

Science and Technology Committee

Oral evidence: Commercial genomics, HC 33

Tuesday 15 October 2019

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Watch the meeting

Members present: Stephen Metcalfe (Chair); Vicky Ford; Bill Grant; Graham Stringer; Martin Whitfield.

Questions 1 - 54

Witnesses

I: Professor Anna Middleton, Chair, Association of Genetic Nurses and Counsellors; Dr Matthew Hurles, Head of Human Genetics and Senior Group Leader, Wellcome Sanger Institute; and Professor Anneke Lucassen, Chair, British Society for Genetic Medicine.

Written evidence from witnesses:

- [British Society for Genetic Medicine](#)
- [Association of Genetic Nurses and Counsellors](#)
- [Wellcome Sanger Institute](#)

Examination of witnesses

Witnesses: Professor Middleton, Dr Hurles and Professor Lucassen.

Q1 **Chair:** Good morning. Welcome. Thank you very much for joining us as we continue our inquiry into commercial genomics. For the record, could you state who you are and which organisation you are representing?

Dr Hurles: I am Matthew Hurles. I am head of human genetics at the Wellcome Sanger Institute. I also co-founded a company. I am not speaking on its behalf, but I notice that it is one of the bodies that has submitted documents to you.

Professor Lucassen: I am Anneke Lucassen. I am chair of the British Society for Genetic Medicine. I am also a clinical academic in Southampton.

Professor Middleton: I am Anna Middleton. I am the departing chair of the Association of Genetic Nurses and Counsellors. I also work at the Wellcome Genome Campus in Cambridge.

Q2 **Chair:** Before we kick off, I need to ask whether you have any declarations of interest. Matthew, you have already mentioned the company.

Dr Hurles: I have none other than that.

Q3 **Chair:** Thank you. Obviously, genomics can tell us an awful lot. It is a very useful technology and there has been an increase in the amount of commercial activity undertaken. What information can genomic tests provide? What can't they provide?

Dr Hurles: I would break it down into three areas. There are areas where genomic data is useful now, areas where genomic data is potentially useful in the future and areas where it seems unlikely to be of major use.

Where it is useful now is in things like ancestry—determining people's populations of ancestry. That is in a non-medical space. Most of the other applications are in the medical space. In the medical space, there is diagnosis, especially of disorders caused by single mutations and single genes. Those can be diagnosed prenatally or after birth. There is also screening for the same kinds of disorders. That can occur prenatally. It can even occur pre-conception, if couples understand that they are both likely to carry a variant that will cause a disease if both of them pass it on to their offspring. That is often known as pre-conception screening. There is then prenatal screening, which can be done either as part of IVF or during a pregnancy. NIPT, which you have heard about in some of your documents, is one example of that.

There is also the potential for screening after birth to pick up the risk of later-onset conditions that are caused by mutations and single genes.



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Sometimes these are called incidental findings, because one finds them when one is looking for some other kind of information from a genetic test. Sometimes they are called secondary findings. I think you will see both in the literature that has been submitted to you. That is the screening and diagnostic side of things.

Then there is the issue of people responding differently to different kinds of medical interventions. One person might be given a drug and it is ineffective. Another person might be given a drug at the same dose, and it will have a very severe negative effect. In fact, that happened to my father. He had to be resuscitated after being given morphine. These things are relatively common in the population. That is often known as pharmacogenomics. A lot of the evidence is there and it is very robust.

Related to that is stratified medicine—the idea that people’s genetics may influence their response to a particular medical intervention, which could be drugs or it could be other things. One of the big areas where it is used is cancer. The idea is that people who have cancer and have particular mutations may respond very well to particular drugs. That is known as stratified medicine.

That is the set of things where it is very obviously useful now. One thing that is coming in the future is the ability to predict the risk of commoner diseases such as type 2 diabetes. We use the phrase polygenic risk scores, because the disease is caused not by any single mutation but by a combination of variants that all subtly influence risk. There is a lot of interest in that currently, for a number of reasons. One is that the science is advancing rapidly. The second is that healthcare systems are very interested in preventive medicine and this potentially fits that bill.

