HOUSE OF COMMONS

Science and Technology Committee

Oral evidence: Genomics and genome-editing, HC 854

Wednesday 8 March 2017

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Watch the meeting

Members present: Stephen Metcalfe (Chair); Victoria Borwick; Dr Tania Mathias; Derek Thomas; Matt Warman.

Questions 106 - 187

Witnesses

I: Dr Edward Hockings, Founder, Ethics and Genetics; Professor Michael Parker, Director, Ethox Centre, University of Oxford, and Non-executive Director and Chair, Ethics Advisory Committee, Genomics England; Peter Counter, Chief Information Officer and Project Manager, Genomics England; and Alison Hall, Head of Humanities, PHG Foundation.

II: Professor Sir Mike Stratton, Director, Wellcome Trust Sanger Institute, and Chief Executive Officer, Wellcome Genome Campus; and Dr Jean Abraham, Academic Honorary Consultant in Medical Oncology, University of Cambridge.

Written evidence from witnesses:

- Ethics and Genetics
- Genomics England
- PHG Foundation
- Wellcome Trust Sanger Institute

Examination of witnesses

Witnesses: Dr Edward Hockings, Professor Michael Parker, Peter Counter and Alison Hall.

Q106 **Chair:** Welcome. I am sorry for the slight delay in starting this morning, but I understand there were some issues with the trains so we just had to wait till we could get under way. Thank you for your patience. To start with, perhaps you could introduce yourselves and tell us who you are representing this morning.

Peter Counter: Good morning. I am Peter Counter. I am the chief information officer at Genomics England. I spent most of my career in IT—30 years with IBM. Just before joining Genomics England I was the CTO at the HSCIC, now NHS Digital, and wrestled with the consent and data issues there. My responsibilities in Genomics England are the running of the IT services and the programmes to change and update them.

Alison Hall: I am Alison Hall. I am head of humanities at the PHG Foundation, which is a non-profit independent health policy think-tank. It has a special focus on how genomics and other emerging health technologies are translated into more effective and personalised healthcare. I lead the regulatory and ethics work at the foundation and work in a multidisciplinary team with scientists, public health physicians and bioinformaticians. We have a particular interest in how genomics services will be developed, including issues around data sharing.

Professor Parker: My name is Mike Parker. I am the director of a research centre at the University of Oxford called the Ethox Centre. I have a long-standing interest in the ethical implications of the clinical and research uses of genetics and genomics. For the last 15 years or so, with three colleagues in genetics, I have been running a national forum for the discussion of those issues called the Genethics club. I am also the chair of the ethics advisory committee for the 100,000 Genomes Project.

Dr Hockings: My name is Edward Hockings. I am the founding director of Ethics and Genetics. We campaign for transparency, openness and responsibility in the biosciences.

Q107 **Chair:** Thank you very much indeed. This first session is looking at the ethics of genomics. Perhaps you could each tell me what you think of the approach that Genomics England is taking towards these ethical issues and whether you think it is as robust and as good as it could be, and in the public interest. Who would like to start?

Professor Parker: Perhaps I will start with the broad approach—we might want to talk about details later. The chief medical officer has to take a lot of credit. Within two weeks of the announcement of the initiative in December 2012, I was invited to chair an advisory group leading up to the initiation of the project, so I think that shows a

commitment to thinking about ethical issues early on, which is a good thing. I wrote a letter as a result of that working party, which was designed to inform the design and conduct of the project, and later on I was asked to be the chair of the ethics advisory group. I think there is a follow-through there, which is important.

The project has an in-house ethics team, which works within Genomics England and can identify and address ethical issues. Another important element of the approach has been the emphasis from the start on the involvement of patients and participants, partly on a number of engagement issues or activities, which we can come to, but also the active involvement of patients on a number of committees. As a broad model, I think it has much to commend it. Clearly, there are other ways of doing these things, but, as an ethicist, I have been impressed by the way they have done them.

Q108 **Chair:** Would anyone else care to comment?

Dr Hockings: The 100,000 Genomes Project forms part of a series of initiatives in bioscience policy. This includes the integration of personalised medicine into the mainstream healthcare system, which is due to take place later this year, regulatory approval for mitochondrial DNA transfer and the approval of genetic modification for viable human embryos. These unprecedented steps have been taken as part of the Government's ambition to improve the delivery of healthcare, but it is also motivated by economic policy, specifically the attempt to turn the UK into a global leader in research and development.

To this end, bioscience policy has recently been framed in terms of commercial value. For instance, in regard to "research opportunities and mainstream use of genomic medicine across the NHS," NHS England affirmed that these offered a "major contribution to wealth creation and economic growth in this country." Furthermore, the body tasked with providing ethical guidelines in the 100,000 Genomes Project—the ethics advisory group—refers to the project's "potential to bring real benefits to individual patients and their families, to the NHS more broadly, and to the UK economy."

The 100,000 Genomes Project set in this context is an example of how making genomics part of an economic strategy risks unduly permissive policy and the neglect of best practice. The Government initially claim that genomic data files "from the 100,000 Genomes Project to which academics, researchers and industry members will have access will be anonymous."

Freedom of information requests revealed, however, that the Government's claims were misleading. As we reported in *The Guardian,* it transpired that all data used in the 100,000 Genomes Project is in fact pseudonymised. As such, public understanding of the level of access that is afforded to third-party actors in the 100,000 Genomes Project was distorted from the very beginning. Whereas anonymous data is stripped

of anything that would permit the identification of the individual in question from the data, pseudonymised information, in the Department of Health's own words, contains "age or age range" and "wider geographical information." The information made available to third parties also includes clinical data pertaining to an individual's medical history potentially spanning decades. This is a particular concern because, if the public are misinformed about the level of data access, we cannot know whether there is broad public approval for existing policy. While the public may approve of genomics to improve medical care, the same may not be said about allowing data to be used for specifically commercial ends.

Q109 **Chair:** Thank you for that. Alison Hall, you want to come in.

Alison Hall: Edward covered a lot of ground in his response and I would like to concentrate on a couple of those issues. One is consent. Of course, we are talking about a process—not just a short document that signifies a conversation or a dialogue. The process of consent within the 100,000 Genomes Project has been well thought out, but, as Edward says, it serves multiple purposes. It serves research and clinical purposes and other objectives too. That is why it is inevitably complex and it covers areas that would not necessarily be part of clinical practice, such as looking for additional findings and re-contact for other research purposes. That is one point.

The issue of pseudonymised or anonymised data may well be something we come back to, but it is a feature of genomic information, especially the way it is used clinically, that sometimes the boundary between anonymised data and pseudonymised data is not clear. With clinical use, you need to combine the genomic data with information about the patient, their clinical features—what is called the phenotype. It is the ability to bring that information together that is important, and that creates regulatory and ethical issues—the identifiability of data. We can talk a bit more about that later.

Q110 **Chair:** Would anyone else like to comment?

Professor Parker: It is important to point out or highlight the fact that the approach to consent and the consent materials that are used in the project were subject to scrutiny by the research ethics committee—not my committee but an independent HRA ethics committee—and that the materials were developed with patients and groups through consultation. They have been evaluated since and the participants have been happy with those, but those materials are very explicit and highlight the fact that these potential risks exist. The participants involved have a conversation in which these issues are discussed, and it is clear that we need to develop evidence-based approaches to the model of consent and the way we think about these things. But the project itself has done a good job at highlighting these issues and addressing them in the consent process.

Q111 **Chair:** Thank you. Has the advice of bodies such as the independent taskforce on data and the CMO's ethics advisory group been listened to? Have they been a helpful addition to the landscape?

Professor Parker: I can speak for the CMO's committee and perhaps Peter will want to say something about the other issue. I was the chair of one and am the chair of the other. I have been asked to review progress of the project and to ask others to review the project against the letter that I wrote and sent to the CMO. Interestingly, before the project was actually started—with no prior involvement from me—we wrote that letter, which attempted to set out what the requirements were for the project to be seen to have been done well; so we are reviewing that. There has been a carry- through, I think, yes.

Q112 **Chair:** Does anyone else want to add anything?

Alison Hall: In relation to understanding and information, what the public and what patients understand is a critical issue. I welcome the fact that this taskforce has been set up with this objective in mind. There is a wider point when it comes to talking about genetics and genomics about literacy and understanding, and we may well talk about that later in relation to educating the workforce within the NHS about genomics, but there is a wider public understanding point too that is important to address. We must understand the public's expectations of how their data will be used—for research and clinical purposes.

Q113 **Chair:** How do you evaluate whether the approach—the ethical practice—being adopted is working and understood by the public?

