# Minutes of the First Ordinary Meeting

*Held on Thursday 14th November 2019*

*'100,000 Genome Project: Transforming Healthcare'*
*Professor Sir Mark Caulfield, Co-Director of the William Harvey Research Institute and Chief Scientist for Genomics England*

Professor Caulfield started his lecture by outlining that each of us have a 3.3 billion letter code – this is our DNA – our genome. It is individually unique to each of us. Within the code are exomes - segments of DNA that code for all our proteins. Amazing and rapid advances in the technology of DNA analysis in the last 10 years had made the 100,000 Genomes Project possible: in terms of both speed and cost. Just a few years earlier the cost to analyse this many genomes would have been several trillion dollars as opposed to the £300 million it has cost. Sequencing of the genome in 100,000 individuals by a collaboration led by Genomics England is providing amazing new insights into our life and health and providing new opportunities for clinical investigation and treatment across a range of health areas.

The journey towards capturing these genomes began in 2012 around the time of the London Olympics. This was not only led clinically but also politically. Sir Mark paid tribute to the political leaders who had the foresight and vision to invest in this world leading endeavour. This included the then Prime Minister David Cameron and the Secretaries of State for Health Jeremy Hunt and Matt Hancock. The plan achieved success in December 2018 when the trajectory of 100,000 genomes was reached. Now the aim is to analyse 5 million genomes. Sir Mark paid tribute to colleagues in Liverpool the Northwest and North Wales for their contribution to the success of the project.

The project had focused on rare diseases, susceptibility to infection and cancer. This endeavour brought together not only the DNA of individuals but also their current clinical information and permission to use their future clinical information. Altogether 21 petabytes of information is held on secure servers that are constantly assessed for security. A substantial innovative information architecture was specifically established for this programme. The Biorepository for the Project is situated in Milton Keynes. In addition 13 Genomic Medicine Centres have been established including one in Liverpool. The endeavour has required close cooperation between the National Health Service and many universities.

Clinicians who refer patients for analysis were provided with the detailed report in much the same way that they receive reports for other investigations. A high-level of clinical detail they provide gives a greater likelihood of a report that is helpful to the patient and their clinical team. 123,000 samples were received of which 119,000 provided a whole genome and in 104,000 a full report was provided to the NHS for validation and patient feedback. In around one in four, a meaningful variation or abnormality was detected. In around half the patients with cancer, genomic signatures were identified which enable that person to receive a specific experimental therapy via a trial, or a medication available from the NHS. This was an exciting opportunity for highly personalised medicine.

Rare and inherited disorders are individually uncommon but when added together they make up a very substantial proportion of health disorders. Because of their rarity progress requires international collaboration, something the project really promoted. Professor Caulfield spoke about the very first patient identified with such I disorder. This patient had a sugar transporter protein abnormality (glucose transporter 1), which was amenable to treatment with a ketogenic diet. In providing the best advice to families in such circumstances it was helpful if there was a larger family structure and a high-level of clinical detail. Even apparent minor features in the clinical details could be the key to diagnosis.

Professor Caulfield then outlined three more patients where abnormalities of metabolism were identified. The testimony of these parents and families was moving. Where treatment became identified it was life changing even miraculous. Even in cases where no new treatment was identified families were still extremely grateful that they now knew why their child was so affected.

It could also be very useful for consideration of having further children. In the case highlighted above it turned out that the patient had a *de novo* mutation and the parents did not carry the mutation.

For cancer tissue samples, being involved with the project was changing important aspects clinical practice for teams. It had been clearly demonstrated that storage in formalin ruined samples for DNA analysis. A whole new approach using fresh vacuum packed samples stored at 4° centigrade ensured samples were suitable for genomic analysis. Altogether 17,000 cancer patients joined the project and analysis of the tumour genomes was focused on 136 specific cancer driver genes. Professor Caulfield elegantly demonstrated how matching the genomic analysis to electronically held hospital episode statistics could provide great clinical insights without inconveniencing the patient. An example would be a cancer relapse identified by a repeat attendance at hospital – without having to recall the patient for a research appointment. Of course this could only be done with prospective informed consent.

Professor Caulfield spoke about the collaboration with Professor Sir Munir Pirmohamed (who was present in the audience) to identify genes associated with drug toxicity. Other opportunities included identifying cancer risk genes such as *BRCA-2* and the like but much more care and thought needs to go into this area. The reason it is that knowing that you <u>may</u> have a risk is important but itself can bring risks of worry and concern. The fact is that for many genes known to be sometimes associated with disease, on many other occasions they do not appear to cause any health problems. Such genes may be modified by other genes and by lifestyle and environmental factors. There is need for much reflection and thought in this area. It is in such areas where direct-to-public testing can result in a difficult situation for individuals. Sir Mark urged real caution for individuals and for providers.

A big message from Professor Caulfield was that we had at our disposal a world class repository of information arising from the 100,000 Genomes Project was available to researchers. He was very keen indeed that this resource was used for the maximum benefit of citizens and patients across the world. This world class clinical and research programme is backed up by an equally impressive education programme with the provision of 1200 Masters level courses for example.

The future looks even brighter. As well as moving on to sequencing 5 million genomes, a new digital referral platform is undergoing beta testing. There is the opportunity to look beyond DNA and into RNA and hence move into Multi-omic sequencing and analysis. As well as continuing to look at rare diseases there are opportunities to look at newborn screening to see if the current newborn screening programme can be improved using this methodology. In addition there is the opportunity to further explore pharmacogenomics.

As impressive as the science and Informatics are, the participation and oversight of the 35 strong Participant Panel ensure the governance is class leading. An external public and patient consultation indicated that key features of the NHS Social Contract including reciprocity, altruism and solidarity provide a strong framework for engagement in genomic medicine. They indicate their concern about use of these data for law enforcement, insurance or marketing purposes or genetic manipulation.

This was a fantastic lecture from a world-class leader in his field and the audience were duly spellbound. Liverpool Medical Institution was very fortunate that Professor Sir Mark Caulfield was able to speak to us this evening. One member of the audience was in fact a Participant in the project and summed up beautifully the amazing impact that this had had for her and her family.

Steve Ryan