Q4 Chair: I am sorry to interrupt you, but we have heard previously that the genetic part of potential disease is actually quite a small part of it. It might indicate that you have the potential to get a disease, but it will not say, “Yes, you will,” or, “No, you won’t,” because lifestyle has a much greater influence on that outcome than genetics. Is that a fair comment?

Professor Lucassen: It is a fair comment, and a really important comment to remember. I agree with all of Matt’s outline, but what is often forgotten is that a genetic test result needs to be heard in context. On its own, it does very little, particularly in a healthy population. It might predict something quite well. If you have a strong family history, say, of breast and ovarian cancer, a particular genetic finding might explain most of that family history, but if you find genetic variation in a healthy person you need much more context around that.

That is clear to lots of people, but it is not clear to others. There is sometimes a sense that people conflate the ease of the technology with the ease of predicting what comes out of that information. That is not at all the case. More often than not, particularly when people take a commercial test, the information is much less clearcut than they expect. Some examples recently have been of people who have had a commercial



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test, for example, for ancestry, where, as Matt said, it is commonly used; I have heard the figure of 26 million for the number of tests that have already been sold worldwide.

What people then do is send off the data from their ancestry test to other companies for secondary analysis. Although those companies say on their websites, “Do not use this for health interpretation,” often people may not notice that or may feel that, because what they have heard about genetics is so clearcut, it does not apply to them. They go off and have their test reanalysed and come back with information. Strangely enough, the higher the risk, the more likely the information is to be wrong. That is to do with the technology of the test.

For example, take the Angelina Jolie gene, as it has been called—the BRCA1 gene. Some recent data from colleagues in Exeter showed that most of the commercial tests that analyse the variants in that gene are likely to be false positives, if you get a result back saying that you have one of those gene variations. Of course, even if that happens in only one woman it is a big issue, because getting risk-reducing surgery of your breasts and ovaries is a major operation, let alone if it is not warranted because you have a false positive result.

Q5 **Chair:** Absolutely. Anna?

Professor Middleton: Only 5% to 10% of disease is strongly genetic, and not all genes are the same. The best way of working out whether a gene is going to cause disease is to look at the family history. If you can see generations of disease in a family, it is very likely to be strongly inherited. There are some conditions where you need many genes together to get the condition, and other diseases where only one gene fault equals the condition. It is very complex. A lot of the commercial testing is not really looking at single, high-risk, disease-causing genes; it is looking at a whole spread of many genes.

Q6 **Chair:** To be clear, when an ancestry test is done, that test will be different from the one that would be done if you were looking for a specific genetic disease.

Professor Lucassen: In the health service, if you were looking for a specific genetic disease, you would tend to target the particular gene that you suspected and analyse that in detail. The ancestry tests look at several hundred thousand variations throughout the entire genetic code, how those have changed in populations over the last several thousand years and how your ancestors have migrated across the globe. Interest tests should not be used for health interpretation.

Q7 **Graham Stringer:** That is because you are getting different detail from an ancestor test than you would get from one looking for variations that would predispose you to a disease.

Professor Lucassen: You might appear to get the same information. The ancestry tests also look at genes such as BRCA1, BRCA2 and other



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high-risk genes. Depending on the technology used, that is where they might find the false positives. If they are reporting on health risks, they might then report variations in the gene that are not actually there.

Dr Hurles: I mentioned two kinds of applications. To diagnose single-gene disorders, you need a different kind of test from what is done with ancestry. The kind of work that I mentioned that is potentially coming—on polygenic risk scores—involves exactly the same kinds of information as the ancestry test.

Professor Lucassen: Yes, but people often assume that they are the same. People think that a genetic readout is a genetic readout. They hear a lot about how accurate it is, and they do not necessarily understand—why should they—that the readouts are very different, and that certain readouts should be used only for very common variation and not for very rare variation.

Professor Middleton: If a member of the public is genuinely concerned about an inherited condition in their family, the best way to get an answer to that is to go through the NHS and to have a test from an accredited laboratory.

Chair: I was about to come on to that.