Alison Hall: That is a very good question because that is something that needs to happen. The 100,000 Genomes Project needs to have work in place to evaluate those outcomes or those measures, but it also needs to evaluate other issues as well, such as the way these data have been used to inform diagnoses, management and treatment of patients.

Professor Parker: It is perhaps worth saying that a number of evaluation activities in relation to the consent materials are under way, one, as recently reported, which was being conducted by the PPI groups in the GMC groups around the country, which interviewed patients and participants about their experience and whether they thought the materials and the consent process worked well. Largely they thought it did, but they made some suggestions.

The Department of Health is also funding an evaluation of the project, which is being undertaken by Nick Mays and his team at the London School of Hygiene. One thing I have done through my role as the chair of the ethics advisory group is to encourage social science research and to try to get groups around the country to do projects completely independently looking at the experience. There are a number of projects around the country that are doing that work. It is a bit early days for them to report on that, but we are developing models for evaluation and we need to look at which of those work.

Q114 **Dr Mathias:** Professor Parker, perhaps I could ask you first what may seem a straightforward question. What is the benefit of generating the genomic data in a centralised database?

Professor Parker: My background is in ethics. I am not a scientist or a clinician, so I cannot answer that question from a scientific or clinical point of view. From an ethics point of view, clearly, there are important benefits to be gained from genomics and data-driven genomic research at the interface between clinical practice and research. That potential is of ethical importance.

There are a number of ways in which data could be managed. Many research projects, for example, around the world use approaches to the data sharing and research that involve sending data to other collaborators. The model developed by the Genomics England approach, which involves researchers—whether commercial, academic or clinical—coming into a secure space where their research can be audited and observed and what they have done can be checked, has huge value from an ethical point of view. When you speak to participants, for example, they are tremendously reassured by the fact that their data is going to be used only for approved purposes and those uses can be checked. That has been very reassuring. You can only do that if it is managed in a central way.

Q115 **Dr Mathias:** Peter Counter, would you like to comment?

Peter Counter: A key thing to understand is that we do two separate things in Genomics England. One is the research, as has been discussed, but we also return results to individual patients. It is those two things happening at once that make, for me, one of the very interesting things about the whole enterprise—the join of the clinical and the research worlds.

The value of having all the data in one place you would not have thought at first sight was valuable for the individual flow of an individual genome to be interpreted and fed back, but I am told by my science colleagues that in fact they use a wide view when interpreting a genome. They do not just say that is the result and, therefore, here is the answer, like you might with a blood count or something. They ask: who else has had a similar phenotype; who has had a similar genotype; where else can we go? Because this is a young science, they look across; particularly for rare diseases, they look across all the data that we have. Particularly where the diseases are very rare, you may only have a few instances, and to split those up would be very difficult. The bigger the database, even from the clinical point of view, the better, and certainly from the research point of view that is obviously true.

Dr Mathias: Thank you very much.

Alison Hall: Can I add something?

Dr Mathias: Yes, I am sorry. We have good answers, but if there is

something to add, yes.

Alison Hall: I want to add that I agree absolutely with Peter that it is important very often, to interpret these very rare variants, to be able to compare them with the variants from a patient who is unrelated, but that does not necessarily have to happen in a centralised database. One thing as an organisation we have been pressing for is more clarity about the infrastructure and the processes that enable NHS labs to share these sorts of data between themselves so that they are able to access that genomic variant data and the relevant features of patients who share similar conditions.

Q116 **Dr Mathias:** You have some misgivings.

Alison Hall: No, I do not. I have misgivings over the fact that the database necessarily has to be centralised.

Q117 **Dr Mathias:** What are those misgivings?

Alison Hall: I do not have misgivings that they will not necessarily cover the range of diseases that exist in practice.

Q118 **Dr Mathias:** What is your concern about it being centralised?

Alison Hall: It is that there will not be sufficient access to support a clinical genomic service.

Dr Mathias: Access—

Alison Hall: I mean from all the clinicians who need to be able to access these data in the future.

Q119 **Dr Mathias:** So there is restricted access.

Alison Hall: Yes. There are others systems in place. It may be a question of access but also the range of the conditions that are being looked at, because within the 100,000 Genomes Project around 200 diseases have been looked at, but within clinical practice there are, let us say, a thousand diseases. Is it the right type of database to support clinical genomics practice? That is my question.

Q120 **Dr Mathias:** Peter Counter, was your appointment an acknowledgment that there needed to be more focus on co-ordinating the project and managing the data, do you think?

Peter Counter: They did not exactly tell me all the reasons for my appointment, but that is certainly one thing that I have done. I have tried to bring more practical and industrial rigour to the way that we do our IT and make sure that projects are better co-ordinated, plans are better laid and those kinds of things. That is, I believe, why I was appointed. It is certainly what I have been doing.

Q121 **Dr Mathias:** At our last session we discussed delays in the project. Have technology delays caused delays in the project or are there other reasons

for delay?

Peter Counter: There is some delay in the project. We are probably a year or so behind. We are planning to finish the 100,000 genomes being sequenced in 2018 instead of 2017. I have heard discussion of the project going on for some years into the 2020s in the previous evidence that I have read. Just to be clear about that, we are finishing the sequencing in 2018, but, once you have all the data together, the research needs to carry on for some time after that. There have been some delays. They result from doing something extremely novel and new, at a novel and new scale, and in particular there have been all kinds of issues around the data that we have been trying to collect; some IT issues and some science issues, as you know, around the way that cancer samples are collected and processed. A whole set of things has come together. I do not think you could point at any one thing and say that is the reason why we are a year behind. It is just new, different and big.

Q122 **Dr Mathias:** And a learning curve. Professor Parker, do you want to say anything?

Professor Parker: That is absolutely right. The reason the project exists is to show that this can be done and done at scale. One of the aims of the project, as we heard, in addition to the benefits to current patients, is to transform the NHS into a service that can offer the benefits of genomics more widely. That transformative aspect of the work has taken time and is an important challenge related to the scientific one. A good example, speaking as a non-scientist, is the transformation required of pathology services for cancer samples, for example. Many of these challenges were perhaps, to some extent, foreseeable, but not in detail. Work was needed to be done on those.

Q123 **Matt Warman:** We are talking about genomics as though it were a very separate thing. In your view, is genomic data fundamentally different from medical data?

Alison Hall: My view, and that of the foundation, is that there are certain characteristics of genomic data that can make some of it extra-sensitive and extra-predictive, but the majority of genomic data is not informative and may not be used for informing future health problems. The idea that all genetic data should have special protections placed around it is not scientifically credible. Unfortunately, regulators tend to worry that, because some of this data is special and confers a lot of information about future health problems and can be used for discrimination, or people can be stigmatised on the basis of it, all genomic data needs to be lumped together and treated as exceptional. What we are really talking about with genomic data is a different sort of assay rather than the test. What is important is that the test, and any sort of test—weight or blood pressure—can create information that can be used to determine your future health and could be the basis of discrimination.

Q124 **Matt Warman:** Is it fair to say that, going back a number of years,

people made exactly the same argument about every new generation of tests and we now do not put medical data in a different category of security, depending on arguments that were had 30 years ago, and we will probably end up in the same place about genomic data in the future?

Alison Hall: I think that is right. Looking ahead, other sorts of omics data too may well fall outside this special category but be more predictable and more useful for determining future health.

Dr Hockings: If we look at relevant international normative guidance and legislation, they give us a very different picture of the nature of genomic data. If we look at UNESCO in this regard, they maintain that since genetic data can be predictive of genetic predispositions, extending even over generations, it has a special status. By contrast, in their report, Caldicott 2 stated that genetic information should not be treated any differently from other forms of information and genetic information is not in itself always identifiable. There seems to be an immense difference between the view taken here in the United Kingdom and that given in relevant international normative guidance and legislation. That is a real problem and cause for concern because, ultimately—

Q125 **Matt Warman:** Which are you concerned by more—our attitude or theirs?

Dr Hockings: Exactly, because the very permissive regulatory environment that has emerged here has largely been driven by commercial interests in addition to other interests. That is what accounts for this vast difference—this difference in attitude toward genetic data.

Q126 **Matt Warman:** Is it fair to say that we should adopt a different attitude to the security of that data, or should we not say that patient data is patient data and it should either be as secure as we can make it or not? Why are we drawing a difference, or why are some people seeking to draw a difference?

Professor Parker: To answer your first question first, as a link, there are a number of ways in which genetic data are different. One reason we are here today is that it adds potentially huge clinical value to our understanding of disease and treatment. It is special in ethically important ways, some of which are to do with consent and how we manage the data, but some of which relate to the huge benefits that can be obtained from that. I personally, for example, very much welcome the data strategy that was published last week, which stated the idea of introducing sanctions for data misuse and the malicious identification of people from a database.

