HOUSE OF COMMONS

Science and Technology Committee

Oral evidence: Genomics and genome-editing, HC 854

Wednesday 8 February 2017

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Watch the meeting

Members present: Stephen Metcalfe (Chair); Victoria Borwick; Chris Green; Dr Tania Mathias; Carol Monaghan; Graham Stringer; Matt Warman.

Questions 1 - 105

Witnesses

I: Professor Sue Hill, Chief Scientific Officer, NHS England, Professor Mark Caulfield, Chief Scientist, Genomics England, and Dr Julia Wilson, Associate Director, Wellcome Trust Sanger Institute.

II: Professor Sir John Burn, Non-executive Director, NHS England, Professor Dame Kay Davies, Non-executive Director, Genomics England, and Dr Helen Firth, Clinical Lead, Deciphering Developmental Disorders Project, Wellcome Trust Sanger Institute.

Written evidence from witnesses:

- NHS England
- Genomics England
- Wellcome Trust Sanger Institute

Examination of witnesses

Witnesses: Professor Sue Hill, Professor Mark Caulfield and Dr Julia Wilson.

Q1 **Chair:** Good morning and welcome. Thank you for joining us today for the first session of our new inquiry into genomics and genome-editing. For the record, could you state who you are and in what capacity you are before us today?

Professor Hill: I am Professor Sue Hill, chief scientific officer at NHS England.

Professor Caulfield: I am Mark Caulfield. I am a clinician of 32 years and a researcher in genomics of 27 years. Since June 2013, I have been chief scientist for Genomics England and the 100,000 Genomes Project.

Dr Wilson: I am Julia Wilson, associate director of the Wellcome Trust Sanger Institute, one of the largest genome institutes in the world.

Q2 **Chair:** Thank you very much. As I said, this is the first session of our new inquiry. This morning we will focus on genomics, particularly the human health aspects of that. Could each of you give us your individual take on how genomics can help to improve human health outcomes?

Professor Hill: I will answer from an NHS perspective. Genomic technologies have been used in the NHS since the 1960s. They have been directing care since that time, although not necessarily in a systematic way across the NHS, in all clinical specialties or for all patients. That technology and its adoption have increased over time, as the technologies have emerged and as evidence has been built for their clinical utility, for example. That has been driving diagnosis and treatment of both rare and inherited disease and cancer for some time.

The 100,000 Genomes Project—and the availability of whole-genome sequencing as part of it—has provided a catalyst for change in the NHS's consideration of where whole-genome sequencing should be used in the future to underpin a more personalised approach to medicines and other treatments. It can help both to predict and to prevent disease; to make a precise diagnosis, by coupling the outcome from whole-genome sequencing with other diagnostics and other clinical and phenotypic data; to drive the personalisation of treatment, by understanding the genetic mutation and what it means for how drugs and other agents will interact; and, finally, to drive a more participatory role for our patients and public, in terms of the role that genomics and all of the genomics pathway can play in driving a more preventive healthcare system that is focused more on health than on illness. It provides a mechanism for us better to use the resources available in the NHS for diagnostics—in the region of £8 billion—to help to direct the spend on drugs, which is around £15 billion at the moment, but is set to rise. It is about how we use genomics better to personalise treatments and interventions.

Professor Caulfield: I agree almost entirely with that answer. The technology evolution over the last decade positions the national health service in our country to bring diagnoses to people with rare inherited disease, half of whom might, in the previous system, go through their life unable to obtain a genomic diagnosis. If we get a diagnosis, we may be able to intervene for some of them—or, at least, to develop treatments in the future. There are now an increasing number of treatments for rare inherited diseases.

In cancer, we know that in certain settings you can choose the medicines and optimise them to the person's individual cancer—or, at least, to a group of cancers, at the present time. That is not universal, but a project like this has the opportunity to take it to a new level, built off the fantastic platform of a free-at-the-point-of-care health system, such as we have.

Dr Wilson: I agree entirely with what has been said. I will add a slightly different dimension. Another aspect is pathogens or infections. We can already use genomics to track pathogen outbreaks and to get actionable information on drug resistance and things like that. I would also take it a step back, to basic science. I know that you asked about healthcare, but, while genomics can offer patients diagnoses and best treatment, that information can also feed back into fundamental research, drug discovery and the design of precise drugs for specific genetic diseases, be it rare genetic disease or cancer. We already have some super examples of where cancer genomics has led to targeted treatments. Having an NHS programme like this will also enable the research community to develop those new, better and more accurate treatments, for better patient outcomes.

Q3 **Chair:** My next question is about the speed of adoption and the general uptake and development of this. How quickly do you think that it will develop, so that it is readily available across the whole healthcare system?

Professor Caulfield: Today, we have geographic equity of access to the 100,000 Genomes Project across the whole of England. Scotland, Northern Ireland and Wales are joining the programme, with funds from those devolved Administrations and funding from the UK's Medical Research Council. There will be UK-wide coverage of the programme, in some form, in this year.

In addition to the 100,000 genomes, we have built a platform that means that there are now genomic medicine centres of excellence spread regionally—that is, distributed geographically across England. I will let Sue comment on that. It means that we are unifying and making more uniform—in other words, standardising—the whole approach to genomic health. That is one way in which we should refer to this now. We are entering an era in which this is not simply a research tool, but is in the clinic. There are fantastic programmes that have been the trailblazing platform for the 100,000 Genomes Project, such as Deciphering

Developmental Disorders, which we have built off. Now, as the NHS and Genomics England, we are transferring this into healthcare.

Professor Hill: I will come at the question from a slightly different perspective. As we start to plan for the NHS in England, part of the planning for that population in rare and inherited disease and in acquired disease like cancer is to ensure that we match the right technologies to the right application in a particular clinical condition. The strategy within NHS England, as we start to plan for the end of the 100,000 Genomes Project, is systematically to introduce a genomic testing strategy for rare and inherited diseases and for cancer that will eventually cover everything from point-of-care testing devices right up to whole-genome sequencing, at the very top of the testing pyramid.

We must use this opportunity in some way to rebalance the type of investigations that are being undertaken, to make it an affordable system for the future, to drive out any inequities that may be there and, at the same time, to drive up quality, through the standards that need to be set. The laboratory infrastructure must work together as a national laboratory infrastructure, rather than individual laboratories that may serve a population well—or not so well—with a range of different expertise. The future is also about understanding the type of expertise that we will need to interrogate large datasets from whole genomes and the associated clinical and phenotypic data.

Q4 **Chair:** Does anyone want to add to that?

Dr Wilson: Genomics is coming into the healthcare system, but I do not want anyone to be under the impression that it is easy. Each one of us has 3 billion letters of code. About 5 million of those are different between us. It is expertise in the interpretation of that that is required. The UK is excellent at genomics, but it is very complex. We need all the building blocks in place to deliver this accurately.

Q5 **Chair:** There is undoubted benefit from this for patients, given what it can potentially lead to. You talked about the £15 billion cost of drugs. Is this technology likely to lead to a reduction in costs—is that one of its drivers—or will better understanding of our genome and genomics lead to greater and higher expectations and, therefore, higher costs that we may be challenged to meet?

Professor Hill: We need to break this down into different components. First, there is no doubt that often the testing strategy in the NHS is to include another diagnostic test and not to remove any. That is why it is important that we take this opportunity to look at an overall testing strategy and to make sure that, year on year, that is refreshed, depending on the scientific evidence that emerges.

Secondly, for the individuals, particularly those with rare and inherited disease, there is a known diagnostic odyssey. Some will have been in and out of the healthcare system, utilising healthcare resources. A good

example is a patient who received a result in the 100,000 Genomes Project. It had taken them six years to get a definitive diagnosis. There are others that report 12 years or longer—all with evidence of increased healthcare resource utilisation.

There are other potential benefits around the matching. The pharmacogenomic profiling associated with this could drive the use of appropriate medicines, rather than a one-size-fits-all medicine approach. Some patients may not require a particular intervention because there would be no response.

When thinking about our strategy for the NHS, we should think about the gaps in the five year forward view—how we can improve quality and reduce inequalities—about a more population and preventive healthcare approach, and, thirdly, how we can get efficiencies and value for money out of the system. We believe that there are benefits for all three of closing the gaps that have been identified, as well as to the taxpayer and to UK plc, with the alignment with research and development and the industry strategy.

Q6 **Dr Mathias:** You talked about the use of genomics for developmental situations and cancer. Is it also just as relevant to degenerative conditions?

Professor Caulfield: It could be. Some degenerative conditions manifest in the rare inherited disease realm, so we are looking at some of those disorders.

Q7 **Dr Mathias:** I am thinking more about Alzheimer's, dementia and macular degeneration.

Professor Caulfield: That is a really important area. Those tend to be more common and complex disorders. The project that we started included ones that would be tractable to direct healthcare benefits today, but I see this technology moving into areas like that. I also think that now, as a result of the 100,000 Genomes Project, the price and cost of doing this—in terms of an NHS test—is affordable. It also means that it is affordable in a research context, so we can do the scale of projects that we would need to do to answer the question that you have posed.

Q8 **Graham Stringer:** Why was Genomics England set up as a limited company? Were other structures looked at? What were the particular benefits or upsides of this structure? For that matter, what are the downsides?

Professor Caulfield: It was established as a company before I was seconded to work in it. My understanding of the basis of that is that there was desire for the project to move at speed and pace, but, at that point, the Department and Government did not want to create any more arm's length bodies. Essentially, we work as a company, with the primary shareholder being the Department of Health and the Secretary of State, on behalf of the taxpayer. We operate and procure the services that we

need to deliver the project in accordance with all Government and EU procurement processes. We have been able to move at speed and pace. That has allowed us to get further through the project and to form partnerships with greater agility. As a result, this has been a good boost.

I do not see any downsides of it, because we work extremely closely—seamlessly—with our partners in the national health service in England. I am an NHS clinician. I think that this has been a very good way of delivering the programme.

Q9 **Graham Stringer:** With just one shareholder, it sounds very similar to an arm's length body. How is it different? What is there in the difference in the structure that enables you to move more quickly and effectively?

Professor Caulfield: We are able to move through procurement processes with greater speed and pace. We have been able to form a partnership with the world's best sequencing company. We tested the world's sequencing companies. It has allowed us to do that far more quickly.

Q10 **Graham Stringer:** Why would being in an arm's length body have slowed it down?

Professor Caulfield: My understanding is that one of the reasons might be that you would need to enact a law. To create an arm's length body, you would need a statute. Because the project was designed to move very rapidly, to transform the NHS and to bring equity of access, this was felt to be the best way of doing it.

Q11 **Graham Stringer:** What lessons have been learned from the human genome project? Have you acted on any of those lessons?