Q8 **Bill Grant:** You suggest, and I tend to agree, that they should go through the NHS. Are there restrictions and certain criteria to be met before you will receive that through the NHS?

Professor Middleton: Yes.

Professor Lucassen: Yes.

Q9 **Bill Grant:** Should that be broadened? Could it exclude some people at risk? Are the criteria right?

Professor Middleton: The first port of call is your GP. If you have a strong family history of, say, breast and ovarian cancer, your GP will make a referral to a clinical genetic service to have that discussed in more detail. If you are a healthy person who is just generally worried about being a carrier for cystic fibrosis with no family history of that and no concerns about something specific, the GP would not make a referral to clinical genetics.

Q10 **Bill Grant:** The GP would do a risk assessment on the individual. If they fall outwith the criteria, where does that person go then?

Professor Lucassen: Quite often they can get recommendations about screening, rather than about genetic testing, dependent on their family history.

You are quite right to ask whether family history alone is enough as a screening test. Sometimes it will not be, because sometimes people do not know about their family history. They may be adopted, for example,



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or they may have lost touch. Those are the examples I am particularly worried about. They are the examples that we have seen come into genetic services around the country, where people do not have a terribly strong family history but have had an ancestry test, and have thought, "Let's analyse it for these health variants as well," and have come up with what they think is something that predisposes them highly to breast and ovarian cancer. They have then entered the health service with their result saying, "I didn't have the family history that met the criteria, but I have this result and I would like risk-reducing surgery."

Those are the ones that are more than 90% likely to be wrong. That creates an awful lot of confusion and extra work. I would like to see more attention being given to that space. I suspect that the companies themselves would be very happy to engage in that, but we have not yet found a way of doing it.

Dr Hurles: There are some areas where there is the potential for people to access diagnostic or screening tests where the NHS is not providing them for them. Obviously, the NHS tries to come to a balance as regards cost-effectiveness. You can correct me if I am wrong, but I think that the guidance on non-invasive prenatal testing is that, if your risk looks likely to be above one in 150, the NHS will offer you a test. If your risk is one in 160, you may still feel that that is the right thing for your family.

Professor Middleton: The problem with the commercial testing is that often it is done direct to the consumer, without the support and information around what it actually means and without helping the public and patients to make sense of it.

Q11 **Chair:** Are there any commercially available tests that have proven clinically useful that the NHS does not offer and perhaps should?

Professor Lucassen: Not as far as I am aware.

Dr Hurles: I can think of one example—maybe two examples—but it is largely in a space where the science is moving very rapidly and is able to access tests that confirm that a particular variant is actually the cause of a disease. I am thinking of epigenetic testing, for example. There is work that my group and others have done, where we know that there is a lot of clinician appetite to try to get that confirmatory test, which is not currently offered in the UK.

Q12 **Chair:** But it is commercially available.

Dr Hurles: Yes. That would be one example. In the NIPT space, currently there is testing for three conditions. There are many more severe paediatric genetic conditions. I am aware of a couple of companies that are offering tests that screen for more than three conditions. It is very early days, but one can envisage that people will want to expand those tests in the future.



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Professor Lucassen: I agree with that. The other area that you mentioned where there is probably more commercial availability that could be harnessed by the NHS is in the pre-conception space. Testing to find whether both members of a couple are carriers of a recessive genetic condition is not currently offered by the NHS. The NHS waits for a child to be born with that condition before it offers screening to family members. That is another area where commercial testing that is not available on the NHS could be useful.

Chair: That is very useful.

- Q13 **Graham Stringer:** We are told in the evidence that a lot of the commercial companies are not very transparent. Is there anything that can be done to check or regulate the validity and interpretation of their results?

Professor Lucassen: I think they probably are quite transparent. Certain companies have excellent websites. The problem lies more in the expectations of the people using the test. That is why I might say that it is not so much about regulating the companies as about improving the information around what a genetic test might and might not tell you.

- Q14 **Graham Stringer:** The interpretation of the tests.

Professor Lucassen: Yes.

- Q15 **Graham Stringer:** Do you have criticisms of the way any commercial companies are interpreting the results?