Protections need to be in place. Societies or different countries will take different views, but for patients, participants and health professionals to have confidence that genomics is being used wisely, it is being subjected to public scrutiny and engagement. We need those background protections and we need to make sure that what is being proposed is being explained clearly. Beyond that, it is not much different from any

other health information. We need to pay attention to all health information.

Dr Hockings: With the 100,000 Genomes Project, the policy makers have decided to exclude the public from having a meaningful, instructive debate about the risks and wider implications of these initiatives. They have systematically maintained that genomic data is anonymisable, that there are no real risks and serious implications, when in fact this is not true. If you look at any authoritative study, there is a consensus that it is technically impossible to anonymise genetic information. In addition to that, currently they are using a typology that is made up of the terms "depersonalised" and "personalised," and "deidentified" and "identified." These terms are not without controversy. The question I have is: why is it that they have abandoned the terms "anonymised, "pseudonymised" and "identifiable," and they are now using a set of terms that are highly contentious?

Q127 **Matt Warman:** Can you explain perhaps why what you are talking about is not simply an issue of semantics?

Dr Hockings: On one level we have the issue of whether it is technically possible to anonymise a whole sequenced human genome, and there is a wide consensus that it is just not possible to do that. There are a number of studies that show that it is very easy, in fact, to re-identify a genome that has been codified. That is one thing that we have to bear in mind here. With regard to the typology that Genomics England now uses, my question is: why is it that it has now shifted to a typology that is very contentious, when it previously used a typology that is the sort of standard within the context of information governance? This strikes me as a sleight of hand.

Q128 **Matt Warman:** I do not want to get entirely trapped down a cul-de-sac, but I feel you should have the opportunity to come back on that.

Peter Counter: I will take your first question first: is there any difference? My colleagues have given different perspectives, but from the IT perspective there is a difference in that genomic data is very big and is, therefore, not really amenable to being copied in the same way that other data is. The standard way in the health service whereby data is used clinically in an identifiable way and for research in a de-identified way is simply to copy it to a different database without some of the identifiers in it. That is not very practical when the data is petabytes large. We have huge amounts of data resulting from the 100,000 Genomes Project. The idea that you could just copy it somewhere else is not impossible, but it is very difficult.

Q129 **Matt Warman:** On a slightly different track, progressively we have dealt with ever larger amounts of data as computers and technology have got better, so that is likely to get a bit easier over time anyway, is it not?

Peter Counter: It will get a bit easier, but it is not—

Matt Warman: Not any time soon.

Peter Counter: Moore's law is running out in these contexts. Yes, it will get easier, but then the numbers will be bigger and bigger.

Q130 **Matt Warman:** I suppose what I am driving at is that you cannot necessarily use that argument to be complacent on the security.

Peter Counter: No, absolutely. I am just saying it is different from that point of view. It gives an added dimension to the difficulty. There are two or three things there. I would take issue with the words "very permissive" in terms of our regime. We are not very permissive. We are absolutely dedicated to protecting the data in all the ways that it should be protected. We take all the same steps as anybody else running identifiable data to make sure that it is restricted in who can access it; that it is behind all the relevant firewalls, that it has encrypted access and the permissions are very difficult to get hold of to access it. Only a few people in Genomics England can access the identifiable data. We take all the possible precautions that we can to protect the identities of our participants.

On the question about the words "anonymise" and "pseudonymise," I am afraid, as to all of them, that different people use them in different ways. "Anonymous" quite often means aggregated. It is impossible, as Edward points out, to anonymise completely any personal-level data. It is not just genomic data. When we first started talking about this, there was the time, you may remember, when David Beckham broke his foot playing for Manchester United. You could go to Manchester Royal Infirmary and find somebody with a broken left metatarsal admitted on a certain day and you would find David Beckham's health record. It was completely anonymous, but you could still identify him.

Inherently, patient-level data can never be treated as perfectly anonymous. One definition is that it must, therefore, be aggregated, so people use it like that. Other people use it to mean with all the identifiers stripped off and no way of re-identifying. That is another use. In the ICO code of practice they talk about "anonymous in context," which is where you use the data with the level of de-identification that has happened to it—the level of things that have been taken away. It might leave an age or a this or a that, but the level of de-identification, in the context that it is being used and without other data being brought to bear on it, results in it being anonymous; it cannot be identified. You could identify it if you broke the agreements that you had signed and you brought in other data, but "anonymous in context" is a very useful concept from the ICO.

The final usage is the normal colloquial one, which says that your name and address have been taken off it. That is the way in which it was used in our original consent material. It won't be clear to anybody coming in who you are.

Pseudonymisation is also subject to similar differences of use. Normally, it means a pseudonym is applied to the main identifier; in the NHS, it is usually the NHS number. You substitute the NHS number either with a different number, which is what we do—we have a GEL participant ID that we substitute in place of the NHS number—or it means you encrypt the NHS number, in which case you could then, in theory, decrypt it if you had the key. It is also used for pseudonymising other parts of the health record, so you might pseudonymise a date of birth, an address or a postcode. It has those characteristics as well.

These are quite difficult and technical issues. So, what we have been trying to do in our consent material and the way we discuss this is to make it really accessible and to have people understand. First, the consent material makes it very clear that there is a small likelihood or small risk of being identified in certain contexts. Although the word "anonymous" was used originally, it is made absolutely clear in the rest of that discussion on the consent form that anonymous does not mean you could never be identified from this.

Secondly, we also say in our consent material that, if we do not find a diagnosis for you, if we do not find something from the clinical test part of the work, we will continue to search in the research environment, and if we find something we will let you know. We cannot let you know if it was completely anonymised, so there must be a way of re-identification, some kind of pseudonym that was there.

Thirdly, we need to link it. We have other data coming in from other sources, clinical data, which means that the researchers can say, "What does the genome look like? What do the medical records look like and how do they match up together?" Again, to make those linkages you have to have some kind of identifiers in there, but we are extremely careful with all this stuff. We are absolutely assiduous in the way that we protect that data.

Q131 **Chair:** I am conscious that time is running away from us. I notice that two of you would like to make a comment. Have you finished, Matt?

Matt Warman: Shall we hear them?

Chair: Yes, but could I ask you to be very brief and answer only if it adds to what we have already heard?

Alison Hall: The distinction between anonymised data and pseudonymised data is important in the light of the general data protection regulation, which will be coming in in the next 18 months or so, and that, for the first time, includes pseudonymised data within its scope.

Dr Hockings: Why is it that the Government always maintain that all data, whether it is summary care records, care.data, the HSCIC or the 100,000 Genomes Project, is anonymised? It has come to light that in

fact data that was made available via the HSCIC was made accessible to private insurers, such as BUPA, in an identifiable form, yet the public are always told that all data is anonymised and that there are no risks with such an undertaking. That is the key concern.

Professor Parker: Just to be fair, as the chair of the ethics advisory group from the beginning, I have had a look at the materials as they have gone through, and there has been a constant emphasis on the importance of clarity with participants about the potential for risks. This is a project with consent; it is very different from care.data and other initiatives. It is not the only way of doing this, but it is a model that seems to have gone down well with participants; the evaluations have been very positive. To be fair to the project, they have dealt with these things in a pretty open and straightforward way.

Q132 **Matt Warman:** I have one very quick and not entirely related final point. There has been a suggestion that, on a pure cybersecurity angle of this, every trust should be mandated to have a CTO on the board. Do you feel that would be a useful step to further maintain the public confidence that you have been talking about by implication? It looks like a maybe.

Peter Counter: I am all for raising the profile of IT issues in trusts and indeed in any other organisations. In my view, there should be a C-level IT person to answer the issues and to look at it. That applies to trusts, public companies and other companies as well. I do not think that of itself will fix the whole issue.

Matt Warman: Of course not.

Q133 **Derek Thomas:** Is the NHS in a position to integrate the infrastructure, workforce and processes established by the 100,000 Genomes Project into routine NHS care?

Alison Hall: There are a number of issues here. There are issues, as I mentioned earlier, around the healthcare professionals and the workforce knowing enough about genomics to identify the patients who will benefit most from having testing and to understand the results that are returned to them. That is an issue. There are issues around the data sharing, and I alluded earlier to the need for a designated NHS infrastructure that would enable data sharing, and the computing power to compute those data.

You mentioned the word "integration." There is a question about how much we use what has been built for the 100,000 Genomes Project and simply carry it over into clinical NHS services, or whether we need to build something that is better fitted to what a clinical genomics service would do. That is where the need for evaluation comes in, not just of the ethics but of the other issues I mentioned earlier, such as the way that these results inform patient care and management—those sorts of issues.