Professor Caulfield: It is the absolute foundation of this. That project was extremely expensive to do. If we simulate the cost from our project, doing the 100,000 genomes would have cost $320 trillion. That would have been unaffordable when the first human genomes were announced by the President of the United States and our Prime Minister. Today, the price is much lower. This year, we are paying a unit cost of about £600 per genome. That is extremely affordable for a healthcare test. It also means that we can begin to bring it into the health service rapidly and, therefore, to get access to diagnoses for patients and treatment change.

Q12 **Graham Stringer:** Have you done an estimate of the rate of return on the investment in the 100,000 Genomes Project?

Professor Caulfield: At present, there is significant co-investment by our primary sequencing partner in the UK, which might not have come to the United Kingdom but for this project. It has invested in a new European headquarters and has created about 70 jobs in Cambridgeshire. Those are 70 high-tech science jobs. It is also co-investing about £162 million alongside that. This is a major investment. It sees it as a flagship

healthcare project that it can use as a platform to get generalised use across the world.

Other companies have also partnered us. We have a consortium of companies that are in a pre-competitive arrangement, so that we can maximise the opportunity to draw wealth into the country, as part of the life sciences and industrial strategy. They are working with us in pre-competitive space to try to make sure that the data that we produce and the environment that we create are suitable for development of new diagnostics and medicines.

Q13 **Graham Stringer:** Have you estimated a rate of return?

Professor Caulfield: Not a precise one. However, I can come up with a figure and send it to you later. It is not the area I am focused on. I have given you some examples.

Q14 **Graham Stringer:** I understood what you were saying. The international human genome initiative estimated that it got a 140-fold return on that investment. That is why I asked the question.

Professor Caulfield: That would be after some considerable time. Typically, the investment is not necessarily linear. In other words, you often need a number of years for the adoption and then the generalisation, to get the return on investment. We can come up with a figure.

Dr Wilson: Yes, we can. The UK was the largest contributor to the original human genome. The Sanger Institute contributed one third of the sequence. The UK is one of a handful of global hubs where we have this expertise in genomics and data related to it. We have created a cluster here in the UK, based with genomics industries and interpretation industries. The benefit to UK plc is much greater than the health benefits. We need to nurture the ecosystem that we have created. The public-private partnerships that we have between academic and industry, as well as other commercial partners, are quite unique. We really need to capitalise on that. It is very scalable, as a lot of this technology is based on know-how and expertise. The UK is extremely strong in that.

Q15 **Graham Stringer:** Finally, what progress have you made in linking up with the devolved Administrations, particularly in Scotland and Wales? There has been some comment on particular diseases that you have chosen to study. How did you arrive at those decisions? How have you communicated that to other stakeholders?

Professor Caulfield: One of the earliest things that we did, in October 2013, was go to Scotland to talk to the Scottish Administration about joining the project. We then went to Northern Ireland and Wales. They will all be in this project in the next few weeks. As I mentioned earlier, some of that funding is from the Medical Research Council and some is from the devolved Administrations themselves. In many cases, they will

adopt the procedures and processes that we have piloted and worked together to develop in the NHS.

With regard to your second question, the clinicians facing patients with these diseases, researchers around the country and our industry partners nominated the diseases we work on. You can go to our website and look at the disease nomination page. Then we look at the disorder. The key characteristic for us to adopt it is unmet diagnostic need. In other words, if a patient with a rare disorder could get a diagnosis from a conventional test that is cheaper, they should probably have that. Our duty is to bring diagnosis to people who cannot achieve it in any other way, in the current set-up in the NHS. We want to maximise the value of the genomes.

We are now working across 210 disorders, all of which have been nominated by the health system—either by health service clinicians and healthcare teams or by researchers who think that these are important diseases to work on. In cancer, it is the same. Cancer clinicians and experts and our researchers have nominated the diseases to work on. It is quite important to cover a range of cancers, because we need to know how generalisable this technology is for healthcare adoption. Some cancers are much tougher to sequence than others, because they have a lot of normal tissue in among the cancer. That makes it very difficult to read the genome properly. You have to read it many times to make sense of it.

Q16 **Dr Mathias:** My question is probably for Professor Caulfield, but I would welcome comments from other witnesses, if they have knowledge on this. The 100,000 Genomes Project was expected to finish this year. I understand that it is now estimated that it will be complete in 2023. Can you explain why the progress is slower than expected?

Professor Caulfield: Yes. We anticipate finishing the 100,000 Genomes Project by the end of 2018. That is later than we originally hoped, but I will explain why. When you do a groundbreaking project like this, you often discover a number of elements—building blocks—that you need to make the project work that are just not there. We have had to do things like create a sequencing centre that would allow the research capacity that already existed in the UK to continue to function on the projects it was working on.

Q17 **Dr Mathias:** That was not predicted at the outset.

Professor Caulfield: No. We knew that we would have to do that. That is a facet of the project that you have to build, so it takes you some time to create it. It did not slow us down.

What slowed us down the most was that cancer proved much more challenging to do. There was a major issue with the way in which we previously prepared cancer tissue. When we take a biopsy or remove a piece of cancer, we drop it into a preservative. That preservative is toxic to DNA. It causes damage in the DNA. When we started the project, we

did some pilots, as you would expect us to do. We found that, if we used the generalised approach in the NHS at that point, we would get a very poor-quality genome, and not one that would be generalisable. To give you precise details on this, one centre in Britain lost the A and T elements—those two letters of the genome. Another centre was losing the letters G and C.

Q18 **Dr Mathias:** But you got this in the pilots.

Professor Caulfield: Yes—we got it in the pilots. We then worked with Sue to re-engineer the whole way in which the NHS approaches molecular pathology. That took a lot of time to achieve. They are now supplying tissue to the programme as fresh tissue, not in the preservative. That is what has taken the time.

Q19 **Dr Mathias:** The estimate was incorrect, but until you did the pilots—

Professor Caulfield: Yes.

Q20 **Dr Mathias:** Then you gave your estimate as 2023.

Professor Caulfield: No. There is another facet to this. We also had to build a semi-automated analytical pipeline. When we surveyed the world, we found that people had elements of bits of the software and various components, but they had not engineered them together into a pipe so that the data could flow through. When you are doing 100,000 genomes, you cannot be picking up large files and moving them from place to place to analyse the data. We have had to build that. That has also taken us longer than we hoped.

Genomics England has an extension to its mission. That is primarily to concentrate the UK's knowledge base in genomics. From 2018, we will not be leading sequencing. If NHS England commissions sequencing from 2018 onwards, which it is considering doing at the present time, Sue will take over. We will stop sequencing and move to managing the knowledge base—the research interface—supporting the NHS with new diagnoses from the research base and generating the wealth that we are required to generate.

Q21 **Dr Mathias:** Are you confident that it will be complete in 2023, or can you not be sure?

Professor Caulfield: Our current mission finishes in 2020, with the end of the current CSR round.

Q22 **Dr Mathias:** Are you confident about that?

Professor Caulfield: Yes.

Q23 **Dr Mathias:** Great. Do you think that the NHS was not prepared adequately?

Professor Caulfield: No. Sue is better placed to answer that, to be honest with you, but let me give you my view. There was limited genomic

testing and there was not equity of access across England, for various reasons. This was because we approached a tipping point, when this technology was mature enough to be brought into the health system. I should let Sue take over and give you a fuller answer. I think that the NHS has fantastic people, who were doing a really good job, but perhaps without enough resource and the latest technology. That is what we are changing together.

Professor Hill: This has been a major NHS transformation project. One of the principles of the 100,000 Genomes Project was that patients would be recruited from routine clinical care and treated in routine clinical pathways, because the overall aim was to ensure that the NHS mainstreamed genomic technologies into routine care by the end of the project. The project required patients to be consented and to go through quite a long consent process.

Q24 **Dr Mathias:** Is it a consent form like that or a one-page consent form?

Professor Hill: It is slightly longer than one page and not like that, but it is extensive. The important part of consent within this project is when they receive the appropriate information, on which they base their consent. They give consent based on whether they want only to receive information related to their primary presenting condition or whether they want to receive additional findings, some of which may influence reproductive choices. As part of the 100,000 Genomes Project and the creation of the research repositories, which include both samples and data—the outcome of whole-genome sequencing and the linking clinical phenotypic data—patients also need to consent to those data being used in a de-identified form, but with very carefully controlled access.

That was one element of it. The second was the processing of samples, whether from blood or from tumour, to very high standards, to enable the optimal outcome from whole-genome sequencing. The third was to gather the data—quite extensive clinical data—to inform the interpretation and, eventually, to have mechanisms to validate and give feedback.

In NHS England, we have created 13 genomic medicine centres, operating across populations of 3 million to 5 million, in general. That means that, by the end of the project, there will be 85 participating NHS trusts. Often, more than one hospital within a trust will participate in the study.

Q25 **Dr Mathias:** Which clinics are involved? Are patients recruited in all kinds of clinics?

Professor Hill: Part of the inequity has been that most patients have been able to access genetic testing through clinical genetics services. In some ways, that has acted as a gatekeeper to access. Within this project, and because of the approved disease list, it has required extension into other clinical specialties, such that in some of our genomic medicine

centres, for example, 80% of the recruitment is coming from outside clinical genetics—from neurology, cardiology or dermatology. Having multiple hospital participants has required the informatics and data infrastructures to be able to speak to one another and to populate the datasets, for example, sometimes pulling, in an individual hospital, from 600 stand-alone systems. We have not prescribed how they do it, but we have set the requirements for data standards and datasets and the requirement for interoperability, while they develop the local solutions. We now have 13 genomic data hubs in the NHS as a result of this project.

Q26 **Dr Mathias:** Have you had any feedback on how much extra time that has taken up in clinics?

Professor Hill: We have been very clear from the outset that this should not impact in any way on the routine "business as usual" at clinics.

Q27 **Dr Mathias:** Have you had any feedback from the clinicians?

Professor Hill: No, not at all. The informatics developments have sometimes been done as part of additional infrastructure that has been funded by the Government. In total, £20 million has been allocated to develop the informatics infrastructure. The funding that they have received—either per sample, from NHS England, or as additional resources—has provided the infrastructure cost to make sure that the project is delivered across these geographies. However, we have wanted to ensure that this could be done, as much as possible, as part of routine care.

Q28 **Dr Mathias:** Has that infrastructure added to or decreased patient contact time with the clinician?

Professor Hill: The time that has been added is the consenting time. Therefore, innovative solutions have needed to be found. If you are consenting an affected individual and, perhaps, two family members, that takes some time.

Q29 **Dr Mathias:** Is that where the infrastructure you talked about has gone?

Professor Hill: By and large, the additional resources that the NHS genomic medicine centres have received have been to supplement the consenting process. However, there have been innovative approaches to how that happens. In conjunction with Genomics England, we have established a national information line, so that patients and professionals can get information that helps them when they have that interaction with the clinician, before they give the final consent.

Q30 **Dr Mathias:** Will the involvement of Wales, Scotland and Northern Ireland help timewise?