Professor Lucassen: Yes. I have criticisms of the secondary analysis in particular. They say that they will not reveal health information, but they reveal information that is then interpreted as health information, and the context around it is lost completely. As Anna said, the information provision that you would receive in the NHS is not there, so why would you know to take that result with caution?

Professor Middleton: In the small print it is often written, "Don't use these tests for clinical reasons. They are based on research findings." However, in the marketing of the tests they say, "Go to your doctor if you are worried about this. The results of this could change your life and change your behaviour." That implies that you can use them clinically, but in the small print it is very clear that they are not to be used clinically.

Dr Hurles: There are three areas where one could think about regulation. The first is the quality of the data that they generate. There are existing quality schemes that look at that. The second is the quality of the interpretation that they give. Thirdly, if companies are seeking to make money out of providing genetic interpretations that have potential psychosocial impacts, they should be making sure that the provision of counselling around that is appropriate. Counselling will not necessarily be appropriate for every kind of genetic test—I am not sure that counselling



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is necessary for ancestry testing, for example—but, in the situations where it is, that is an area where I do not think the companies are doing well. Anna can speak much more to that.

Professor Middleton: Despite recommendations from the European Society of Human Genetics and the American College of Medical Genetics and Genomics, which all state very clearly that genetic counselling should be provided pre and post test when you are testing for serious, life-threatening conditions, most commercial companies do not offer any level of support. They might signpost a customer to a YouTube video saying how great it is to be informed of your genetic risk, but they do not actually pick up the pieces. Those patients then turn up at clinics in the NHS very anxious and expecting the NHS to pick up the pieces.

Professor Lucassen: Within the NHS, there needs to be greater awareness of this. To go back to the example I listed earlier, I know of several cases of people finding a surgeon who was willing to do the operation on the basis of the test result, because the surgeon believed the test result, only to find that that test, which they thought was highly accurate, was an artefact and that the result was not there when they were tested in the NHS. We need much better awareness within general practice and within surgery that a genetic test is not always what you think it is and that the result should not be taken at face value.

Q16 **Graham Stringer:** How would one move to improving the system of interpreting and understanding those results?

Professor Lucassen: From professional guidelines. We are working with the Royal College of General Practitioners on guidelines for GPs on what they should do when people come to their surgery with one of these results. That is likely to be the first port of call for most people who get a result that makes them worried about their health, so that will be very important. We must spread that out to secondary care areas as well, so that surgical teams, for example, do not think that when they get a result it can be taken at face value, without further scrutiny.

Professor Middleton: We have lots of guidelines and recommendations on this already. They have been around for many years, but there are no teeth. The commercial company is not required to adhere to them.

Q17 **Graham Stringer:** Would you recommend a regulator with teeth?

Professor Middleton: Yes.

Dr Hurles: Yes.

Q18 **Graham Stringer:** My final question is not really related to the questions I have asked so far. This is an area of science that is moving very quickly. What do you think the next major steps and improvements to increase knowledge in this area will be? How will the area change?



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Professor Lucassen: I hope there will be an understanding of the nuance. The discourse about genetics has been very much about high-risk genes and strong predictiveness. As Matt said, we are moving into areas of common risk, where environmental risk factors play much more of a role and where the genetic result may categorise you in a higher or lower-risk group. From a public health perspective, that will be very useful, but not so much for individual predictive value. Getting that message out and making people realise that, without the context around it, their genetic test result is not that useful would be a really important development.

Professor Middleton: We are moving massively into the digital era, with Matt Hancock's announcement on the Topol review, which is looking at the future of the NHS in five, 10 or 20 years' time with respect to genomics, AI and robotics. We are looking at genomics being integrated into the smartwatch and into all sorts of risk calculations. I guess that the risk of all of that is losing the nuance and the personal experience of what all of it feels like and means. There is definitely a need to slow down a little on digital implementation and to think about the people behind the risk.

Professor Lucassen: The context, genetically. A test result on its own means very little most of the time.