Q134 **Derek Thomas:** Before the others come back, can I move on? Of the genome sampling that has been taken, are you able to tell me what proportion have seen results being returned to patients and how long—

Alison Hall: Well, I—

Q135 **Derek Thomas:** I do not mind who answers, but you might want to respond to both and I am conscious of time. How long did they take to receive a diagnosis and, on that basis, would they have been better off just being treated under normal NHS pathways?

Professor Parker: Peter may have something to say about that, but I think Professor Mark Caulfield is going to be giving evidence later, so you might get an answer to that from him, or I am sure Genomics England could be asked to give a written answer to that question. I do not think any of us is qualified.

Peter Counter: I can tell you we have returned about 1,500 of the results. These are 1,500 families, equating to about 3,000 genomes so far.

Derek Thomas: That is quite small.

Peter Counter: There is a tranche of probably a further 3,000 genomes waiting to be processed and we are looking at a pipeline for doing the rest. We have been building these things in progression, so the first thing we had to do was to take the sequences and the data and so on. We are now focusing on the interpretation pipeline and trying to make that as fast and as straightforward as possible, but there is quite a backlog to get through. Some of those have been waiting a long time for the interpretation to come back. There will come a point later in the year when we have caught up with the backlog and we will be processing those through at a reasonably quick rate within a few weeks.

It is exactly that kind of process that Genomics England has been trying to blaze the trail for: how do you do this, what automated services do you need, and how does it all work, to get the thing ready for proper commissioned genomic tests from the NHS? So, yes, a lot of the lessons can be learned and a lot of the things we have built can be reused, and it will eventually happen. I have absolutely no doubt they will be embedded in the NHS eventually with a lot of the lessons that we have been able to contribute.

Alison Hall: There is an issue around timeliness—whether these results can be returned within a patient journey. There are also issues about pathways for each of these clinical specialties, mainstreaming these processes out into the healthcare more generally. Are the pathways in place? Then, of course, there is the issue that you mentioned of funding. Are these tests paid for by commissioners? All these elements need to be in place.

Q136 **Derek Thomas:** Of the 3,000 that you referred to, because of the concerns we were hearing about—extra consent and your interpretation time—is it fair that people may have received a diagnosis slower than they would have under traditional pathways, and, if so, does that matter?

Peter Counter: Most of the rare disease people who have come through—and they have been pretty well all rare disease so far, although there has been a small number of cancer returns—have been undergoing tests for most of their lives. The ones that we have got into our programme are the ones where the standard tests have not yielded a result. For somewhere between 20% and 25% of the time, we have been able to provide a diagnosis for the first time through whole genome testing, which was not available on the NHS before.

Q137 **Victoria Borwick:** What a fascinating discussion this morning and how wide-ranging. I want to go back to the opportunity of the data being used for research. We have had it explained to us about the anonymisation and the safeguards in place, which is very reassuring. I understand that the national data guardian proposed that patients could be able to opt out of their data being used for research. Is that right? Is Genomics England's approach to consent compatible with that, or will there be a conflict there?

Alison Hall: We have been working with the national data guardian since her review last summer, because she identified some of the very special issues around genomic data—the fact that there is a blurring between direct care or clinical care and secondary uses such as research. The PHG Foundation, along with the Association for Clinical Genetic Science, was involved in an evidence session looking at these issues. That was held in October. We explored the issues around identifiability, around the use of testing to inform either direct care or research and how easy it was to draw a distinct boundary—it is not always easy—and then, going back to the consent issues that we talked about earlier, the extent to which explicit consent or implied consent is needed for those various uses.

I know that the national data guardian is working on a report from that evidence session, and in her review last summer she proposed a consent model or a preference model that was predicated on having this clear distinction between direct care and other secondary uses. I know that is something that she is going to consider with her panel and produce more evidence on in the next few months.

Professor Parker: To answer your question about withdrawal, the options for someone who is currently in the study are that they can withdraw in two different ways: one, they can withdraw from any further contact but allow their medical data to be used in research; the other is to withdraw completely so that there is no further use and no further contact. The decision was made early in the study. We might take a different view when we think about genomics more generally, but this was a limited resource to fund 100,000 genomes to establish the case for a genomic NHS, to make the case, and so it would be very difficult under those conditions to say to people, "You can be part of this, but you can't decide not to be part of the project." It is about resources.

Q138 **Victoria Borwick:** It is self-limiting. The question we wanted to get at was this. If a genomic disease is discovered in a family member, in what

circumstances should relatives who may not have thought about being tested, or even may not have agreed to being tested, although they perhaps would not know if the circumstances were different, be informed? To tackle illnesses, often familial patterns are interesting, so perhaps you could talk about how you would cope with telling relatives.

Alison Hall: Professor Parker and I have been talking about this for the last decade at least.

Professor Parker: Maybe I will start then. If you were to ask me what the really important ethical issues in genomics are going to be in the future, quite apart from the 100,000, one of them is going to be resources and how we priority-set in this area. Another is going to be how we think about families and that kind of information. There is a real need for a debate about that. It seems to me that there are two aspects of this. One is confidentiality, as it were—how we think about information, when we think it is right to inform family members, and whether the current standards elsewhere in medicine ought to apply here.

Q139 **Victoria Borwick:** It has been well publicised for breast cancer genes, and things like that. If a sister, mother or many family members have died, are you saying that you would now tell them?

Professor Parker: I am saying that the GMC, for the first time in its confidentiality guidelines, has highlighted the possibility that genetic information might lead to cases in which breaches of confidentiality might be justified. They have started to investigate it.

I have a different kind of question that I think is important. Do we think it might be legitimate in certain circumstances, where a mutation is identified that is relevant to a family—where it is not confidential, as it were, but is the name of a mutation in this particular family—for a clinician to be able to use that as part of their clinical toolset when they are dealing with patients who come from the same family?

Q140 **Victoria Borwick:** Do you mean that they could highlight it to inform others elsewhere?

Professor Parker: I am strongly of the view that we ought to move in that direction, but it is not something that can be done without a wider public debate, transparency and participation.

Q141 **Victoria Borwick:** If something was discovered, it could be put in a research paper, and others might be able to contribute to that research.

Professor Parker: That happens any way, does it not? I was thinking more along the lines of researchers and clinicians who have been working with a large family for many years and are aware of the name of a mutation. Another family member comes in, says they are a bit worried about their risk and asks whether there is a test available. Clinicians ought to be able to say, yes, there is a test available, as long as that

does not raise confidentiality issues; if it does that, then we get into the space that the GMC is interested in and we ought to think carefully about all those options.

Q142 **Victoria Borwick:** Is there currently a consensus as to what would need to come in?

Professor Parker: Alison is probably the person to answer that, as she has done a lot of work on consent and confidentiality.

Alison Hall: Within clinical genetics services, there is a well-established practice of giving patients letters to give to their relatives. At the moment, the practice is not that the professionals would contact relatives directly. That is often because the balance of benefits and harms and informing individual patients is quite finely balanced and may be very dependent on the particular circumstances of the case. As I mentioned earlier, the fact that you have a genetic variant, except in some very rare conditions, does not necessarily mean that you are going to get the disease. There is the issue of penetrance of that variant leading to future disease as well. There is a host of different things that need to be taken into account.

Q143 **Derek Thomas:** How should we decide which diseases and cancers to prioritise in an emerging field like genomics? Should it be purely based on areas with willing researchers and businesses?

Alison Hall: Are you talking about within the 100,000 Genomes Project or rolling out for clinical practice?

Q144 **Derek Thomas:** Let us deal with the 100,000 Genomes Project initially and what is happening right now.

Alison Hall: Others might be better placed to speak to that.

Professor Parker: I can give a non-scientific answer, but Professor Caulfield, when he speaks, can answer that properly. It seems to me that the decision has to be made, or has been made, to focus on diseases where there is a need, where there is a real potential to make a difference, clinically and scientifically, to contribute to the debate, and where there is the greatest potential to transform services in the NHS to show that it is possible for there to be a genomic NHS. Those decisions were made partly on clinical grounds, partly on scientific grounds and partly on where you can make a difference; but, as I say, Mark Caulfield is the person to answer that question.

Q145 **Derek Thomas:** Hopefully, we can address this. What is the impact of aiming to eradicate diseases on communities of existing sufferers, and are we doing enough to address any potential impacts on them?

Professor Parker: It is very important that the work that is done in genomics has genuine public engagement and involvement from patients—patient engagement. That needs to be wide-ranging and inclusive. For example, in my role I have established a diversity

sub-committee with Nadeem Qureshi to look at how these things might have impacts on diversity, black and minority ethnic populations, in particular, and how services can be set up in a way that is accessible, appropriate and useful, but I do think these issues need to be addressed.

