Interview: Sir John Chisholm â?? Executive Chair, Genomics England

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Sir John Chisholm, executive chair of Genomics England â?? a company set up and owned by the UK Department of Health to run the 100,000 Genomes Project, which aims to sequence 100,000 genomes from NHS patients with a rare disease and their families, and patients with cancer â?? discusses the companyâ??s milestones, the role of the NHS, and where the UK stands in terms of medical research globally.

Can you introduce yourself and Genomics England to our international readers?

Following a colorful career in the automotive and tech industries, where I founded Cap Scientific Limited, I am now executive chair of Genomics England. Genomics England is a company that was essentially established to deliver the 100,000 Genomes Project. This flagship project will sequence 100,000 whole genomes from NHS patients with rare diseases, and their families, as well as patients with common cancers.

In genomics, in order to provide a service for a patient, the results must be compared to all the other patients. It is only by collecting the knowledge across the whole population that we understand what can be done for the specific patient. Participating patients will have the opportunity to benefit from clinical insights derived from the sequencing of their genome while at the same time contributing to knowledge which will be valuable to the whole patient community. It is from that knowledge that world leading therapeutic products and processes will become available to all patients.

The project represents a great opportunity to translate our world-class genomic science into world leadership in genomic medicine. My expectation is that Genomics England will eventually be credited with creating a dataset of de-identified whole genome sequences matched with clinical data at a scale unique in the world.

What benefits will this deliver for patients?

It is estimated that one in seventeen people are born with or develop a rare disease during their lifetime. At least 80% of rare diseases have an identified genetic component, with 50% of new cases of rare diseases being identified in children. However, it can take considerable time and expense between a patient first presenting at a doctors and receiving an accurate diagnosis. The time taken to sequence a whole human genome has been dramatically reduced and will become more affordable for routine use as the price continues to fall.

How far would you agree that the NHS lends itself to this endeavor given its centralized structure?

Absolutely. The Cameron governmentâ??s initial premise behind establishing Genomics England was that we possess something in this country that does not exist anywhere else: excellence in science combined with a truly free-at-the-point-of-delivery, nationwide, publically funded healthcare system that attends to citizensâ?? health needs from cradle to grave. The UK performed one third of the human genome project, and the UK is the only market worldwide where we see a working genomics structure. Furthermore, we benefit from a thriving clinical system, and of course a single payer market: we are able to implement decisions that impact the entire system from a centralized network. If we scrutinize the two big gorillas in this world: the USA and China, we immediately become aware of how fragmented their approach to public health is. It is difficult to pull them together into a coherent approach.

A further advantage to working in this country is the extraordinarily strong coherence emanating from the commanding heights and pervading the entire apparatus. By this, I mean the strong political consensus that has been established right at the very apex of the health system, and which trickles all the way down to the grassroots science, bottom-up initiatives of charities. In other words, there is a strong sense of solidarity and commitment to unifying decisions.

What milestones have you reached since foundation?

Given the political impetus we had when we started, we had to get going fast. So we chose to piggyback on existing programmes such as the rare diseases programme at Cambridge University and Cancer Research UK â?? given their experience with the Stratified Medicine Programme. Our learning from both of these was that the scale of our project would require considerable reengineering of existing processes and protocols.

Following this pilot phase, NHS England partnered with us to set up and deliver the main programme. They established 13 new NHS Genomic Medicine Centers. Without their involvement, we would not be here today: they provided the structure that could learn from our initial lessons so that we could make progress and build a highly complex working system. The process took four years to get to the 50,000 marker, which we announced a few weeks ago, and we intend to complete 100,000 by the end of this year, so are now entering what I refer to as â??the functional stage.â??

To build an automated end-to-end system we have searched the world for products and ideas that can contribute to our end goal. For every piece of technology we sought to bring in, we have always adopted a process of â??Bake Offsâ??: if somebody says they have a product, we ask them to test it against the inputs that we operate. Initially, we found that very few people were capable of

completing the task in the way we wanted and achieving the degree of accuracy and integrity that we required.

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Is the UK at the forefront of medicinal progress?

In terms of genomics, no one would dispute the fact that the UK is a world leader in population genomics, largely due to the fact that we are the first in the field. France, Denmark and Japan amongst others have projects in the pipeline, but no-one other than ourselves is operating at scale in a real health system yet.

A critical strategy we undertook at the beginning was to appreciate that fundamental to any genomics project is patient and public support: it only works if people allow you to use their data. We set up a process of consent that was absolutely thorough. We spent a lot of time deliberating about how best to educate and raise awareness. The understanding of the ethics of this and the convincing patients of the importance of this endeavor was absolutely critical. For someone who has a life-threatening condition who requires invasive surgery, our process to obtain consent for research use of their data could take considerably longer than that required for the surgery.