Professor Hill: I will provide one response and then let Mark give you another. We have been working with each of the devolved Administrations to create the same genomic medicine centre approach, working to the same specifications and the same clinical and other

leadership that we know is required to make this happen. Even though they are not necessarily operational within the project, they join in with all our infrastructure that develops the leadership here—the sharing and embedding of good practice, our national events, our weekly calls and our weekly missives to the NHS. That keeps everyone in touch with one another.

Professor Caulfield: I think that that will bring advantage, in several ways. For various reasons of clinical expertise, some of the people in devolved countries are cared for in England. They now have access to this project, both through that and through their own home nation. Importantly, we may have only one family with an inherited eye disease in England, but if there is one in Scotland, one in Northern Ireland and one in Wales, that gives us a much better chance of line of sight on diagnosis. If you have one family, it can be really tough to sort these diseases out, even with a whole genome. There are real advantages. What we have succeeded in achieving is UK-wide equity of access to the programme.

Q31 **Dr Mathias:** Are you getting data from abroad as well?

Professor Caulfield: At the moment, we are not. In the future, with the NHS, we may look at partnerships with other countries, particularly ones that do not necessarily have the population size to build the infrastructure that we have built, but where the added value of those nations being part of the data centre could allow us to get line of sight on diagnoses from around the world. We are also working with Julia's team at Sanger. I will let Julia speak about DECIPHER.

Dr Wilson: DECIPHER is based on Deciphering Developmental Disorders, a study of 13,000 families with rare genetic diseases and children with developmental disorders. It was almost the proof of principle that you could roll out genetic testing for diagnoses within the NHS. All the genetic information that we got was put into a database. That database is accessible by clinicians. It is also federated to other rare disease databases around the world. When clinicians go into it, not only can they look at the rare disease population in the UK, but they may be able to match to other patients elsewhere on clinical phenotype and genotype.

Q32 **Dr Mathias:** Is the UK leading on this?

Dr Wilson: DECIPHER is the largest rare disease database that is federated into this system.

Q33 **Dr Mathias:** So we are leading.

Dr Wilson: Currently, yes, but we are part of a global ecosystem. As we segment diseases into smaller and smaller populations, we need to bring in data from elsewhere. Genomics has always been based on open science, freely accessible data and interoperability. In a research setting, that is what we have been doing for 25 years. Now, as more genomes are sequenced in a clinical setting, it is about keeping the enabling tool that

we have always had to compare and contrast globally and to get the statistical power that you need for the diagnoses. The Genomics England project is absolutely groundbreaking, in the sense that, up to that point, most genomes were done in a research setting, but we need to be cognisant of how genomics has been successful in a research setting—through openness, federation and responsible sharing of data

Chair: I recognise that this is a huge area and that there is an awful lot of ground to cover, but all of us—on both sides—need to make more rapid progress. If we can keep the questioning snappy and the answers a little truncated, that will be fantastic.

Q34 **Chris Green:** Professor Caulfield, the extra funding for the 100,000 Genomes Project that was announced in the 2015 spending revenue—the £250 million—was intended to last until 2021, which would take it past the end of the project and make it available to deal with legacy issues. Given the delays, will more funding be needed and for longer?

Professor Caulfield: Not for the primary project. We negotiated a very good arrangement for the NHS in the area of sequencing, so that prices for our sequencing fall. We never pay more for the same volume of sequencing than anyone worldwide, so our prices fall through the life of the project.

The project is on track and on budget at the moment. The extra funding is to create the UK's knowledge base. At this moment, we are working with the NHS in England and the Department of Health to delineate how that money will best contribute to making sure that the United Kingdom stays at the forefront of these diseases. This is not extra money to deliver the primary mission. It is about extracting even greater value, to make sure that the full value of the research platform for clinical interpretation in the NHS and for wealth generation, as Julia outlined earlier, is fully realised and matured.

Q35 **Chris Green:** This is one of those areas where you start a new project, break new ground and then have to realise what new work you had not anticipated needs to be done.

Professor Caulfield: Absolutely. We would be honest and say that we have learned some things that were not obvious at the outset, one of which I alluded to in an earlier answer to Tania.

Q36 **Chris Green:** How do you think that the prospective life sciences strategy and the proposals in the industrial strategy Green Paper will help the UK's work on genomics?

Professor Caulfield: One of the key differentiators of the United Kingdom is its extremely strong life sciences industry and activity, based within our research institutes or universities. We have a really strong opportunity right now. Life sciences will be at the heart of the industrial strategy. We hope that this particular programme will be a centrepiece of it, because we think that the moment is right. At present, the Department of Health's own survey and other independent surveys place this project at the forefront and in the vanguard of the world. We have a fantastic opportunity for this nation both to make this a genomically enabled health service in the future and to draw in the essential wealth that would attend that, to make sure that we remain at the forefront. That means that, as a collateral benefit, we will bring in new medicines

and diagnostics for patients, because we will become a place to do stratified healthcare.

Q37 **Chris Green:** If the Government gave you more funding, it sounds like you could spend that quite well. Have you had any indication from the Government that more money may be forthcoming?

Professor Caulfield: No.

Q38 **Chris Green:** None. How is Genomics England, and the genomics industry more broadly, drawing on private firms for experience, technology and funding?

Professor Caulfield: We now work with a number of companies in the UK and overseas. The majority of the companies we are working with as partners to deliver the project are UK-based. Some are in the United States. There is then a 13-company consortium we work with in the pre-competitive space, as I described earlier. They are international companies and range from small and medium-sized enterprises up to very large pharma. Part of our mission is to kick-start or to continue what others have done as trailblazers, which is to generate a genomic industry here.

Dr Wilson: At the Sanger Institute, we have multiple collaborations with commercial partners, but we have one exemplar. It is called Open Targets and is working with two large pharmaceutical companies, GSK and Biogen. It is enabling them to identify drug targets to develop along their pipeline and to reduce the number of late-stage failures by having genomic information attached to their drug development pipeline. There is investment in the low tens of millions in the Cambridge area to develop that.

At the Wellcome Genome Campus, we have also opened a biodata innovation centre, which is dry lab space—"dry lab" refers to computational research—for companies wishing to be immersed in the genomic intellectual environment that we have created there. They can access the free resources that we develop—the databases and information—and base their industry there. That biodata innovation centre was opened officially by the PM in November and is already at capacity. There is real demand from small start-up industries to occupy this space in the UK. As I said earlier, we are one of the global hubs for this type of research. We need to capitalise on that.

Q39 **Carol Monaghan:** The Government want to establish a European hub for genomics at the Wellcome Genome Campus. What are the main aspects of that strategy? What are the challenges that Brexit may pose for it?

Dr Wilson: The opportunities are there for us to take. They are in academia, in having a highly skilled workforce, in the knowledge base in the UK and in the collaborative ecosystem that we have between the NHS, academia and industry. The ingredients are all there. The Wellcome Genome Campus is the Manchester United of genomics, so we will attract

talent globally. There may be only two or three in a particular area around the world. We will attract and recruit them. Brexit has changed that, although not in the sense that our funding has changed or any legislation has changed. We have about 30% non-UK staff. On the wider campus, you are probably touching 40% of staff who are from the EU. They no longer feel welcome, so that is a threat to the growing industry that we have. We can grow homegrown talent, but it will take some time. We have some skills shortages, in bioinformaticians and the ability to interpret genomes, but we will continue to mitigate those.

Q40 **Carol Monaghan:** We know that a lot of the genomics companies currently working or operating in the UK are foreign owned. Is that a problem? You mentioned growing our own talent. What further steps should we take to grow our own talent?

Dr Wilson: It is certainly not a problem to have foreign companies wanting to locate here. They want to locate here because of the heritage of genomics in the UK. They want to be part of that system. That is not a problem.

Growing our own talent is about having education courses for bioinformaticians and in computational science. There is competition for the life sciences industry from the banking industry and from software developers. Academic salaries will never be comparable to those in the financial world. We can grow our own, but part of the beauty of science in the UK is that we bring in people from different disciplines or mindsets and get them to look at the same problem from different angles. The value added from that is something that you probably do not get with just homegrown talent.

Professor Caulfield: I agree with what Julia has said. I will turn to Sue in a moment, but I will give you an example of how we have done this specifically in the 100,000 Genomes Project. We have placed a massive education programme along that, to grow our own capacity here in Britain. What Julia has said is absolutely correct. Britain has some fantastic and talented people in this area, but we also need to have a coalition of all intellects working on this. That requires us to have the ability to attract and engage international talent in this nation, if we are going to benefit from it. That is an incredibly important thing. If there is anything that you can all do for us, it is to make sure that we can still attract those people to the United Kingdom, so that we can still be the world's first. We are an incredibly attractive country to come to, to work in life sciences. If we have the talent base, the industry will follow us.

Q41 **Carol Monaghan:** You are no doubt aware of the report from this Committee that called on the Government to give immediate guarantees to people in science and research. We hope that those may be forthcoming.

Professor Caulfield: We are grateful for your support.

Professor Hill: One of the things that I led before I moved into NHS England was modernising scientific careers, so I have had a major focus on how we modernise careers for scientists who work in the NHS. That has continued. As my role is cross-system, I also work in Health Education England and on the accompanying education and training programme.

One thing that we have done—in response to a report that was jointly chaired by Janet Thornton, then of the European Bioinformatics Institute on the Cambridge campus—is respond to the need to develop a proper career structure for bioinformaticians in the NHS, to develop that capacity and capability within the NHS. As part of the accompanying education programme for the 100,000 Genomes Project, new training programmes have now been introduced, including programmes up to the level of, and equivalent to, specialist registrar training for doctors.

Those courses are becoming increasingly attractive to people working not in the NHS, but in academia. There is more opportunity to think about that collaboration in science, across the science sectors. Within the NHS, at least, we have looked at what skills will be required and have started to address that issue, as well as strategically aligning the workforce development with the service development to deliver this project. That extends from awareness training and engaging primary care right up to a highly specialised workforce, with different training and education interventions, for example.

Could I make a comment about Brexit? As we move forward in the national health service to a strategic approach, where we embed whole-genome sequencing and the data that need to accompany that to enable it to be interpreted into the NHS as part of the diagnostic repertoire that is available, there is a real opportunity not only to drive international collaborations in genomics, but also to align the NHS, as part of its routine care, with research and development and with industry collaborations in a way we have not been able to do before, because they have generally been stand-alone research projects. That will be increasingly important. Julia made the point that when, through genomics, we have smaller subsets of patients identified it will be important for us to be able to collaborate across the world—and with pharmaceutical industries, for example—and to be able to lead those types of initiatives from the UK. We are thinking of that strategic alignment in the context of Brexit.

Q42 **Carol Monaghan:** I am conscious of time, but can I ask Dr Wilson a final quick question? The Sanger gets Government funding at the moment—no?

Dr Wilson: The Sanger Institute is core-funded by the Wellcome Trust. We get no Government funding. It is trust-funded. The additional funding comes from charity funding.