Alison Hall: There are two issues, going back to the point I made earlier. Genomic diseases—rare diseases—are relevant in every clinical specialty. Genomic disease has the potential to happen in every community, but, looking at it slightly differently, communities of patients with particular rare diseases are having an increasing voice in getting research done or even drugs being developed for their disease. Among some populations, some patients with rare diseases are being heard and have an increasingly important role.

Q146 **Derek Thomas:** Can we move on? What is your view on whether it is appropriate prior to a couple deciding to conceive, in terms of genomic screening? What should be the limit of conditions that are screened for and fed back to parents? I do not know if that is something—

Alison Hall: Clearly, increased knowledge about genomics means that it has potential to be used to prevent disease. You mentioned the word "eradicate" earlier. Knowledge of your carrier status could be used to inform your risk of having an affected child. For some diseases, that is really important. The other issue, though, is that I am not supportive of general profiling, of people having whole genome profiles to determine their risk of disease at this stage, because it has been shown in research that each of us carries genes that we think should be fatal and yet we are clearly alive. We are at a very early state of knowledge with this. It would be premature to do that sort of thing.

Professor Parker: Clearly, there are broad societal questions here, but it is worth highlighting the fact that there are families currently with rare diseases where women are going through multiple miscarriages, IVF, PGD and a range of testing to avoid having a child with a disorder. There is the potential here for some of that additional suffering to be avoided as a result of this kind of testing. There are these broad questions but there are also some specific identifiable cases where this could be of huge value.

Q147 **Chair:** Dr Hockings, do you have any view?

Dr Hockings: No.

Q148 **Derek Thomas:** As Victoria says, it is a fascinating subject. Do you think the genomic advances we are seeing will benefit all members of society? Will it just become something that we all benefit from?

Alison Hall: Do I think or do I hope?

Q149 **Derek Thomas:** Do you hope and believe that that will be the case?

Alison Hall: Part of what the PHG Foundation does is to try to work towards a future where genomic knowledge will inform better health, and

that is better healthcare within health systems but also better health for citizens. I hope that that is the sort of future we are working towards.

Professor Parker: Genetic health services and genetic services are currently not accessed equally. There are differences; there are groups that do not access these services for a whole range of reasons; and it is really important that we move towards trying to ensure that those people who need services get access to them. There are a number of ways in which that can be done, and that is something that requires debate too, but I hope that genomic medicine, partly because it is hopefully going to be done in a structured, publicly transparent way, subject to discussion, and in an inclusive way, can be a model for how that can be done.

Dr Hockings: The adoption of an open model of consent has to be supplemented with a guiding framework that states clearly who can have access to genomic data and for what purposes. Particularly within the context of the likely enlargement of the 100,000 Genomes Project, in its submission to this inquiry the Department of Health stated that it anticipates the 2020 vision for genomics will be characterised by the routine use of whole genome sequencing in clinical pathways and a single national genomics knowledge base. It is useful, therefore, to focus on the bigger picture, that is, the likely expansion of the 100,000 Genomes Project, and what constitutes legitimate use of whole sequence genome data.

The care.data debacle is further proof of why it is essential to cultivate with the public greater foresight about the long-term implications of genomics. A fully sequenced genome is a wealth of information that contains very sensitive information, such as, in some cases, a predisposition to mental illness. If this kind of information is readily available, this could be extremely harmful to people. We need to be very clear about what constitutes acceptable use of genomic data.

Chair: There are a couple of points, briefly, that Dr Tania Mathias would like to pick up on.

Q150 **Dr Mathias:** From Peter across to the right, could I quickly ask your opinion, first of all, on whether you think the main driver behind the genomics project is commercialisation, patient benefit or something else—in your opinion? Do you have any knowledge of data being given to insurance companies without consent?

Peter Counter: As we said in our submission, we have three fundamental aims, which were given to us equally. One is patient benefit, another is the research—finding new treatments and new ways of diagnosing—and another is commercial benefit to the country. Those three, in the context of a proper consent and privacy arrangement, are the three. Definitely no one of those is pre-eminent, certainly in the discussions that I can tell you we have day to day. No one of those takes priority.

Q151 **Dr Mathias:** What about my question about any data going to companies?

Peter Counter: We are expressly forbidden from giving any data to insurance companies, and I can assure you that no data from Genomics England has ever gone there.

Alison Hall: From my perspective—from an independent perspective—all I can say is that, yes, I think the 100,000 Genomes Project has been set up with those three objectives equally in mind, but that might mean, as I said earlier, that we need to carefully evaluate the elements that need to be taken forward to underpin a clinical genomics service.

Q152 **Dr Mathias:** In your opinion, is one driving more than the other?

Alison Hall: I think it is at an early stage, and it is difficult for me to say. As to the insurance point, I do not have the knowledge to answer that.

Professor Parker: Patient benefit is absolutely the priority in my experience, in every conversation I have heard, and that is current and future patients. I am involved in many scientific projects of a range of different kinds, and it is increasingly apparent that to do good research, which improves benefit, there is very often the need for technology companies, technology partners, of various kinds, and you cannot do this work without that kind of involvement.

Given that that is the case and we want the best care for patients, as a society we need to foster those relationships and make sure that the UK industries that relate to that benefit from this. Essentially, for me, and my experience in every conversation I have ever had has been that—for example, with the chief medical officer and so on—patient benefit is the priority. It is just a recognition that the research requires a collaborative approach.

Dr Mathias: Thank you.

Dr Hockings: Given that we are most likely moving towards a national genetic database, potentially at a 50 million scale, there is going to be pressure from the public sector on policy makers.

Q153 **Dr Mathias:** In your opinion, what is the main driver?

Dr Hockings: I do not think commercialisation is the main driver, but it is certainly one of the main drivers.

Q154 **Dr Mathias:** On the other point of data being given to companies without consent, are you aware of any evidence of that?

Dr Hockings: I am not aware of any concrete examples, but the Government's record in this area provides very few assurances. Within the context of this likely move towards a national genomics database, we have to be mindful that there will be pressure from the private sector on

policy makers to widen the parameters within which whole genomic sequence information can be used.

One last point is that we are concerned that this drive towards commercialisation could result in the institutional lock-in of commercialisation in the biosciences—genomics and the biosciences more generally.

Dr Mathias: Understood, thank you.

Alison Hall: Can I add something finally? We have a concordat and moratorium on genetics and insurance, so that provides some reassurance that insurers will not use predictive genetic test results to discriminate or stigmatise.

Q155 **Chair:** Can you ever envisage a day when that may not be the case, bearing in mind that things change?

Alison Hall: Yes. It is under regular review, so it is possible that that could come to an end. It is being reviewed this year, but it was just to say that is some reassurance.

Chair: Fine, thank you. Conscious of the time, I thank our panel very much indeed for their attendance this morning and their insightful answers. It was a very informative session. Thank you very much indeed. We are going to move straight on, if we may.

Examination of witnesses

Witnesses: Professor Sir Mike Stratton and Dr Jean Abraham.

Q156 **Chair:** Good morning, welcome, and thank you very much indeed for joining us. For the record, could you state your name and who you are representing this morning?

Dr Jean Abraham: My name is Dr Jean Abraham. I am a University of Cambridge academic honorary medical oncology consultant. I run three large research areas. I am co-chief investigator of the personalised breast cancer programme, which is a sequencing programme. I also run an international breast cancer trial and a cancer pharmacogenomics programme.

Professor Sir Mike Stratton: My name is Mike Stratton. I am director of the Wellcome Trust Sanger Institute and chief executive of the Wellcome Genome Campus. I was medically trained, but I have been a scientist for 30 years. My interest has been in cancer genomics, both in the context of finding cancer susceptibility genes, such as breast cancer genes, and looking into the somatic mutations that take place in all cancers, which underlie the genesis of all cancers.

Q157 **Chair:** Thank you. Again, welcome. Can you tell us what potential genomic medicine has for the treatment of cancer here in the UK and, I suppose, around the world?

Professor Sir Mike Stratton: We are already seeing the fruits of cancer genomes in terms of the knowledge of cancer genomes and their impact on patients. By sequencing cancer genomes and finding the so-called somatic mutations that have occurred during the course of a lifetime of an individual and that are responsible for converting a normal cell into a cancer cell, we find key genes that, when they are mutated, are responsible for that conversion. Those genes, or the proteins that they encode, become targets for the development of new drugs. This is not fanciful rhetoric any more; this is something that has happened multiple times, and we have many new drugs that have been approved by the various regulatory authorities and that have been found on the basis of identification of these mutated cancer genes that are now in clinical practice and have transformed the treatment of many patients.