People must understand that diagnostic genomics only works if we are able to compare peopleâ??s data against everybody else. The data becomes part of a data set, which reflects a connected approach. We cannot guarantee that every individual will benefit from the insights we have collected, but the data is still just as vital for science to make progress.

How does the GENE consortium (now called the Discovery Forum) interact with the 100,000 Genomes Project?

The primary purpose of the genomics analysis we do is clinical care. The research environment that we offer to industry is derived from that but involves stripping out all of the identifiers. We take every care in ensuring all data sets are de-identified. We retain the primary responsibility for privacy in this way. Part of the undertaking we give to patients when we do the rigorous consenting process is to say that the data will never leave the NHS: the data is part of the NHS.

That creates a difficulty in research because unlike other data sets, the data is not given to researchers to take away. As an explanatory analogy, we operate what we call a â??Reading Libraryâ??, as opposed to a â??Lending Libraryâ??, whereby you can read the books, but you cannot take them away. We offer the opportunity to researchers to observe the data, to manipulate it and to perform calculations on the data (and to take away those calculations) but never to take individual data away.

When we started, one of the chief objectives was to discover how this would be useful to industry. Genomics is revolutionary to the pharmaceutical discovery process whereby a lot of pharma discovery processes are bottom up from cell biology, whereas the genomic approach is top-down calculation from the genome.

From a systems engineering point of view the key challenge is how to manage the vast data flow and the mathematical statistics to break down data into individual genes, and to then look for the differences in the genes. So far, it is a mathematical, statistical process. To go from that mathematical statistical process to a medical discovery, you need to combine the genomic data with deep clinical phenotyping.

There are a few pharma companies such as Alexion that have been born in the era of genomics. Classic pharma companies with a much longer heritage often find themselves with huge labs which tackle different discovery models which is why we sought to establish the â??GENE Consortiumâ?? of pharma and biotech companies who would help us with the understanding of what would be useful to them. We saw very quickly that we would have a very large data set, and that we needed to expand the community.

When the GENE Consortiumâ??s task had been completed, we formed the Discovery Forum, which represents the next stage of co-opting in the industry. At their first meeting, there were 100 attendees from foreign and British companies. The idea is to create a large learning and sharing forum, which meets quarterly. The companies involved vary from Big Pharma to biotechs to those involved in developing pipeline tools for helping discoverers, to the finance community seeking out new investments.

Who will benefit commercially from this initiative?

The scientists who perform the research, but primarily the patients. By the time that my grandchildren approach my age, they will regard healthcare nowadays as no different from bleeding someone for a fever in the Middle Ages! They will be so appalled at the idea of throwing dangerous toxins down the throat of a patient with some vague idea that it will be usefulâ??even though we have no certainty that the effect will always be the same. Genomics will make todayâ??s chemotherapy a therapy of the past.

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How successful have you been in the genomics industry, and where do you see the potential going?

There are already successful companies like Genomics PLC and Congenica who are the pioneers of the industry in the UK and there are companies that have located here in the UK that would not have done so were it not for us. There is no question that we are ambitious to make the UK the worldâ??s center for precision medicine. We compete against Boston and San Francisco amongst others.

My aim is to make it a no-brainer for anyone that wants to be in the precision medicine business, anybody who is serious and that needs to have an investment in the UK. The ecosystem we have here is like no other. If you look at the Wellcome Genome Campus at Hinxton, on that same site, there are 2,700 genomic specialists, which is the largest single concentration in the world.

What are the steps to make that vision a reality?

We are still very early on in the process of releasing our data to industry. There are currently over 30,000 genomes in the research environment and by the end of this year it will be at the best part of 100,000 genomes. Research is not an instant process. We will see the first real insights coming this year in publications and we are building momentum in what we are doing. We will be the first nation in the world to commission genomes on routine care, which involves mobilizing an infrastructure that we have built on the back of the 100,000 Genomes Project to build into the NHS core offering. That means that the potential data set is the size of the UK, our long-term goal.

In the genome, we will find the basic answers to all of these conditions. It is very complicated, and we will need a tremendous amount of data. We know that most conditions are not monogenic, and therefore driven by combinations of genes and regulatory areas. Because of that, the size of the data you need to unpick that is not in the thousands, but in the hundreds of millions. That is why it will

take us time, although I am convinced that in a decadeâ??s time we will have created an ecosystem that is at least world-class and we hope the best in the world.

We have a unique offering here in the UK that we would like everyone to benefit from and we are open for business.

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