Q43 **Carol Monaghan:** Do you see that, in the long term, it will generate

enough revenue to be self-sustaining? I am thinking of possible NHS revenue.

Dr Wilson: The Sanger Institute is what you would probably call a basic academic research institute. It does not have any role in diagnoses or patient management. Genomics England is in that sphere, in the world of genomics. The Sanger Institute will continue to reinvent, to understand the new things in genomics and to feed through new technologies and genes associated with diseases. Those will be fed into Genomics England. The Sanger Institute is a research institute. It is one of the jewels in the crown, but we have no strategy to provide services and to become self-sustaining. It is all about pure academic, blue-skies research that will fundamentally impact on healthcare down the line.

Q44 **Dr Mathias:** Dr Wilson, can you tell me again whether you were comparing your institute or the campus with Man U in this field? What is our Man U?

Dr Wilson: I was thinking of the UK as a Man U for life sciences—that we recruit globally and are a very attractive place to do science, because of the funding, the infrastructure and the culture.

Dr Mathias: That is fine; I have got it. I just want to say that there are other football clubs, like Hampton & Richmond Borough football club.

Chair: Before we list all 88 teams, shall we move straight on?

Dr Wilson: I should not have used that.

Professor Caulfield: The proof is that Man U is not top of the premier league—which you are.

Q45 **Dr Mathias:** Professor Hill, do you think that NHS budget constraints may influence the growth of potential genomics in the UK?

Professor Hill: I go back to the point that I made earlier. Genomics was mentioned in the five year forward view, which has been looking at the sustainability and long-term future of the NHS. Coupling genomics with the developments in data analytics was the critical component. In future, it is about addressing the three gaps that have been identified in the five year forward view.

One is to deliver better outcomes—quality outcomes. Some of it is about using it to drive a shift in the burden of disease and, therefore, to change the way in which healthcare resources are utilised. There is some evidence emerging in the project that, if a genomic diagnosis had intervened earlier, there would have been significant cost savings for the system.

The second is inequity of access, which also drives us more towards the late stage of disease or towards not using genomics to the best effect and, therefore, making the best decision about treatments. The third is that the finance and efficiency gain will not just be in the potential to

improve outcomes and to move the burden of disease. It will also be in the ability, first, to provide a genomic testing infrastructure that offers value for money, is scalable and can meet the increased demand, by changing the technologies as the evidence increases; and, secondly, to use it much earlier on, including in cancer, better to align it with our medicines. A key part of our strategy is recognising that it is part of sustainability for the future for the NHS and that it has to be done within an available budget.

Q46 **Dr Mathias:** So you think that the five year forward view has budgeted for this, to some extent.

Professor Hill: It has to be done within the available budget. That is why it is so important that we take the learnings from the project and from all the other expertise from other research projects and say, "What type of testing strategy do we want for the future to make it equitable, but within the envelope that we have available to fund this at the moment, with the opportunities for significant cost savings over time, when it is better aligned to medicines and other interventions?"

Q47 **Dr Mathias:** There is a Deloitte report that says that precision medicine tests have saved costs in only 20% of cases. Does that make you still confident about budgetary projections for us?

Professor Hill: The work on precision medicine approaches that has been done to date has been in very well-defined populations. We are talking about moving this into much more mainstream clinical specialties.

Q48 **Dr Mathias:** So it is an unfair comparison.

Professor Hill: It will be an unfair comparison for the future. The learnings from the 100,000 Genomes Project and the data that are emerging already—Mark may want to talk about this—are showing, first, that we can get a greater diagnostic yield. That evidence is not just from the 100,000 Genomes Project, but from other projects that have been looking at whole-genome sequencing: DDD and other studies. The second issue is the level of healthcare resource utilisation and the pathway that patients have taken before they have got a diagnosis. It is taking this whole-pathway approach, rather than just a single test, with a single medicine.

Q49 **Dr Mathias:** Are there genomic clinical pathways now embedded, or being embedded, in the NHS?

Professor Hill: Yes. There are pathways that are embedded, as part of NHS England's approach to introducing personalised medicine. At NHS Expo last year, we published a document called "Improving outcomes through personalised medicine." That set out how, as we look towards 2020 and beyond, we will take forward an approach to embed genomics and other tests within the genomics pathway, as well as other diagnostics, in certain conditions. We want to take it from a population base—for example, better to diagnose familial hypercholesterolemia or to

reduce adverse drug reactions from warfarin therapy, which is associated with a large number of hospital admissions, and other drugs—right up to using whole-genome sequencing in very targeted areas.

Q50 **Dr Mathias:** So you can track warfarin to the genome.

Professor Hill: No. For warfarin, there is a fairly simple test.

Q51 **Dr Mathias:** That is not related to the genetics.

Professor Hill: You are about to hear from Professor Sir John Burn, who is an expert in genetic testing of warfarin therapy. There are relatively simple genetic tests that can be undertaken to guide warfarin therapy, but these are not being taken up systematically in the NHS. Part of what we will do in NHS England is look across pathways—from a population base, from primary and secondary care, and up to tertiary care—to understand what the pathways are where genetics or genomics could be used to target therapy.

Q52 **Matt Warman:** I want to talk about data and consent—so that will not take long. There is obviously a lot of debate about whether the broad consent model covers things such as the future commercial use of genomic data. As a starting point, do you feel that broad consent covers what all these data go on to be used for?

Professor Caulfield: We have an ethics advisory committee that advises us, made up of experts. We then worked with the Health Research Authority to develop our materials. The national research ethics committees then approved them.

In that process, we consulted participants. Their view is that our materials adequately describe, for their understanding, what they are enrolling in. That is really important. As we move forward with this, it may be possible to make those materials lighter in content, but the participants have liked them. We have just done another consultation exercise, which has allowed us to reduce them by 30%.

To answer your question, they robustly describe exactly what we will do with the data—the uses. It is very clear that commercial entities will be able to work on the data. It is also clear what the unacceptable uses of the data would be.

Q53 **Matt Warman:** The media reports that indicate that some patients feel that they were not fully informed would suggest that there is still some more work to do. Is that fair?

Professor Caulfield: I am unaware of any media reports that suggest that. Patients have said that they are fully informed. We have a participant panel, made up of people who are enrolled in the project. They are incredibly supportive of the material.

You may be referring to evidence presented by one group that suggests that there is a confusion around how the data are handled in terms of

identifiability. That arises because sometimes people use the word "anonymous" or "pseudonymised." I will explain what is meant by that. When you anonymise the data, the technical effect of that is to disconnect the data from the original person. What that means is that I cannot add other data, because I no longer know the true identity of that person. It would not be safe in a healthcare setting to do that.

In our project, we adopted a different model. We want to be able to follow these people, to give them insights into their health for their entire life course. Therefore, we use what is called pseudonymisation. In other words, we remove the direct identifiers, which makes it very difficult for anyone to identify them. There is no name, address or postcode. There is an age and a year of birth, but nothing more precise than that. That allows the research community of what will be 2,500 researchers to work on de-identified data, to drive up the value. However, if we could not connect that back, I could not return diagnoses from the research environment to the identifiable person. There is a confusion in the evidence that you have received about the use of the word "anonymous." We are not using anonymised data. We are using pseudonymised data, where we have removed the identifier.

In terms of the value proposition of this project for patients, for health and wealth, this is exactly the right model to adopt. We should be transparent and open. Our patients understand that they are doing this. We have had no complaints from any patients whatsoever about our consent. Indeed, we have had support for it.

Q54 **Matt Warman:** None the less, is there a fundamental issue around the commercialisation of genomic data: first, that we have not worked out what that will look like for the future; and, secondly, that we then have to explain it to people in such a way that they consent to something that almost does not yet exist?

Professor Caulfield: You make a very important observation. It is fair to say that we are on a path of public trust and confidence. Paramount to everybody in this part of the room is public trust and confidence in genomics and genomics health. We are very up front about what the companies will be doing with this—the goal is to bring new diagnostics and medicines to patients. However, there are some people who worry about it. We need to acknowledge that. We have done some work, as part of a genomics conversation. You can see the report on our website; it is there for everybody to see. About half of the people who responded said that they were very happy for companies to have access to their data. The other half who responded said that they had some concerns.

In our experience in this project, Sue and I have found that, if you explain to the mother of a child with a rare inherited disease that this is about giving the biological insights to those entities so that they can bring the treatments to patients, usually she will leap at it. If you are suffering with cancer—as a lot of us here will, I am afraid—you will want to have the best chance of getting the right medicine. If this will develop a new

medicine, you will be up for it. We have listened to the patients and are doing what they want. As long as they tell us to do this, we will do it.

Q55 **Matt Warman:** You mentioned the journey. Part of that journey will be the general data protection regulation from the EU. Do you think that the profiling regulation around that will affect the 100,000 Genomes Project?

Professor Caulfield: We are looking at that right now. I do not have the answer today. With some measures, it depends on how we adopt that into UK law. I honestly cannot answer the question today, but we are working with the Department of Health to look at how it might affect the project—and, indeed, any future consent that Sue and I put forward to the national health service for the post-2018 part of the project. It is interlinked with the earlier question about what we do in the future with law that comes from the European Union.

Professor Hill: Can I make one point about consenting? One of the key lessons that we have learned is about the importance of the information-giving stage, before people enter into a final consent discussion. For example, I attended a Saturday morning clinic at the Royal Free hospital at which all 50 patients with polycystic kidney disease who had attended were recruited to have the 100,000 Genomes Project discussed with them. Because they had a group information-sharing discussion and were open and transparent about the project, all 50 of those patients consented. The information-giving part is as important as the consent. It is important not to decouple those. That is why, as we move forward with the public and with our patients, we have to think about creative ways of engaging them, involving them and creating the right materials to make sure that no part of our population is disadvantaged in any way.

Q56 **Matt Warman:** Finally, there is funding for Genomics England up to 2021. What do you anticipate happening after that? Is it likely to be folded up or sold on?

Professor Caulfield: It is difficult to answer that precisely. At the moment, we are very focused on the delivery of the project and the plan between now and 2020. If, working with the national health service and our partners at Sanger and other institutes around the country, we have developed a vibrant genomic industry, I would hope that the data centre would continue in some form, given that we have made a commitment to longitudinal and life course follow-up applications. Genomics England might not be running it; it might be the national health service.

It is going to be a massive benefit to future health in this country. It will tell us all sorts of things. Earlier, Sue alluded to the possibility of drug response testing or adverse event testing. What if you and I could walk around with a card in our pocket that said which medicines we probably should not have, because of our genetic make-up? That is a significant cause of avoidable admissions to hospital in our NHS every year. These are the unexpected benefits, almost. We have not yet begun to scratch the surface of them. I hope that it will have a continued mission, but it

may not be in the form of Genomics England. That will be a matter for the Government.