More of that to come is, I think, the major agenda, because, although that has happened for a subset of these cancer genes that recommend themselves for a number of reasons as targets, there are many more cancer genes that we have not been able to exploit in this way. A very substantial part of the ongoing research in the wider cancer research community, genomics and others, is to use those to find new ways of developing drugs. That is a massive wave of research right across cancer.

Dr Jean Abraham: To address your question but from a slightly different angle, in the personalised breast cancer programme that I run with Professor Carlos Caldas, we are seeing benefits at different levels. We are seeing benefits at a local level—for the patients. We are discovering carriers of mutations who would not normally be risk assessed, which has an impact on them and potentially their family as well. We are seeing the benefit for local researchers.

I run an international breast cancer trial and my patients come through Cambridge. Normally, when you run a trial, you recruit for five years, get the data, clean the data and apply for funding to do the research, which takes about seven years. For patients who go into the trial and also into this project, I now get their genomic data as they are being treated, so I can see the results of their genome differences as they get their treatment. That is something that is transforming in many ways—transforming as a researcher and also for the patients, although maybe not immediately for those patients because you have to accrue enough data to make a proper statement. Then we link up our project to national initiatives run by Cancer Research UK and via the national NIHR portfolios with international collaborators. The benefit is on multiple levels.

Q158 **Chair:** Obviously, as you said, Professor Stratton, there is more to come, but what does that more to come, from both of you, look like, and is the landscape here in the UK supporting that work? Are we going to be leading in this area?

Dr Jean Abraham: The Genomics England 100,000 genomes effort is incredibly important. It deals with bringing genomics into the clinical setting and providing geographic equity of access to that type of data.

The programme in Cambridge is a good example of finding that you can do it because we are delivering our results within 12 weeks, which is making a difference to clinical practice. By the time we have recruited 2,250 breast cancer patients, we will be able to say something quite substantial about the different subtypes of breast cancer and how you treat it.

Professor Sir Mike Stratton: In short, there is much more to come. There are many more drugs to be developed and I have already touched on that. I can give you two other examples of the way in which cancer genomics will influence cancer treatment and, potentially, cancer detection. One example is that cancers are leaky; they leak DNA, which then circulates around the body, and, although that accounts for only a small amount of the DNA in the blood, you can tell that it is cancer DNA. Therefore, in the next few years, as a result of research that is going on in the UK and elsewhere, methods are being developed for monitoring the tumour burden purely on the amount of cancer-derived DNA that is circulating in the blood. You can imagine a patient who has been treated, their tumour has gone into remission but the tumour starts to come back. It may be relatively small, it may be beyond the detection of current imaging techniques, but because it begins to leak DNA it may be detectable.

There is a whole wave of research in that regard that will allow us to introduce new ways of monitoring cancer. Indeed, that particular approach is even being thought of for early detection of cancer—detection of cancer in population-wide screening programmes. That is at a much earlier phase, but these are ideas, concepts, that promise to revolutionise the way in which we envisage cancer.

Q159 **Chair:** It sounds as if there are a lot of positive moves and it is turning in a good direction. What would you like to see improved in the support being given to this area?

Dr Jean Abraham: I guess Mike and I will come at it from slightly different angles. Mine will be from more of a clinical implementation approach. To get the project going in Cambridge, we have had to rest it on five different pillars of support. Some of that is to do with infrastructure. We are fortunate that Professor Caldas and the team have built over the last 20 years a biopsy pathway. The infrastructure that is available there enables fresh tissue to be collected from tumours, which makes a huge difference to your sequencing data quality. Those sorts of breast translational teams are all there already.

The second is institutional support. We have had high-level support from our regius professor, from the cancer centre director and from the various people who need to support it to make the project work. We have also had external support from Cancer Research UK, albeit not funding. Our own charity, Addenbrooke's Charitable Trust, which funds the feasibility portion of the project, has focused very much on local patient

care and has helped us to draw in patient advocates. Again, patients are key to this.

The last thing is, I guess, good will, because, although there are three people currently employed on the project, one of the largest pieces of work that I have had to do is an effort of diplomacy and team building, bringing together people who already have a very large workload but are willing to take on a bit more for the benefit of a research project; but the benefit is paid back, in that, because they see the results within 12 weeks, there is immediate feedback that makes them continue to work on the project; it cannot be underestimated. Our pathology services, radiology and much of the infrastructure need to be there.

Professor Sir Mike Stratton: I see this from an international perspective. One major opportunity that offers itself to us with respect to the future of understanding cancer and of optimally giving the right treatments to the right patients is to use genome information to predict the outcomes for individual cancers. We do that to a certain extent now, but the opportunities for doing that are much greater. To achieve that, we will have to do what has already been touched on, which is to aggregate data from thousands, tens of thousands, hundreds of thousands and then millions of patients. That data aggregation is going to be a complicated thing to achieve and it is going to be complicated from the perspective of the data infrastructure that is going to be required, the regulatory issues that we have already touched on and the fact that carting this data around the world is almost impossible now because it is so huge. We will have to find ways of interrogating data that is held in many different parts of the world but to bring it together in some virtual way.

There is an infrastructure issue there, but there is also an issue of getting a buy-in and cultural change about that sharing of data, from the drug companies as well as anybody else; because there will be clinical trial data that needs to be shared, it will need to be associated with genomic information on clinical trials, and that will provide a foundation of reasonable numbers of cases that will allow us, in future, to assess those associations between genomic indices and individual patient outcome. That cycle of research, generating predictions for individual patients, generating more research and generating more predictions, is the virtuous cycle that we need to achieve, and that is a worldwide and cultural issue.

Q160 **Victoria Borwick:** How do we ensure that basic research taking place at institutes such as the Sanger are effectively translated into clinical benefits for our patients?

Professor Sir Mike Stratton: The primary way in which we achieve that is by generating data, making it available and making our discoveries available. That is the conventional challenge in which research has made its way into clinical practice. That has happened from many discoveries. For example, at the Sanger Institute, the discovery of a key mutated

gene in malignant melanoma 15 years ago, disseminated throughout the literature, led many drug companies to develop drugs around it. Those drugs are in clinical practice. We do have quite a good way in scientific research of disseminating information and encouraging others to use it.

At the Sanger Institute and in many other institutes around the world, there is also the spawning of commercial enterprises, translational enterprises, which are directly using the results of our research and that of other people in order to translate it. For example, at the Genome Campus we have recently built a new building called the Biodata Innovation Centre. The whole theme of the campus is genomes and biodata, and in the Biodata Innovation Centre we are encouraging small and medium-sized companies to come on to the campus, which is about 2,000 people, all of whom have interests in genomes and biodata. It is a hub for that sort of work. These small and medium-sized enterprises come in and use the critical intellectual mass, which is our key resource on that campus, to build their own businesses and to translate directly and build commerce on the sorts of discoveries that we are making.

Q161 **Victoria Borwick:** That is incredibly exciting; I think that is a really good use of it. Just going back to one of the other earlier questions, I want to make sure I have understood that we do not conflate the basic and the clinical research uses of genomics and whether we should, as a country, as we are looking forward, be careful about not overregulating, or underregulating for that matter. Do you have a view on that?

Professor Sir Mike Stratton: Can you be more specific?

Q162 **Victoria Borwick:** What could be the impact of policy on overregulating or underregulating? I do not want to conflate, as I say, the basic and the clinical research that is going on. I want your views on what we should do to make sure that we carry on with the innovation that you have been describing.

Professor Sir Mike Stratton: The UK is in a pretty good position with respect to its scientific tradition and culture, its infrastructure and resourcing of basic cancer research. I am very emphatic that basic cancer research has to be driven in that science-based way in which we allow individual scientists to think, through their imagination and creativity, of new ways to find knowledge about cancer. That is a major strength of the UK. We need to maintain that absolutely because that is the basis on which the discoveries are made that are subsequently translated. We do have that buy-in still into basic cancer research, as indeed into basic research of other types, but it is absolutely important to maintain that commitment, that belief, in basic research as the fundament of everything.

Dr Jean Abraham: Cambridge is a micro-environment of research that you will not find probably anywhere else in Europe, to be honest. On the hospital biocampus as well, much of the research done, and what Mike was referring to earlier with the ctDNA—the circulating tumour work—was

developed there. Much of that research came hand in hand with work with clinicians, so there is a real direct link between the clinical work and the basic research. As with the work at the Sanger, it is published and we share the data, and it is another approach.

Victoria Borwick: It is making a difference.

