduced and she showed some developmental improvement."

Her parents' genomes were sequenced as part of the project – to help make sense of the child's genome by filtering out anything unrelated to the disease – and the research team found that the child had a new mutation which her parents didn't carry.

"So they can now go on to try for another baby in the knowledge that it's extremely unlikely the same thing would happen. That's reassurance, which is one of the really important things in modern medicine," Mark adds.

Mark is Chief Scientist at Genomics England, the Department of Health-owned company in charge of the 100,000 Genomes Project, which is sequencing genomes from 75,000 people affected by rare and inherited diseases, cancer and infections. Every cancer patient will contribute two genomes – one from a healthy cell and one from their cancer – for comparison. Three genomes will come from rare disease patients – one from the patient and two from close blood relatives.



How it began

The "NHS transformation" project arose at the London 2012 Olympics when a group of scientists met then-Prime Minister David Cameron. "They advised him that the moment was right to transform the NHS so that genomics could be applied to health," Mark says.

It was nine years since the Human Genome Project had been declared complete, in 2003, and the ability to sequence had accelerated – where it once took years it was now possible to sequence a single genome in a day.

The government initially provided £186m and other commercial partners co-invested, including a sequencing partner Illumina, bringing the total estimated value of the project to £300m.

A further £50m a year for five years was promised in the 2015 Comprehensive Spending Review in order to "take the project to the next level and ensure that the genomics knowledge of the country could be concentrated in one place", Mark says.

"That would provide globally reliable datasets for people to work on, drive up the value for diagnosis and treatment in the NHS but also bring new medicines and diagnoses to test on this dataset in Britain. It draws inward investment into the UK – our mission is to deliver both for health and wealth gain for the country."

Overcoming challenges

But the infrastructure needed to carry out the work was not in place when the project began. Thirteen genomic centres of excellence around England, a sequencing centre and a data centre with a semi-automated pipeline to carry out the analysis were needed for the project.

"Each genome is on a big file – about 66 gigabytes. You can't just send these over the internet; you need to have a data centre," Mark says.

Embedding the project in the NHS – which covers 13 NHS Genomic Medicine Centres across 85 NHS trusts across England – has also been a challenge, now that the project has grown to cover Northern Ireland, Scotland and Wales.

Progress made

So far, the project has possession of 22,237 genomes, and over 30,000 people are enrolled in the programme. It has returned around 3,600 reports to clinical teams who care for patients with rare diseases, and about 500 cancer reports.

The project is linked to cancer drug trials which deploy medicines targeted at particular genetic mutations. Cancer reports highlight the mutation present in the genome and researchers can then suggest these particular drugs to the patient.

Diagnoses for rare disease have also increased by 20-25%. "We're bringing new answers to people who previously the NHS would not have been able to provide an answer for. We're stratifying healthcare by targeting the right therapy to the right patient at the first opportunity."

Participants have been "at the heart" of the project, Mark says. A participant panel sits on the projects' committees, such as the access review committee and ethics advisory committee, and holds the project's leadership to account of behalf of other participants.

Press coverage of the project has been generally supportive too. "Although we addressed an area which is difficult – combining big health data with genetic data – we've managed to avoid pitfalls, and that is down to the strong involvement of the participants."

ALL ABOUT MARK

- ✔ Mark graduated in medicine from London Hospital Medical College in 1984.
- ✔ He trained in clinical pharmacology at St Bartholomew's Hospital and developed a research programme in molecular genetics of hypertension and translational clinical research.
- ✔ He has directed the Barts National Institute for Health Research (NIHR) Cardiovascular Biomedical Research since 2008, and been an NIHR senior investigator at Queen Mary University of London since 2013.
- ✔ He is an NHS consultant in the Barts Blood Pressure Clinic within Barts/ William Harvey European Society of Hypertension Centre of Excellence.
- ✔ Mark is one of the top 200 most highly-cited genomics researchers in the world.

The future

The next phase of the project is to bring in 2,600 researchers to look at the data.

"Our duty is to get research communities, where we don't get a diagnosis initially, who will continue to work on this and drive up its value for healthcare and achieve diagnoses where there is a diagnostic need. Nobody has ever done this in this way before in genomics."

But genomics is just one part of the jigsaw. Mark sees the future of diagnosing and treating diseases with multiomics, including epigenetics. "What the genome is made into when it's translated by RNA into protein, into functions in the body – a multiomic approach will probably lead us to understand much better the architecture of disease." BMS