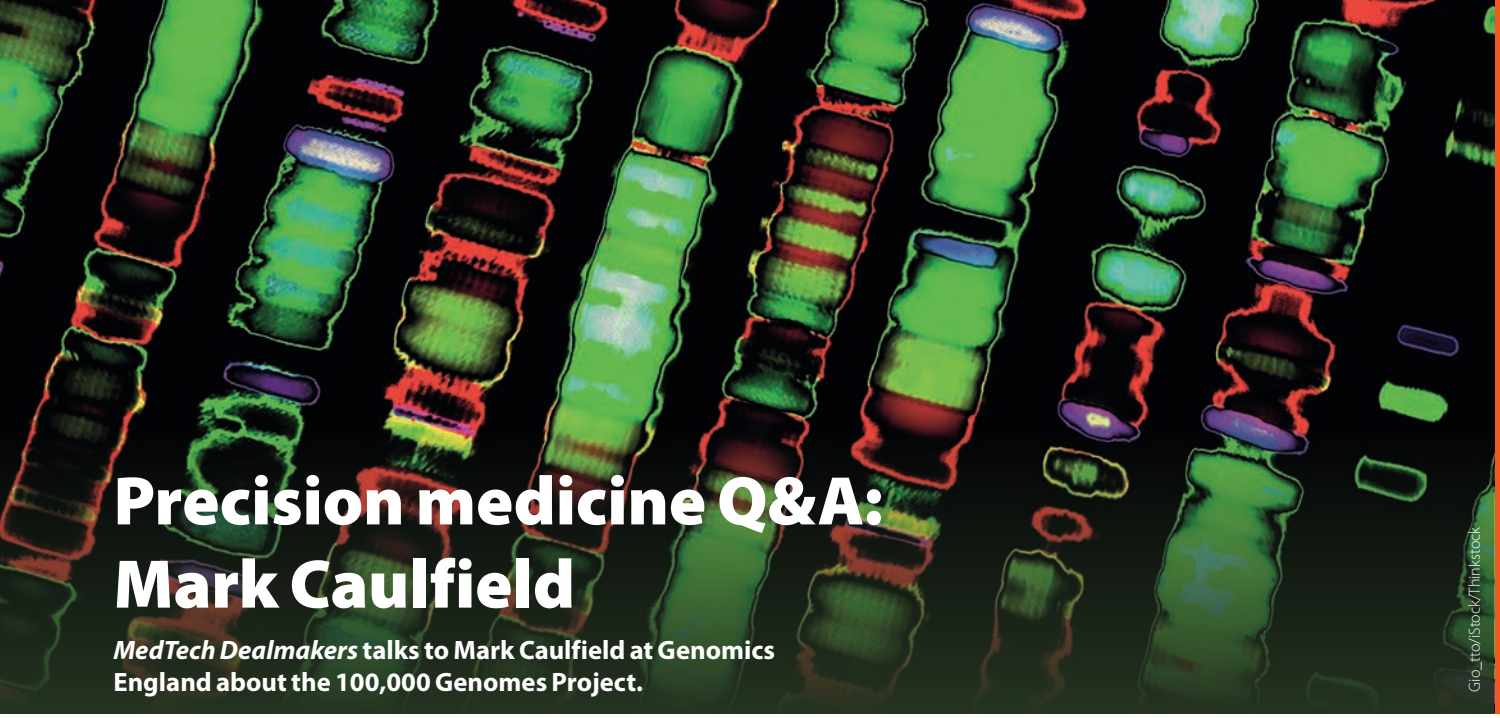

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Precision medicine Q&A: Mark Caulfield

***MedTech Dealmakers* talks to Mark Caulfield at Genomics England about the 100,000 Genomes Project.**

Next-generation sequencing technologies are now providing rapid access to genomic data on an unprecedented scale, opening up new opportunities for precision medicine based on genomic insights. Various government initiatives are now seeking to catalyze efforts to exploit such opportunities. The 100,000 Genomes Project, run by Genomics England, was set up in 2012 to sequence 100,000 whole genomes from the UK population, focusing on cancer, rare diseases and infections. Raveena Bhambra, editor of *MedTech Dealmakers*, spoke to Mark Caulfield, chief scientist at Genomics England, about how the project came about, the partners involved and its progress so far.

Q ***What developments made it possible for the project to be initiated?***

Two developments made the genomes project feasible. The first was the substantial advances in next-generation sequencing technology. The second was improved analysis and understanding of how to analyze genomes. This is still a work in progress, and the gold standard is not yet established, but there are now a number of opportunities either commercially or through research-led innovation to have more robust analytical pipelines for genomic data handling.

Q ***What milestones has the project achieved so far?***

Working with NHS England, we've established 13 genomic medicine centers of excellence that cover the entire geography of England—essentially 52 million people—and begun to build the infrastructure to deliver the program at scale. In partnership with Wellcome Trust and the Wellcome Trust Sanger Institute, a £27 million center has been built in Hinxton, Cambridge, that is just being fitted out. This is one of the largest sequencing facilities in the world and is effectively the first NHS genome sequencing center.

We have established a pre-competitive consortium with industry that involves 12 different companies, ranging from small/medium-sized enterprises to large pharmaceutical companies; some are focused on diagnostics, some are focused on enabling technologies and others are focused on making medicines. This consortium has allowed us to shape our data center and made the program more fit for purpose in terms of industry involvement.

Another big milestone was advertising and persuading over 2,000 researchers, clinicians and trainees to join us in what's called the Genomics England Clinical Interpretation Partnership. These people have volunteered to help us to drive up the quality of the data and to improve the return in terms of diagnostics for patients. If we do this successfully, there will be opportunities not to just develop diagnostics but potentially to prime therapeutic innovation.