Dr Jean Abraham: It is making a huge difference. If we do not focus on basic research, you will not move the clinical research forward.

Q163 **Victoria Borwick:** That is a very good way of putting it. Do you have any views on regulation, overregulation or the current frameworks?

Dr Jean Abraham: It is a balance. The earlier questions about ethics and safety are very pertinent here. We have some remarkable patients who at a very critical point in their lives are willing to give up their time, tumours and samples for research. Therefore, we have to protect their data safety and so on, but at the same time we do not want too much regulation so that we cannot collaborate.

Victoria Borwick: As we get to this brave new world, hopefully we will be able to phrase it correctly. Thank you very much.

Q164 **Dr Mathias:** Dr Abraham, you talked about that good will with the extra work. Are there other obstacles for the researchers and clinicians working together?

Dr Jean Abraham: Probably over the last decade, or five or six years, the ability of clinical workers and research workers to come together, particularly when they are all based on one biocampus, has improved. With projects such as the personalised breast cancer programme, probably the most critical thing that we have done is set up what we call our oncogenetics review board. When a patient is seen to have a mutation or pathogenic variant of note, that mutation is discussed in the setting of their clinical situation and then it is taken and validated or verified elsewhere, and brought back for discussion.

Q165 **Dr Mathias:** So you have a discussion group.

Dr Jean Abraham: Yes. It is like an expert panel, if you will.

Q166 **Dr Mathias:** That is more time.

Dr Jean Abraham: Exactly. None of that is in your job plan and all of it is done through good will.

Q167 **Dr Mathias:** But it works.

Dr Jean Abraham: It works at the moment, but, if you are going to roll this out nationally, you have to think about the resource and time commitments of those people.

Q168 **Dr Mathias:** No lunch breaks. Professor Stratton, do you see particular obstacles between researchers and clinicians moving forward working

together?

Professor Sir Mike Stratton: Over the last 20 years, particularly in the world of cancer treatment, I have seen a remarkable reduction in the gulf between clinicians and basic researchers. If you go back 20 years, I would say there was considerable scepticism among many clinicians that basic cancer research would yield the sorts of information that would change the lives of patients. Some significant seminal discoveries in the late 1990s completely changed that perspective. I do not want to put too much of a gloss on it, but we have a remarkable world in cancer research where clinicians and basic scientists—people dealing with patients and using the fundamental technologies—are working together ever more to generate new discoveries and their implementation.

Q169 **Dr Mathias:** Is work being done to link the data from the genome project and the cancer genome project with data in the cancer registry? Is that being linked up, do you know?

Dr Jean Abraham: I think Jem Rashbass is involved with the cancer registry and with the 100,000 Genomes Project. I think Mark Caulfield will be a better person to direct that question to, quite probably, but I am sure there are conversations being had there.

Q170 **Dr Mathias:** We heard about the problem with the cancer biopsies and that learning curve. Are there any other challenges in cancer genomics?

Dr Jean Abraham: Do you mean on a practical level?

Dr Mathias: Yes.

Dr Jean Abraham: We always use fresh tumour biopsies. We collaborate with Illumina, and they have always said to us that that will give the best quality sequencing data. In the project, we do not select patients at all in terms of what is called tumour cellularity. If you take a biopsy, you do not know, without looking, how much tumour DNA there is in there. Some patients will have 50%, 60% or 70% tumours, and some will have 5%. That will make a big difference to your sequencing data and the quality of it. There are practicalities like that. We are finding out through the personalised breast cancer programme the proportion of our patients who have low and high cellularity, and what kinds of results that leads to. It is a learning process. There is that aspect. Then it is down to building pathways, I guess, of radiologists and pathologists, who all know what they are doing, to deliver the right samples in a timely fashion and having the labs that validate the results.

Q171 **Matt Warman:** Is a lack of awareness about genomics among clinicians in general holding back our treatment of cancer?

Dr Jean Abraham: There is a lack of understanding about genomics, because it is such a new revolution in a way. We all got genetics training—or a lot of us got genetics training—but perhaps the new, high throughput sequencing-type data was not part of our training. Certainly, the Association of Cancer Physicians that runs my specialty—medical

oncology—has a specific working group, led by Ellen Copson, who look at training for future trainees in genomics. Similarly, I know Genomics England has a huge education programme. So, yes, it is a problem, but it is beginning to be recognised and addressed.

Professor Sir Mike Stratton: I would agree. It is a question of continuing medical education in genomics as in other areas of technology development. This is a particularly important case because the genomics advances are being introduced at pace into standard clinical medicine. Therefore, clinicians need to learn about them on the hoof, and the technologies are changing so quickly that that is not always so straightforward to do. Nevertheless, it is absolutely happening, and if we again look over that 20-year period we know that clinicians working in absolutely conventional medical practice have to use terminology and technologies that 20 years ago would have been completely unfamiliar to them.

Dr Jean Abraham: The only other thing to add is that there may not be a need for every clinician in every district general hospital to have the same level of expertise as those in academic centres, and that that expertise can be exported. Your model needs to be thought about in terms of how you export that expertise.

Q172 **Matt Warman:** We talked in the earlier panel about whether genomic data was fundamentally different from other patient data. From a patient perspective, the kind of information that you might be told as a result of understanding your own genome is fundamentally quite different, because it is not saying, "If you get your cholesterol down, things might get a bit better." You are telling people about factors that may affect their whole lives and may change their whole outlook. Do we understand the psychosocial impact of this, and are we doing enough with genomic counselling and that sort of area to allow this to be explained to people in a way that is useful and responsible?

Dr Jean Abraham: We are only 52 patients into the project, but already we have had discussions, or are starting to have discussions, with our clinical genetics team about working closer together in joint clinics and so on. There is a lack of counsellors and bioinformaticians, because there are two levels of interpretation that need to be resourced. From the patient's perspective, you need more counsellors, because, as you discover more of these findings, not only do you have to tell the patient you have to but support them with their families as well. That is very important.

Q173 **Matt Warman:** As you say, with only 52 patients, it is probably a bit too early to say, "Here is the nationwide programme for counsellors that we should have," but, as you say, we are doing things at a remarkable pace. We do need to have an eye on that, do we not?

Dr Jean Abraham: I do not think you can wait until the study has finished to start doing that. You have to start thinking through those issues ahead of time.

Q174 **Matt Warman:** What might thinking through those issues look like in practice now and are we doing it?

Dr Jean Abraham: Looking at the resources that you have for genetic services would be important, such as the number of counsellors and the way we work in delivering results. We have separate oncology and genetics clinics at the moment, and I refer my patients from oncology to genetics. We work remarkably closely with that team, so it is more of a phone call and a conversation than a formal referral, but over time those two may need to work together in one clinic setting, for example—that kind of practical change.

Q175 **Matt Warman:** A related but not directly related issue is whether whole-genome sequencing, which obviously provides a lot more information compared with targeted testing, is sensible, whether the marginal cost is worth the effort at this stage or whether we should still think of it as a first-line thing or not. Do you have a view on whole-genome sequencing?

Dr Jean Abraham: Are you referring to it in terms of widespread clinical implementation?

Matt Warman: Yes.

Dr Jean Abraham: The answer is that the jury is out. Projects such as ours and the 100,000 project, in which we also collaborate, will both give you an idea of whether whole-genome sequencing for the whole population is the right way to go or whether you can stratify your populations in some way and be a bit cleverer about it. The big plus of whole-genome sequencing is that you have all that data for ever, whereas if it is targeted and the target changes—

Q176 **Matt Warman:** You might have to go back and do it multiple times and spend more money.

Dr Jean Abraham: Precisely, yes.

Professor Sir Mike Stratton: We have to be pragmatic for clinical implementation at the moment. Targeted sequencing provides most of the information that will be useful to patients now, today—that we have proven can be useful to patients. However, the journey we are on is a journey of accruing more and more data that we are going to put into the mix to predict individual patient outcomes. That is genomic data. There is a lot of it, but it is also wider, including all the rest of the clinical data.

We can already see from a research perspective that there are indices and predictions to be extracted from cancer genomes that probably will only come from having a whole cancer genome. It is to be proven; it needs to be delivered over the next five to 10 years, and then we will be

in a position to see the cost-benefit of going through a whole cancer genome and whether delivering those additional pieces of information makes it worth while. In time, genome sequencing costs are going to drop and they are going to keep on dropping—that is the cost of the analysis—and in time that will be the correct diagnostic. It is what you are doing at this moment and in five years and 10 years—

Q177 **Derek Thomas:** Are we doing enough to provide cancer diagnostic tests in patients, and what barriers have you experienced when trying to do so?

Dr Jean Abraham: What are you referring to exactly by cancer diagnostic tests?