Q57 **Matt Warman:** Are we in a position to evaluate adequately the precise worth of the 100,000 Genomes Project at the moment?

Professor Caulfield: Yes, I believe that we are. We have some primary objectives. The first is to bring benefit to patients. In rare disease, 20% to 25% of the participants in the pilot are now receiving potentially actionable diagnoses in the health system today. We do not yet have concrete evidence around cancer; we are working on it. In terms of a scientific community, 2,500 research intellects from across the world—1,800 from the United Kingdom—have volunteered to help to drive up the data value. We already have metrics supportive of the mission delivery. In answer to Graham, I alluded to inward investment to the United Kingdom that probably would not be here but for the project.

Chair: Thank you very much for your attendance this morning and your insightful contribution. We will move straight on.

Examination of witnesses

Witnesses: Professor Sir John Burn, Professor Dame Kay Davies and Dr Helen Firth.

Q58 **Chair:** Welcome. Thank you for joining us. Apologies because we are running a little behind schedule. For the record, could I ask you to introduce yourselves and state in what capacity you are sitting before us this morning?

Professor Davies: I am Kay Davies. I am a geneticist from Oxford but I am here in my capacity as chair of GeCIP, the Genomics England Clinical Interpretation Partnership for GEL.

Professor Burn: I am John Burn. I am professor of clinical genetics at Newcastle University and the Institute of Genetic Medicine. I am here in my capacity, I think, as the non-executive director on NHS England with a special interest in genomics. I also chair a company called QuantuMDx, which is making point-of-care DNA diagnostic testing devices for the sorts of tests we have heard referred to earlier. So I have a commercial involvement in the field as well.

Dr Firth: I am Helen Firth. I am a clinical geneticist in Cambridge. I am here as clinical lead for the Deciphering Developmental Disorders Project.

Q59 **Chair:** Thank you all very much for joining us this morning. I want to start with the same sort of question that I asked the first panel, which is to get each of your takes on where this is leading us, what kind of difference this can potentially make to people's lives, particularly with reference to whether you think the emphasis should be on individual treatments and helping individual patients, or whether there is a macro aspect to this that is being, perhaps, not fully understood or fully

explored. Let me start with that.

Professor Davies: Let me just start for drug delivery. As we go forward in the next decade, there will be more about patient value and, therefore, although it is not quite precision medicine because not every patient is exactly the same, patients will be classified in subgroups of disease. There is no question that every pharma industry is now looking at a patient's genomic profile alongside what treatment it is going to give. It does not matter whether you are looking at a rare disease or a common disease. In that sense, it is very much a single-patient thing, but on the broader front genomics is transforming the NHS because every single discipline will now be engaged in genetics. That is a lot of extra information that they could bring to bear to any diagnosis, treatment and management. Even where there is not a treatment, things can be changed dramatically to improve the patient care.

Professor Burn: Kay and I have been involved in genetics and genomics all our lives, so we are deeply involved and enthusiastic about it. I would endorse everything that Kay said. This is reaching a point now where it is expanding into all of medicine. I have made the point that the term "genomic medicine" will eventually disappear because we will just call it "medicine," and you will not be able to differentiate any application.

From the point of view of personal versus the broader system, clearly, rare disease is very personal. There are 8,000 of them. They affect of the order of 5% to 10% of the population, which is a big individualistic application. System-wide—you have heard about pharmacogenetics and, of course, also in terms of infectious disease diagnostics—we will increasingly rely on genomic diagnostics. It is fast and cheap; you can do it very quickly. This will also become a genomic technology. It will be very difficult to separate the two. We need to look at the overall cost of healthcare delivery and think about the utility and effectiveness of this. From the NHS England point of view, that is where we are now turning our gaze. There is no doubt it is powerful. The question is how we most effectively deploy it.

Q60 **Chair:** I will come back to that in a minute. Dr Firth?

Dr Firth: It gives you much more precision around diagnosis and it establishes the molecular basis of the disease. That is a big advance in terms of a clinical descriptive diagnosis. It establishes what the condition is, what is likely to happen in the future, it enables you to give better prognosis, what is the best treatment strategy and surveillance, why did it happen, whether it will happen again, and, importantly, for many patients with rare disease, it enables them to network with other patients with a similar disorder. If you truly have a rare or very ultra-rare disease, it may be that there are no patients living in your locality who are facing similar challenges. Once you have a precise delineation of the cause of your disease associated with a particular gene name, then through the internet and so on it is possible to access much better information.

Q61 **Chair:** Thank you. Going back to the point that Professor Burn raised, which was that there is a potential cost implication to all of this and about how we get the best value from this, do you think that this can be used to reduce costs and to make sure that we are being less wasteful, or are we going to be raising people's expectations of what can be treated and, therefore, increasing the expectation of patients and the demands upon the public purse?

Professor Burn: You heard earlier about the diagnostic odyssey and the waste of resources in investigating things inadequately, so there are cost savings to be had there. From the point of view of whole-genome sequencing and the biggest sequencing technologies, it can, undoubtedly, cut costs if it is deployed at scale and effectively. So there is a challenge of the infrastructure and the process engineering, which was referred to earlier. On that score, let me give an example from my home town of the railways. They were introduced in the 19th century. They were invented in the early 19th century by George and Robert Stephenson, who gave us the Rocket.

I have brought along a report on that from the Committee on Trade and Plantations—if I may read a paragraph, it is quite entertaining—whose chairman said in August 1822: "The elder gentleman is unlettered, but professes a rude mechanical aptitude; his son received a modest public education in the City of Newcastle upon Tyne.

"They are possessed of a remarkable fancy, that the steam engine, now employed to drain the collieries in their district, might be adapted for purposes of locomotion; and that, in the not too distant future, such a device might carry passengers between London and the northern industrial districts, at speeds of up to 30 miles per hour.

"Your committee considers this view to result from a distempered imagination, probably occasioned by the severe climate and the privation experienced in colliery districts and by the frequent recourse to spirituous liquors that all too frequently results.

"Representatives of HM's Treasury pointed out to us that the latest mail coaches between London and Manchester, sustained by frequent changes of horse and travelling by turnpike on Mr Macadam's patented surfaces, have achieved the remarkable speed of ten miles per hour; and that…no possible gain in human welfare could result from any attempt to reach a higher velocity."

I am sure you will not write a report like that. Robert Stephenson was given a state burial and was deemed to be the greatest engineer of the 19th century, so we are very proud of him. I think we are in that sort of situation. We have an amazing new set of technologies that are being presented to us, but we have to build the railways for them to run. In order for this to have an impact, we must have data flow and 1.3 million staff capable of accessing reliably and safely that data and understanding it. That requires investment for us to see the true impact of this.

Having said that, whole-genome sequencing is just one of the technologies before us. We also have the existing technologies, exome sequencing, single gene panels and so on, but also right down to looking at single letters. I am involved in the example of warfarin. I am interested in it because we are heading towards spending this year about £400 million of NHS money on drugs to replace warfarin because warfarin is deemed to be a bit dangerous. It is dangerous. About one in 30 of us is very sensitive to it.

This is where the public health thing comes in. If you use a combination of checking a few letters, age, weight and height, then you can make warfarin better than the new drugs, and warfarin costs a fraction of those drugs. So, if we deploy genomics alongside process engineering, we could cut the budget with no loss of health benefit. In fact, the population would have better health. The difficulty is scaling that in. What is happening is that it is easier to switch to the new drugs because they do not need monitoring, and so we are drifting that way. If we deploy genomics in this very specific way, we can move that back so that we can get health gain and cut costs in-year. That is just a practical and tangible example, and there are many more like it. Hypercholesterolemia is another one you heard referred to. I think this can be done now, but for it to be done truly effectively we need to have a system-wide re-engineering.

Q62 **Chair:** Do you think the public need to be involved in this? Do you think they need to have a greater understanding of what this is all about, or is it too early to worry particularly around that, because I think only 12% of people understand what genomics is?

Professor Burn: I am not surprised by that figure. That is, probably, a bit of an exaggeration. Yes, we do need to engage the public in this. People are fascinated by it. I spent an hour yesterday with my 10-year-old grandson's class explaining it to year 6 and they asked lots of very pertinent questions. They were very well informed. People understand at the broad level what this is about, but, yes, we need to engage. If we do engage, then the British public will take this forward. One of the great assets of the NHS is that people are not scared of this. If you go to America, people do not want you to know about their genes because they might tell the HMO, who might give them a higher insurance premium, whereas we get cared for by the system regardless. So people are much more willing. Helen, Kay and I have worked with families all our lives. The families are willing to share this data and want to be involved, and they can really drive it forward.

Q63 **Chair:** Just before I pass over to Chris Green, I want to go back to the point about the caution. Did you say it was in America?

Professor Burn: Yes.

Q64 **Chair:** Do you ever fear that in the pursuit of lurid headlines the technology can be misreported, that people can be misled and that that

would act as a potential barrier to people signing up and giving informed consent in the future?

Professor Burn: Setting aside the issue of alternative facts, the analogy I recently thought of was between tourism and terrorism in the sense that we all want to be able to travel the world and backpack, but at the same time we are terrified of bombers. In the same way, we need to be able to share this data across the whole system to gain full value from it and yet, at the same time, protect the individual. The truth is that it is almost impossible to prevent hacking at some level. Our systems are constantly under threat, so people's data will be released. The better defence against that is to make sure that it is not a disadvantage for that information to get into other hands. That is where having a public healthcare system is very effective.

Q65 **Chair:** I suppose it was just mitigating the concern that people might have, or be told that they should have—"You need to be worried about this"— because it sells an extra paper or something.

Professor Burn: Absolutely. I think that people are very frightened about their personal data being stolen. As I say, in practical terms, most people in the health service understand that we need to share information. If anything, we are too protective and too restrictive about that data being shared.

Professor Davies: If I can interject, I think you underestimate the influence of companies like 23andMe, because a lot of the Joe Bloggses out there on the street, albeit middle class at the moment, are sending their swabs out and they are getting their genomes back. They will be able to interpret that information as it comes. In fact, I could look at mine because I have had mine done. I could have it continually updated. I think that will spread. We need to make sure that the Living Well Now are anticipating what might happen next.

As to the point you make about bad publicity, there is a lot of bad publicity on drug pricing. That gives the pharmaceutical industry an extremely bad reputation, even though it is only a very few companies that practise in that bad way. We need to educate more broadly and we need to do it collectively. That is where GeCIP and Genomics England can play a major role.

Chair: Thank you very much.

Q66 **Chris Green:** Professor Davies, it appears that the 100,000 Genomes Project is considerably behind schedule, with the number of fully sequenced genomes at around 18,000. Why do you think the project has fallen behind?

Professor Davies: It is behind because it is a very challenging project. As you would expect, when you are doing something transformative on a national scale, you can never be absolutely accurate about when you are going to deliver on certain deadlines. What is important to note, though,

is that we are working collectively. It is amazing how many people turned up for the first GeCIP meeting, even though we could not give them any data. These clinicians were collecting data—Helen knows this well—and they were ready to go.