Finally, we now have over 7,300 whole genomes sequenced in various pilot studies, and the main program is now established in rare diseases and cancer.

Q ***A number of technology partners are currently working with the project; what factors did you consider when choosing them?***

All of these partners were selected following an open-competition tendering process. We tested 28 suppliers of annotation services, which look at variants in the genome and annotate them for the likelihood of being contributors of the disease. This is a great help to us because some of these companies invested considerably in developing algorithms to do this. We then selected the best five suppliers for our goals. Each of these companies—Congenica, Omicia, Lockheed Martin–Cypher, Nanthealth and WuXi NextCODE—offers slightly different solutions, and some of them are focused more on cancer, such as Nanthealth. What we are doing now with these companies is to bring them into our data center to establish their algorithms, and they will try to support us by supplying reports back to clinicians.

We also had a sequencing competition at the outset, which a small number of companies entered. Two emerged as having a high-caliber product, and one of those was absolutely ready to do the program, and that was Illumina. We have them as a key partner, and they are developing bioinformatics solutions that they are making available to the researchers at our GENE Consortium. Illumina wants to develop an end-to-end bioinformatics pipeline that analyzes this data alongside the other suppliers that we are working with because we think at the moment it needs multiple partners to be working on

this, as the gold standard hasn't been established. It's important not to rule people out or to exclude particular approaches whilst we are still unclear what the optimal strategy is. We're trying to create an ecosystem in which the best people who have the best products for analysis of these genomes can support us in this activity whilst also making sure that we have the semi-automated pipeline that accelerates the flow of data back to the clinic.

Q ***It's an opportunity for these companies to show what they're made of in this project?***

Yes, the big benefit of supplying such services in this project is that at the end of it, if these companies come in and make this work with us as partners, then they'll have a product that will be of interest to health care systems around the world. We are working with some of the best in the business. Some of them started out in an academic sphere and have then moved into a company, but all of them have differentiated skills to offer, and in this environment it's important to embrace that possibility with your technology partners. It might be that one company has a brilliant solution for part of the pipeline and another company has a brilliant solution for a later part, and if they work together they have an end-to-end solution. The philosophy we're taking with such a large taxpayer-funded project is that we're trying to encourage an ecosystem that stimulates innovation and that doesn't restrict the ability to deliver the best products to patients in the NHS.

Q ***Where do you anticipate the project could have the earliest impact on drug development and/or health care?***

There are several ways in which it might help drug development. In cancer, we plan to compare the germline genome of ~25,000 individuals with their cancer cell genome—so 50,000 genomes in total—whereas with rare diseases, optimally, we would sequence the genomes of the two parents and their affected offspring. So the program will involve about 70,000 people in total, which is a huge repository of information. As it reaches a lot of rare diseases, it could be very good to partner with us and the NHS Genomic Medicine Centres to undertake trials of new medicines, because for some of the diseases we are working on, patients are hard to find. If we have them already identified, it may help accelerate enrollment in clinical trials. We'd like to be running clinical trials in both rare diseases and cancer, providing a platform with other sponsors that helps address the unmet need in these spaces. We'd be delighted to use the framework, the sample size and its reach across the NHS in England to bring the fastest possible benefit to patients and encourage an ecosystem where people bring the new medicines in these therapeutic areas to us, so patients get the earliest opportunity to access them.

We're also establishing a stratified health care and therapeutic innovation Clinical Interpretation Partnership (GeCIP) domain, which is academically based, to look at every protein that comes out of the pipeline for druggability—for example, asking if there is a pocket on the protein that you might target for drug development, or is there a small chemical or large molecule that might target that protein, and is it on a shelf already? Is there human data? If so, could this see the medicine being repurposed from one area to the other? We're also trying to provide a framework for doing trials working with partners such as Cancer Research UK and various rare-disease networks around Britain from NIHR. Finally, we'll have a pharmacogenetics element, which will be looking at how we can stratify a response to medicines.

Q ***Beyond rare diseases and oncology, are there other therapeutic areas that could be viable for a project of this nature in the future?***

At the moment, we haven't got any other foci, and that is because when we started, these were the diseases where it seemed the technology could have the greatest potential to bring utility to patients. We have a contract where we could go up to sequencing 150,000 whole genomes; we don't have the money to do that, but other researchers could approach us to use the framework that we've established and extend the program into other disease areas. This technology is becoming much more affordable, but it is still relatively expensive, and so large-scale programs for very complex diseases would require careful financial thought.

Q ***What's next for the field of genomics and its application in precision medicine?***

Genomics and 'multi-omics' could make a difference in the stratification of medicines and the subgrouping of patients in ways in which we can't see from our current understanding of the biology of these diseases. Understanding the genomic basis of a rare disease is the first step in understanding how you target that disease, and some of our inability to address rare diseases has been on the assumption that there isn't going to be a treatment. However, as soon as we have genomic insights and know something about the biology, then sometimes it is possible for us to develop therapies. So, I do believe that we are entering an era of enhanced precision medicine; it won't work for everything, but I think it will be important in the next five to ten years. We welcome the Precision Medicine Initiative in the USA, and we're committing to working with people around the world—for example, we joined the Global Alliance for Genomics and Health (GA4GH) to learn about the latest approach to federating data. We have also signed Memorandums of Understanding with Australia's Garvan Institute and Canada's Genome British Columbia with the goal of sharing resources and expertise. We will do what we can to contribute to the genomic and multi-omic strategies for improved patient care both in the NHS and worldwide.

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