Derek Thomas: I am reading my notes.

Q178 **Chair:** For example, the test you were talking about earlier—the DNA markers in the blood.

Professor Sir Mike Stratton: DNA that has leaked out of a cancer and is circulating in the blood is at its research stage, as we work out whether that is predictive. My opinion is that it will be predictive and it will allow us to monitor tumour burden, but it is not proven yet. However, with respect to your question about targeted cancer gene screens to prescribe the right drug, those companion diagnostics absolutely go with the drug, and those drugs are part of standard treatment for those particular types of cancer. For malignant melanoma and lung cancer, there are certain treatments that can only be given if the companion diagnostic, the genomic analysis, has been done.

Q179 **Victoria Borwick:** It is personalised medicine.

Professor Sir Mike Stratton: It absolutely is personalised medicine. That is part of the standard now. You cannot give the drug without doing the companion diagnostic, and, if you are observing standard conventional practice now, you should be considering that drug. It is being delivered and it should be delivered.

Q180 **Derek Thomas:** As we improve the diagnostic and the genome sequencing capabilities, are we at risk of being able to diagnose an individual and then not having the capacity within the NHS to treat the individual? Is there a danger of that?

Dr Jean Abraham: Yes, there is. When you do whole-genome sequencing, you find mutations all the time that are reported. We have a tier system for our mutations, so there is a tier 1, which are the results that go back to the patients, and those are genes where there is a strong association with breast cancer in this particular case. I am sure that by the time we finish our study we will find either that we are seeing patients who have mutations for which there is not a trial open with a targeted therapy or that there is a need—Cancer Research UK is working on this— for a national database so that, for example, if you have

metastatic breast cancer but you have a BRAF mutation, which is what Mike was talking about earlier, and there is no trial in your area, you can find somewhere to go to for that trial. Patients will travel a long way when their lives are on the line.

There will be a clinical trial deficit. It is informing what clinical trials we need to develop. This is not just a patient-benefit tool directly telling the patient what they have; it is a research tool telling us in what direction our research and clinical trials need to travel.

Q181 **Derek Thomas:** You are right about patients travelling. I am the MP for St Ives in west Cornwall, so we often travel some distance to get the best treatment we can. Professor Stratton, will the depth of coverage and concerns about heterogeneity and turnaround times limit the practical deployment of whole-genome sequencing in diagnostic testing?

Professor Sir Mike Stratton: At the moment, the turnaround time for whole-genome sequencing in terms of, yes, generating the data but then analysing the data, is an issue with respect to the treatment of individual cancer patients. One needs that information within a couple of weeks in order to make the appropriate decisions with respect to choice of therapies. We would be optimistic—it would be our aspiration—that that will change over time as we are able to deal with the large amounts of data more quickly. There was another part of your question.

Derek Thomas: No, that was it.

Dr Jean Abraham: Just to come back to that point, although ideally you want it back within two weeks, you can still use the data. We set 12 weeks as our target from sample receipt to results back to patient, and we have done that because that is three cycles of chemotherapy. That is a decision point at which you decide whether you go on with more chemotherapy or change to surgery—that kind of thing. There are ways to work that timeframe into your clinical care so that it is meaningful, but you cannot wait a year for your results. You have to have it within a set time.

Q182 **Chair:** Thank you. Are those times that you are talking about a capacity issue, or is there a real reason that it has to take as long as that? What is the quickest it could be achieved with the right equipment and everyone focusing on doing it?

Dr Jean Abraham: You have to bear in mind that it is not simply just about the sequencing. The sequencing could probably be done in 24 to 48 hours, but it is not about that. If you are going to use it in patients, it has to go through many more levels of safety. Those are the steps that take the time. You have to find your mutation, then you have to go and validate it or verify it in another independent system, and you need the manpower to do all that. That is where some of the issues lie.

Q183 **Chair:** But that is a manpower issue. There is no technical reason why this could not be speeded up. What I am trying to get at is, if we are

going to be using this very exciting technology on a much larger scale and we are going to try to roll it out across the whole of the healthcare system, what are the barriers to doing that?

Professor Sir Mike Stratton: The barriers will not be the time taken to do the sequencing, if the timing is the question. There will be some time in getting the sample to the sequencer. If we have centralised facilities that are doing the sequencing, that will contribute a significant amount of the time—those pure logistics. The sequencing itself probably will not take very long so long as you can get the sample on to the sequencer as soon as it arrives at the facility.

Analysing whole-genome sequencing data is a significant demand. You would need to have the computational infrastructure of the relevant size to do that if you are doing it for large numbers of samples. At Sanger, we have probably the largest life sciences IT infrastructure in Europe. It is of the size, more or less, of the sort of IT that is available for the Large Hadron Collider.

Chair: Vast.

Professor Sir Mike Stratton: These are the challenges in dealing with this huge amount of data on a daily basis from large numbers of patients. That gives you a sense of the challenges that there will be. It is the amount of data. If you have a small amount of data—for example, from a very small targeted gene screen—that is going to be much less of a problem.

Dr Jean Abraham: It is doable, though. We collaborate with a group in Heidelberg, who turn it around in four weeks, but they have an in-house sequencing resource and dedicated staff for each step.

Q184 **Chair:** Other than that capacity, there is computing and expertise. As time progresses, computer power will increase and this will become more mainstream and we will get there. Or are there things that we, the Government, should be doing to accelerate this and to make sure that that pathway is eased—that we do not just leave it to, "We will get there in the end"?

Professor Sir Mike Stratton: I think we have identified the areas that can be contributed to, and each of those will be an issue. You are quite correct that, over time, computing power will improve—Moore's law is familiar to you—but the rate at which we are generating DNA sequence and could generate it from patients' tumours is much in advance of the rate of improvement through Moore's law. Computational infrastructure, surrounded by the personnel infrastructure to deliver that quality of data, will be required.

Q185 **Chair:** Around that personnel structure, are we preparing enough clinicians and the staff to be able to work with this technology?

Dr Jean Abraham: In our particular local area, we are very well prepared because that research is embedded in our mainframe, if you like. What you need to consider is doing the same thing in other centres. That will require a certain amount of mindset changing, infrastructure and resource.

Professor Sir Mike Stratton: Over time, these analyses are going to become more and more complex. To analyse a whole-genome sequence and say, "This patient's cancer may respond a little bit better to this drug and a little bit worse to that drug" is not something that an individual can compute. There will have to be processes that are set in place for analysing genomes to produce that sort of prediction. Who is going to do that is a significant question, as is how we are going to do it, because there may need to be regulatory processes for how previously generated data is analysed in order to generate reliable predictions. This is quite a big area of the development of science and diagnostics that has not been thought about or developed in quite this way previously. It is unknown whether this will be done within the NHS or be provided to us by private commercial providers, who will aggregate data from all over the world and process data to provide these predictions, but they have to be reliable, well-founded and up to date, and they will be using vast amounts of data. As to whether it is the NHS or not, I am not sure who is going to do that.

Q186 **Chair:** There is one final question before I wrap this up. In the transition between where we are now and where we would probably like to get to, we are going to have to limit and ration—that is perhaps a pejorative word—or use sparingly the resource that we do have. Are we suitably equipped to decide who will and will not benefit from gene sequencing, those sorts of things, as we work towards expanding the service?

Dr Jean Abraham: That is a wider social question, is it not, in a sense? I do not think any one of us can make that decision. Genomics England has selected certain cancers to focus on and has selected rare disease, and it has done that for very logical reasons. The question is whether you can sustain covering that wide a number of areas or whether you try to do a proof in principle on particular types of cancer or particular areas of rare disease, and then, once you have established you can do it, roll it out wider. It is up for discussion.

Professor Sir Mike Stratton: One needs to counsel caution with the rationing because one needs to take an informed overview. At a particular moment of deploying more resources, yes, that is an issue, but in the longer term individual patients will get the treatments that they require rather than treatments that will not do them any good, and that will save resources. It will be good for the patient, but it will save resources for the health systems as well. We need to take that higher-level view of what the benefits and cost-benefits of this all will be.

Q187 **Victoria Borwick:** So less collateral damage.

Professor Sir Mike Stratton: Exactly. That is right.

Dr Jean Abraham: We have talked a lot about treatment of patients, but there are substantial numbers of patients who come into hospital due to the side effects of treatments that they did not need to have or could have been saved from having, and that is a saving that needs to be taken into the mix.

Professor Sir Mike Stratton: You need a big cost-benefit analysis before thinking of the rationing.

Chair: Thank you. That is an interesting place to draw this session to an end. Thank you very much indeed for your attendance this morning and for your answers. It was very interesting.