Now, the bottleneck has moved to bioinformatics and the analysis of that data that you heard earlier. It is the unanticipated bottleneck Genome England is holding people together, meeting the challenge and then moving on. In the end, I do not think that we will be very far behind schedule. We hoped that we would have 100,000 genomes done by 2018, and that will be an amazing achievement. We will be able to do more because genome sequencing is getting cheaper. It started at $1,000. At JP Morgan this year it was $100. It is not quite $100 for everybody yet. It was $500.

Q67 **Chris Green:** But it is getting there.

Professor Davies: It is getting there.

Q68 **Chris Green:** Is this indicative of the genomics industry more broadly?

Professor Davies: It is, indeed. Yes.

Q69 **Chris Green:** In terms of the slow uptake, is it in part because of the NHS approach to recruiting patients, or is it more to do with the underlying fears of patients?

Professor Davies: In cancer, the problem is in getting the right type of sample, whether it is a fixed sample or a frozen sample. We have now cleared that backlog. That really held up the cancer section of this project. With the rare diseases, it was much easier because clinicians like Helen and John have been working for many years and are used to getting those samples. Nevertheless, we still had genome centres that did not understand that one single patient was not of much value. We needed two to be able to get meaningful information out. Again, that educational process has been a great success by the GeCIPs and various domains coming together, promoting that educational process. Maybe Helen would like to comment on that.

Dr Firth: In terms of education, in the Deciphering Developmental Disorders Project, which started in 2010, we have had annual collaborators' meetings. It has been a huge project with 13,500 families. We have sequenced 33,000 exomes. That is the coding portion of the genome. We have engaged 200 clinicians and accrued data, but we have had an annual updating, bringing everyone up to speed with how the project is progressing and learning more about genomics to try to build competence as the project has gone forward, which has provided a platform for Genomics England to take forward.

Certainly, there is a huge need for upskilling the workforce and for ensuring that people can interpret the data. I would like the Committee to understand just how challenging and complex the interpretation of this

data is. The ability to sequence genomes is running very fast ahead of our ability to interpret the data. That is rapidly becoming the challenge. That is a difficult gap to fill at the moment. It will improve with time, but it is there at the moment. It is a very large issue at the moment.

Professor Burn: If I might add, Chair, because Helen cannot say it for herself, she is one of a small team who ran a brilliant project with 14,000 families giving their parental and child samples to the team at the Sanger and with Edinburgh's support. That has transformed our specialty. Every genetics centre in Britain was feeding into that and being educated, because the best way that clinicians learn is by doing. Getting results back is teaching us how to use that in clinical practice. The DDD project confined itself to the 2% of the genome that is the coding segments, the bits that we really understand, and only gives us the information that we could handle in specialist centres.

What the 100,000 Genomes Project was trying to do was much more ambitious in the sense that it is trying to roll it out to a much wider clinical audience and look at the whole dataset rather than just the 2% that we properly understand. It is, perhaps, amazing that we have got as far as we have. That was a huge leap into the darkness, in a sense. It has proven that we can, in Britain, do this sort of thing. Most other countries would not even begin to attempt it, so it is keeping us at the front of this developing field. We should not underestimate ourselves. We have a tendency to do ourselves down. Almost no other country could even begin to think of taking on something of this scale and complexity in their health service. The fact that it has taken longer than planned is not surprising.

Q70 **Chris Green:** One of the recent north-east GMC newsletters said that it was recruiting, on average, 60 participants for rare diseases and two for cancer a month. Is that a good enough uptake rate? What stops it being higher? What can you do to make it higher?

Professor Burn: As far as cancer is concerned, you have heard that this is about changing the pipeline and getting the samples into DNA extraction at an earlier stage before it has been messed up by the fixation process. The pathology departments are under intense pressure, so trying to adjust that is like trying to re-route the motorway with cones. We have got to keep using the motorways. The pathology departments are dealing with tens of thousands of samples. So they are trying to change their system to provide us with clean DNA at an earlier stage in the process. That takes time.

I do not need to tell you that the health service is under intense pressure, and clinicians have to find time to do this and recruit patients. That has slowed many people down as well.

Q71 **Chris Green:** So this is an additional responsibility that puts pressure on the NHS.

Professor Burn: We knew from the start that there would be additional time costs and resource costs for the health service. We understood that we would have to absorb that. There has been extra resourcing in terms of support for recruitment. Some of the people involved early on did not fully appreciate how hard the cancer part of this was going to be to do that at scale. They are making progress, but I am not surprised that it has taken a long time.

Q72 **Chris Green:** Some have suggested that there is an uncertainty in the health service about genomics being the best route to deliver personalised medicine, so that has been a barrier to its adoption. Should we be focusing on other methods of DNA analysis to achieve the same outcomes, such as exome or RNA mechanisms?

Professor Davies: If you mean RNA mechanisms, at the beginning of this project we just did DNA. Then we went through a phase where we did other omics, collecting RNA and tissue samples so that we might be able to enrich the phenotype later. In order to deliver on the project, we have had to drop that now. Some centres will be able to afford to do it but most of them just won't. We discuss all the time about whether it should be exome or whole genome. If you can get to the point where you can analyse the whole genome, you will always have all the information. You may miss things in exomes, and that will become more critical as you look at some of the rare variants that make you susceptible to rheumatoid arthritis or asthma, for example. You cannot do that by just looking at the exomes. You have to look at the control of the genes that is in the other 97% non-exome material. The moment it becomes cheaper, and I would argue that it is now at that point, you would go for whole-genome sequencing. However, in certain disorders, and developmental disorders is one, you may well have a panel of genes that you know are most commonly mutated and you would use that because it is cheaper. You might produce that panel first and then go on to whole-genome sequencing.

Chair: Thank you, very much. Dr Tania Mathias.

Q73 **Dr Mathias:** Professor Davies, in order to make the investment in genomics viable in the NHS, do we need to have biomarker information for that, and do we have enough patients, if that is the case, with that?

Professor Davies: To deliver an effective medicine, you probably do need biomarkers, and that is very much in early development. It is pre-competitive space, so a lot of academics and people in companies are working to look at biomarkers for different diseases. That will develop alongside the genome sequencing. Again, if you are producing a new medicine for rheumatoid arthritis, you would be looking for biomarkers all the time, but you will not make any sense of those biomarkers unless you can start to put these patients into different boxes because there are so many different types. It is a bit like the cancer story. Every disease is like that. Unless you can subdivide your patient population, your biomarkers will not make sense. The cloud is beginning to lift in that field, if I can put

it in that way, and we are, probably, looking at an era where we can make sense out of biomarkers in the future.

Q74 **Dr Mathias:** Would biomarkers like rheumatoid arthritis be the blood tests that are being done currently?

Professor Davies: Yes. This is the very basic blood tests. I am not an expert on rheumatoid arthritis. You want more definitive biomarkers. Also, you want biomarkers to show whether your particular treatment is working in your particular subgroup, which you define by genomics.

Q75 **Dr Mathias:** So we are not there yet.

Professor Davies: No, but it is developing very quickly, because that is the holy grail for the pharmaceutical industry. It is getting drugs to the clinic faster and more cheaply, and you only do that by defining your patient first at the DNA level.

Q76 **Dr Mathias:** Is there any problem with awareness among clinicians about rare disease patients and genomic diagnoses, or is that hurdle overcome?

Dr Firth: There is a big issue about recognising which patients are likely to harbour a genetic cause for their illness. People, historically, have tended to think that there must be a strong family history, and yet, particularly, in developmental disorders de novo mutations and a new variant arising in a child is proving to be the biggest class. Clinicians recognising when a disorder is likely to have a genetic basis is crucial to ensuring that people who would most benefit from a genomic analysis have access to it because there is so much wealth of variation in the genome. All of us, probably, have multiple variants in developmental disorder genes that look plausible but, fortunately, few people are affected by a severe developmental disorder. So, teasing through and evaluating those variants to achieve a diagnosis is time-consuming and challenging clinically, and you want to focus that activity on the people with the genomes for whom it is most likely to yield a diagnosis, but you could spend just as much time on someone who had no genetic cause for their disorder because there are, probably, just as many variants to look at. That is not a good use of time. Quite a lot of work needs to be done to ensure that the patients who are most likely to benefit have access.

Q77 **Dr Mathias:** That sounds very complex.

Dr Firth: It is going to be quite a lot of years before we reach a point where this is really useful to everybody.

Professor Burn: It is a sort of never-ending journey, to some extent. If I could just tease out a couple of things, first of all, on rare diseases, we have in our heads that there are people with very strange looking bodies, who have a rare disease, and then there are people with common diseases such as diabetes. In all those common diseases there are thousands of people with rare forms of that disease that look just the same. There is a very nice example in the south-west, from Sian Ellard

and Andrew Hattersley's group, where they have identified that about one in 30 of the people being treated with insulin for insulin-dependent diabetes is not actually insulin dependent. They have one of the rare forms of diabetes. There are, perhaps, 40,000 of them in Britain who should be picked out of that clinic, taken off insulin and put on an oral drug instead. They would be much better cared for. Also, it would be much cheaper. We have very dramatic examples where people's lives have been transformed.

Q78 **Dr Mathias:** These are type 2 diabetics.

Professor Burn: They look like type 1 diabetics, but it is actually maturity- onset diabetes in the young. They look like type 1s but they are not, and they are crippled by the insulin because they do not need it.

Q79 **Dr Mathias:** But they are type 2.

Professor Burn: It is actually a completely separate disease. It is a separate disorder.

Q80 **Dr Mathias:** But they have been misdiagnosed.

Professor Burn: They have been misdiagnosed. We have similar examples. My personal interest is hereditary bowel cancer. There are, perhaps, 70,000 or 80,000 people in the country who have a spelling mistake in a mismatched repair gene, which means that they are very prone to get cancer, and those patients need to be treated differently. They have a 70% to 80% lifetime risk. We need to bring them in to see them more often. A new drug has just come out that works for them but not for the common type of bowel cancer, so we can pick them out.

Going back to your biomarker point, several of us are developing biomarker tests to look at the cancer, not for the actual gene fault but just for the spelling mistakes that it causes. The DNA is full of spelling mistakes, called microsatellite instability. It is a very quick and cheap test, but we are now about to hear from NICE that we should do that for every colon cancer so that we can pick out the one-in-six who have that particular subset of genetic predisposition.

Q81 **Dr Mathias:** That is cost-effective because it is one in six.

Professor Burn: Absolutely, yes, but within that group there are the small number of people who have the inherited form. If we can get to their relatives and prevent them from getting cancer, or at least get to them and prevent them from dying of cancer—

Q82 **Dr Mathias:** And get them screened or whatever.

Professor Burn: Absolutely. There are well-trodden paths. It is just trying to pull those people out of the crowd. As we do that, as the technology allows us to look into the routine clinics and pull those people out, we will get improvement overall in healthcare because the people

who were doing badly will be taken out of the clinic and treated differently.

Q83 **Dr Mathias:** In a kind of sci-fi land or for a long time to come, in your full blood count you would get your DNA as well.

Professor Burn: Increasingly, this will be seen as part of your routine investigation. If you present with diabetes, you will be checked for all the monogenic forms up front. We would also look at all those rarer variants that Helen was referring to, to see whether we could nuance your management, but the current evidence is that, as long as we know whether you are obese and your age, that is the best predictor of type 2 diabetes, not doing lots of genetic testing. But that could shift in time.

Helen was also referring to this issue of trying to assign pathogenicity. Finding a letter change in a gene and saying, "Is that the cause?" needs international sharing of data. We have, literally, millions each. I am involved with a project called the Global Alliance for Genomics and Health and the Human Variome Project, which is sharing data between countries so that we can understand which variants are causative for the disease. It may be because your grandmother was Somali, which, obviously, we need to differentiate.

Q84 **Dr Mathias:** That is very helpful. Thank you. Sir John, what impact do you think the £816 million investment in the research centres will make? Is investment in the Biomedical Research Centres going to NHS and university research partnerships?

Professor Burn: Is this from NIHR?

Dr Mathias: Yes.

Professor Burn: Okay. NIHR investment is another jewel in our crown. There has been a phenomenal advance in translational medicine in Britain because we have embedded resources in the hospitals to allow them to recruit into these trials, genomic and otherwise. Some of my friends in Europe are just in awe of the fact that we can recruit at scale. We have given resources to the hospital to pay for that recruitment, rather than you having to raise that with every grant. That is demonstrating a practical benefit, and it is attracting industry to doing trials in this country because we have that infrastructure in place. It makes us a much more powerful research-based centre.

In fact, I had an example just last week of a patient whose life we probably saved because of being involved in one of our research projects. As a result of that, we discovered a serious illness that would otherwise have gone unnoticed. So, research and service go together. The more research you do, the better your service becomes.

Q85 **Dr Mathias:** Right. So we are back to the Man U sort of thing.

Professor Burn: Yes. I prefer to say Newcastle.

Dr Mathias: Which one are you saying?

Professor Burn: I would rather say Newcastle United.

Chair: We really do not want to go back over this ground.

Dr Mathias: But they are British teams, anyway. That is the point.

Professor Davies: On the funding point, it is not just the BRCs. Through Genome England, we have £16 million extra funding for people using part of the database that we have already created who are doing research. That is coming from the MRC, Cancer Research UK and Wellcome. All these other funders are involved in this, so you are getting a lot of extra value, which you will then feed back into the translation of that information to patients because the infrastructure will be there.

Q86 **Dr Mathias:** Excellent. Thank you. As to healthcare professionals, it sounds as though the training is good as far as them understanding which diseases can be referred. It sounds as though that is in hand.

Professor Burn: We have a long way to go in terms of education. That is partly because in the NHS people deal with what works now. We have been talking about genomics coming all our lives but it has arrived now. What I expect, and what we are seeing, is that clinicians are engaging directly with becoming interested in this. We have a genomic medicine masters, which we are running within the NHS, to help raise the standards. Six of our centres are running that. We are putting resources into professional training for people who are already qualified rather than just looking at the beginning of the process. Again, that is another long journey. We are all learning because the technology is moving so fast. We are constantly having to upgrade our knowledge to be able to handle the outputs. Helen, Kay and others in their work have demonstrated that if we can improve the interpretation process—the DDD project was a good example where they did not give you all the noise; they only gave you the signal—we can develop artificial intelligence to increasingly help us process this data so that people on the frontline get a result that they can act upon rather than just getting lots of information that they do not understand.

Q87 **Dr Mathias:** Yes. That will create a virtuous circle.

Professor Burn: In primary care, GPs are particularly anxious about being given information but they do not know what to do with it. We have to send it with the story, not just send them some letters.

Q88 **Dr Mathias:** Are there significant vacancy levels for genetic counsellors in the NHS?

Professor Burn: There is a significant lack of genetic counsellors in the NHS. It is not a profession that we have fully invested in. We need to invest more. A real danger is that we perceive, because it has been mainstreamed, that we do not need geneticists or genetic counsellors any more. Actually, it is the other way round. We are scaling this up. We need

to develop special interests in each speciality, including primary care, but we also need to invest in that core team who are the referral point of last resort when you get something you do not understand or you have to roll it out into the family. The genetic counsellors are particularly valuable in dealing with the healthy relatives, who are not the person presenting at the hospital. That is where the genetics teams kick in. I am very keen, in my NHS England role, to make sure that we do not say, "Oh, we don't need money in genetics any more. Let's give it all to whole-genome sequencing." That is not the practical way forward. This is a new development to build on top of our very strong base. We are very strong in this field.

Dr Firth: You need a combination of clinical geneticists and genetic counsellors because clinical geneticists may have to examine a patient to determine if they have the additional features that might go with this diagnosis that is suggested by the genome analysis. So you need the ability and the competence to examine people and evaluate that information, which is not part of a genetic counsellor training. You need the combination. Historically and internationally, the UK's genetic services have a very high reputation because we have been such an integrated team.

Dr Mathias: Brilliant. Thank you.

Chair: Thank you very much.

Q89 **Chris Green:** Professor Davies, how well do you think the commercial, clinical and research interests are being balanced in Genomics England? Does any one of those areas get a higher priority than the others?

Professor Davies: They are reasonably well balanced. At the beginning, of course, we did not have much commercial intake because some people did not believe we could do it. Then the initial companies came in. Again, we were not quite ready. We have 13 companies now involved in this that are actually in the reading room, reading the genome data that we have. They are not only learning from some of the algorithms that Genome England has developed but they are now beginning to contribute their own ideas about how to analyse some of those data. There is a great opportunity for the exchange of expertise. This is the bottleneck, as we have said before, in the analysis of data and delivery to the clinic. That sort of set-up, which is unprecedented, is going to deliver.

Q90 **Chris Green:** In terms of the Genomics England Clinical Interpretation Partnership, the GeCIP, what criteria are used for deciding who has access to it?

Professor Davies: Academic or hospital clinicians. If you are a commercial entity, you cannot go in there on your own unless it is very well regulated and agreed. Those rules are working very well and are very clear. They have been accepted by everybody.

Q91 **Chris Green:** Why can't the private sector go in there?

Professor Davies: If they went into the reading room and took the information away, there would no longer be a partnership. We need to ensure that they are truly buying into the partnership concept.

Q92 **Chris Green:** So they can only use that data once they have been given permission and there is a huge amount of control.

Professor Davies: They will do that in collaboration with an academic group or a hospital research group.

Q93 **Chris Green:** I suppose, for many people, this would be for the protection of data.

Professor Burn: It is back-to-back data protection.

Professor Davies: That is exactly right.

Professor Burn: The very nice phrase that they came up with was, "This is a reading library, not a lending library." You could come in and interrogate the data for a specific purpose for your commercial development, but you could not take that data away and put it into someone else's server.

Q94 **Chris Green:** How are the findings of GeCIP fed back to the 100,000 Genomes Project?

Professor Davies: I cannot tell you the answer in detail. I do not know whether Helen can allude to exactly how it goes from the GeCIP domains. At the moment, as to the various domains, the neurology domain is run by one individual, who will be responsible for the way that that particular information is fed back into the clinical practitioners at the various points of care with the patients.

Dr Firth: There is a validation and feedback domain that will interface between Genomics England and the GeCIPs to police the bringing of information back from the research domain into the clinical domain, because that requires some management.

Professor Burn: It is still a little too soon to say. We have 2,250 senior clinical members of the NHS and academe involved in the GeCIPs. The data is just coming in, so it has not bedded down yet. You can imagine that as you get more data into the data centre—I am involved with the dermatology one, for example—then the group around dermatology will start interrogating that data, doing research with it and linking that back into their own clinical practice. These are the people who will be deploying it in their specialty units. The idea is to try to engage with the front-line staff in academic medicine who will be using this information. Of course, that is a virtuous circle. They will be feeding their patients in for further evaluation in that process.

Professor Davies: It is very important because you need to evaluate the pipeline. One of the problems is time. How long does it take between when someone gives their sample and when they get the information

back? This is one of the very important questions that the domains and GeCIP generally are looking at. It is at the very early stages, as John says.

Q95 **Chris Green:** Is there an inconsistency or a problem with having a remit to challenge the project while remaining inside it?

Professor Burn: Are you talking about us or for the GeCIPs?

Chris Green: For the GeCIPs.

Professor Burn: I am not sure. Clinicians who are in GeCIPs are not prevented from criticising the service or the resources that they are given. There is a very active debate between the GMCs, the GeCIPs and Genomics England in trying to make this work. To some extent, this was a project that was set up with a chosen number of 100,000, and we said, "Go do it." Basically, the system has tried to adapt to that. We have an answer, and we then had to work out the questions. It is a dynamic process. I certainly do not feel restricted in expressing my opinions to the Genomics England team. I sit on their advisory board, and there is a very constant interplay between all our groups to make sure that we do the best we can with the resource.

Dr Firth: It can be very fruitful in DDD. We have had so far 59 publications from the project and four flagship papers by the core team. The rest have been contributed by co-working with the collaborators in the project, who were all clinicians in the NHS. You can generate a big research momentum by having more eyes looking at the project, and trying to analyse, interpret and understand.

Professor Davies: The other thing is that we do not have one big GeCIP where everybody just gets together. There are individual domains in different clinical specialities. In a sense, they are slightly competing and challenging each other because they want to develop the next technology first. I do not think, in any way, there is an opportunity for suppressing any challenge. We are challenged all the time, and they complain all the time when GEL cannot produce enough sequencing. We are now beginning to feed that pipeline, as I said, so that the bottleneck has gone somewhere else. The challenge will go somewhere else, but it will come from different places within the GeCIPs.

Q96 **Chris Green:** When will the free access to genomics data be available through GeCIP? Is that down the line?

Professor Davies: Some information has already been released, but, to make sure that we have the quality, no one will be very pleased with us if we feed information back that turns out to be of very poor quality. It is steady as you go to start with. When we are very confident that we are producing it at exactly the sort of level that they can make use of, that is the time to open the floodgates. Somewhere in 2017 we would hope to accelerate the feedback to the clinicians who have been providing these samples.

Q97 **Chris Green:** What do you think it will achieve once it is?

Professor Davies: They will start interpreting it. There will be some obvious low-hanging fruit. In fact, I think there will be lots of low-hanging fruit, but the challenge will still remain for most of those samples that we will need to learn how to interpret the data. We need to be collective about that because size matters in the analysis of these samples.

Q98 **Chris Green:** Finally, one of GeCIP's responsibilities is to provide a training environment alongside Health Education England within the genomics education programmes. What does this involve?

Professor Davies: John, the MSC that you mentioned is one way.

Professor Burn: Yes. We set up the masters course, which is an in-work training programme where people drop out of their job to do lectures and practical education. That is one obvious application. There is also a learning-by-doing. The members of the GeCIPs, by getting this data and working with it, will learn about its interpretation and learn its limitations. I am not actually directly involved in running the GeCIPs, so I am not the right person to answer the question. It is creating a learning environment and it has brought us sense.

Q99 **Chris Green:** You spoke about the masters course. Will that be one year full time?

Professor Burn: That is a good question.

Dr Firth: It is one year full time or two years part time. That is the structure that people have been using.

Professor Burn: Our institute is one of the six centres. You have one.

Dr Firth: Yes.

Professor Burn: So we have six places around Britain where people can enrol, attend lectures and develop their knowledge base over a one or two- year period.

Chris Green: Thank you.

Q100 **Chair:** Thank you very much. From what we have heard this morning, a lot of good work is going on and a lot of progress is being made, but there are still, potentially, some barriers to scaling up the whole process. First, could you identify some of those barriers, and, secondly, do you think they are insurmountable or not? You talked about the fact that there is no centralised database and that, potentially, different sets of data are being held on different databases. Is work going on to resolve that issue so it is just a question of being patient and it will happen, or does it need more input from us as policy makers and regulators to push in a certain direction to get things on the right track so that scale-up happens quicker than it might do on its own?

Dr Firth: One thing that we pioneered in the DDD project was linking the 23 genetic services together through DECIPHER, such that we were all able to see variants in other patients. That was the way that we were able to say, "There are patients in Birmingham, Exeter and Manchester all with the same condition," which, obviously, each individual centre operating as an individual would not have cognizance of. That has proved extremely effective. Acting as a collective distributive network of expertise has been a really powerful way for the UK genetic services to function. It would be best to continue to function in that way in the genomics era. It would be helpful to have more endorsement from the regulatory bodies that that is the way they wish us to practise.

Professor Burn: I think that endorsement is a good word, to recognise that we have a long-established tradition in this area and not to lose that quality service at supra-regional and regional level. You also heard about the genomic medicine centres, which is a more ambitious programme of trying to expand into other specialities and expand the footprint of genomics. There is a real challenge, which Sue Hill is leading, about integrating those diagnostic services. That is something clearly to keep an eye on, because, again, we are trying to rebuild the motorway while the road is still being used. We have all these centres busily working while trying to integrate their functions and get their data flows, their laboratories sharing and the data from the diagnostics going to the data centre or to an accessible point. All of that is still a work in progress.

There are really two separate elements here. One is the scale-up and integration of our existing services at laboratory level. The other is the 100,000 Genomes Project and working on how to interpret that data as well as how to acquire that data at scale.

From an NHS England point of view, we are looking very closely, and at the next board meeting in March we will be addressing specifically, how we start to take some responsibility, or take on responsibility, for these diagnostic services as the 100,000 Genomes Project comes to the end of its sequencing phase. Our specialty commissioning committee and our CCGs are going to have some very interesting discussions about how we afford that. We should not get too hung up in the short term. In the short term it is going to be tricky, but we can clearly see, in the longer term, that we have to absorb this into service. I think the Committee might reasonably keep an eye on how that progresses. I am sure you will.

We must also think about how it can be helped, because this is not just about the NHS. It is also about business development and the broader technological sphere. I hope we will see a broad support to get this into practice.

Q101 **Chair:** You mentioned about the interpretation of the data that is presented. I think you mentioned artificial intelligence, or someone did. Do you see that as a significant contribution to being able to scale up the interpretation of a whole set of data?

Professor Burn: In broad terms, yes. Machine learning is going to be critical. We cannot process millions of bits of data individually. It has to be done by the machines. Helen and Kay are experts on this, rather than me.

Dr Firth: One of the reasons we chose developmental disorders as a starting point for this is because those variants that cause those conditions that are apparent so early in life do not tend to be present in the large control datasets, so you can more easily say, "If it is not present in 100,000 exomes, but it is present in this child, that makes it much more likely to be causal." When you look at later-onset disease, there are lots of people who have not yet developed the disorder who have those variants that have got into control datasets. So you need much, much larger numbers to be able to work out whether you are seeing more of that variant in the affected population than in the control population. When you get to disorders where not everyone who carries that variant always develops the disorder, you get incomplete penetrants; then the complexity gets harder still. That is why you are going to need quite complex and nuanced approaches to this, but building large datasets is crucial to interpretation of later-onset disorders.

Professor Davies: That, again, brings us back to the skills shortage and brings an interdisciplinary dimension to this particular programme, because we need physicists who think in a completely different way from the way that the genomics people currently do to bring those out and into the field. We need, probably, to do that internationally. So, anything that the Select Committee could do to help us on that front would be enormously advantageous.

Q102 **Chair:** I want to talk, if I may, about the ethical and social concerns of genome-editing and genomics. The Human Genetics Commission was abolished in 2012. Who now regulates or addresses the ethical and social concerns?

Professor Burn: I was a founder member of the Human Genetics Commission. It is sad that it was disbanded because it was a very effective committee. It gave the public reassurance that there was an independent voice providing oversight. An awful lot of the anxieties around genomics then have become better understood, so I do not think that in terms of genomics it is a great deal different from the general issue about health information and its security. It is just a bigger scale.

The other topic that you will be discussing, namely genome-editing and so on, is like stem cells. That is a much more complex ethical domain. At the moment, it essentially falls under IRAS or the Health Research Authority— our general structure. I do not think there is a major issue there. I do not, personally, have a sense that people are deeply anxious about their genomic data being misused. People in the media will always try to find examples of that and make a story, but it is not a big issue.

The bigger problem of using that data and rolling that information back out to people, and getting health gain without overburdening the health service with the worried well and getting that demand management right, is probably where we have the biggest public issue and not having everyone turning up for a colonoscopy or an MRI because someone said they have a snip, which might mean they get something going wrong in 20 years' time.

Dr Firth: In thinking about this, a contributing factor is the concept of proportionality in terms of data sharing. You said that you match the amount of data shared with the need to share; you consider the risks of sharing and you tune that appropriately at each step. That is an issue that is quite important to consider, because people often talk about data sharing, and you might be sharing one variant and one phenotype, or you might be sharing an entire genome and an entire healthcare record. Clearly, the risks associated with those two activities are very different. So you need quite a thoughtful and complex structure to manage that.

Professor Burn: Chair, I would add that we do have a scale issue. The idea that every time someone looks at your genome you get phoned up and asked if it is okay is like every MP having to contact every constituent every time they have a vote. We have to make this more manageable in terms of consent. My perception is that we tend to over-regulate and people are willing to share or allow the health professionals to share data much more freely than we sometimes are able to do.

Public Health England has some very interesting work going on, which I am involved with, with Jem Rashbass, where you can attach a 256-bit variable to your health record and then scramble it with a piece of software, rather like the old Enigma codes, so you could, basically, just ship data across the internet and it is completely uninterpretable. It would take every computer on the planet 10 to the 49 years to crack it. It means you can take, for example, our genetic registry data and compare it with the cancer registry to see how many of those people got cancer. Unless you know how to untangle the 256 bits at either end, you cannot break that code. It is possible to work out ways of sharing data that are not breachable. It will be a constant anxiety, I am sure.

Q103 **Chair:** Finally, I want to talk a bit more about the regulatory framework within which you have to operate. We are at the start of something, or reaching, perhaps, the end of the beginning. I do not know. Is the regulatory framework that you have to work within for this fit for purpose, or are there things that would need to change?

Professor Davies: I think it is what the Human Fertilisation Embryo Authority covers, really, because that would cover most of what you are referring to for the moment very adequately, and has done in the past. Pre-conceptual diagnosis comes out under that, and mitochondrial transplantations come very effectively under that legislation. I am with John. I do not think, at the moment, we need anything. We have been very good in this country in scoping forward whenever there has been

genetic advance. If CRISPR ever gets to the clinic, which is the next generation, then you may have to put something extra in place, but I personally do not think you need to do that at the moment. Most of it would be covered by existing legislation that we could work with.

Professor Burn: If anything, less regulation rather than more, certainly in terms of clinical trials, which are being strangled by regulatory barriers. The more we can get that to go back would be helpful.

Q104 **Chair:** Therefore, would you see an opportunity, as we move to leave the EU, that we will be able to create our own early-stage research framework?

Professor Burn: As to clinical trials, there are efforts to reform the European Clinical Trials Directive, which has been extremely difficult. That is happening anyway. As far as possible in that domain, we want to stay in line with Europe because we want our drugs to be recognised at the European level. That will not change.

Q105 **Chair:** At the early stage or later stage?

Professor Burn: With the early-stage work, you could see some change. Also, in the field of genomics, this is one particular area where being slightly separated from mainland Europe is an advantage in the sense that there are both historical and religious differences between the British perception of genomics and continental Europe, which often means that, if you set the standard to the whole of Europe you will be more restrictive on much of this work than we would be in the UK. I am not saying that it is a major issue, but there would possibly be a benefit. People are slightly more relaxed about the application of genomic medicine in this country than they are in continental Europe.

Dr Firth: It would be helpful to promote the need for data sharing to provide safe interpretation of variants, because many variants are just not interpretable without seeing them in the context of variants of other patients with a similar disorder, and in the context of the variation that you see in the normal population. If you try to do it without either of those things, it is only a small number of very well-known variants that you could reliably provide safe advice on. There is a safety issue tied up with it. It is important that data sharing does not have negative overtones, because it has some very positive attributes to make the quality of interpretation that is provided safer.

Professor Burn: One specific area is to move towards requiring diagnostic services to share their variants so that we can better scale up the understanding of those. I will give you one example.

I am involved with Global Alliance and the Human Variome Project looking at a thing called the BRCA Exchange. It is a website where we pull together every spelling change in the BRCA1 and BRCA2 genes into one place. We have an expert committee, funded by industry, who want us to do this so that they can sell their drugs. We have scientists in

Australia and America interpreting those 17,000 variants to work out which ones are pathogenic and which ones are not so that we are all singing from the same hymn sheet. We do not want to be in a situation, as has happened in one of my families, where I was telling a family that it was a pathogenic cause of breast cancer, and they were having operations on the strength of that, while their cousin in another centre was being told, based on another paper, and older literature, that it was not pathogenic and they were not acting on it.

We have to try to standardise that. That would be good for Britain because we are in a leading position. It also strengthens our collective laboratory services to make it a requirement that you share data because that will keep us at the forefront of interpretation of that data.

Chair: Very good. Thank you very much indeed for joining us this morning. I have certainly found it very informative. I hope the Committee members have, and I am sure you will look with interest to see what we come up with as part of our report. Thank you very much indeed.