Q19 **Bill Grant:** This is a slightly unusual question, so I seek forgiveness before I start. I am hearing about the possibility of false tests going forward and of people securing a surgeon willing to undertake a procedure and, post that, it was discovered that it was totally unnecessary. Then enter the legal profession. Have there been cases in the past where people have been sued? The originator, I imagine, would be the commercial company that conducted the tests. Has it happened that the legal teams have come in, or is that likely to happen in the future?

Professor Lucassen: As far as I know, it has not yet happened, but we are in the very early days of this being possible. Court cases often lag behind about 10 years after things have happened, so I imagine that it could well be possible in the future.

Q20 **Bill Grant:** Events of today could appear in court a decade from now.

Professor Lucassen: Yes.

Q21 **Bill Grant:** As a result of what might be wrong testing, as opposed to the wrong diagnosis. A test is not a diagnosis as such, is it?

Professor Lucassen: Correct.

Q22 **Bill Grant:** That could happen, but there is no history of it as yet.

Professor Lucassen: As far as I know. I am not a lawyer though.

Bill Grant: That is okay. Nor am I.



Q23 Chair: Does the equipment the tests are conducted on either work and give you an accurate result or not work, or can it give you results that change over a period of time? Does it need to be re-evaluated, reassessed and, I suppose, calibrated?

Dr Hurles: There are two phases: the generating of the data and the interpretation of the data. The interpretation of the data definitely changes over time. We now know that a genetic variant in a particular gene really does cause a disease, whereas we didn't when the test was done. That is the bit that changes most rapidly, and that is one of the challenges for the healthcare system. As we are now doing genetic tests that are much broader in scope—testing all genes in the genome, for example—one has the means for going back and reinterpreting the data. There is huge value in doing that, but it is quite challenging to the system.

You asked about the machines themselves. Typically, competent people can generate high-quality data from those machines. They are pretty robust technologies. It is the combination of the generation of the data and the bioinformatics that causes the variants on the data. It is a very easily assessable thing. In terms of regulation, it would be relatively easy to do.

Professor Lucassen: Matt will have known about this for a long time, but it is quite recent news to me that the rarer a variant is, the more likely SNP array technology is to get it wrong. It is not that the technology is completely robust; it depends on what technology you are using. It is the bioinformatics of it, isn't it? The bioinformatics calls it wrong when it is a very rare variant. Of course, the rarer the variant, the more predictive it is likely to be. Is that right?

Dr Hurles: Yes.

Q24 Vicky Ford: Can I come in quickly on the question of the regulator? Is the issue that the regulator does not have teeth or is it that there is not enough clarity for the regulator and it is not regulated enough?

Professor Middleton: I was not talking specifically about a regulator; I was talking more about the recommendations that are in place from the professional societies. There are loads of recommendations about direct-to-consumer commercial testing, from all the organisations that represent the clinicians on the ground. It is those recommendations that are not being—

Q25 Vicky Ford: So there is not a regulator.

Professor Middleton: It depends which regulator you are thinking of. If you are thinking of in vitro diagnostics regulation, it could come under that.

Q26 Vicky Ford: There is a lack of clarity about the whole regulatory framework.



Professor Middleton: I think that is right.

Professor Lucassen: There is lack of clarity, together with lack of understanding.

Dr Hurles: One of the things that struck me from reading the documents that you received was that many of the companies would like some regulation—a bar that they know they need to hit.

Vicky Ford: That is helpful.

Q27 **Martin Whitfield:** We have already heard this morning that there is a challenge with the education and a challenge with the information. There has also been much mention of the challenge of the counselling. I will take the opportunity to delve into the counselling side of it, without in any way allowing the education of those who are involved and, probably more importantly, the information for and education of the public about these things to go by the way.

It is interesting that counselling was the area that produced the largest group of evidence that has been submitted to us. Professor Middleton, I know that your association submitted evidence, so I will start with you and ask the big question. In the perfect world, what counselling should be offered alongside the testing?

Professor Middleton: It is important to say that the counselling we are talking about is not therapeutic counselling; it is genetic counselling, which is quite different. The interactions are usually just one-off. Genetic counsellors are highly skilled, postgraduate-educated, regulated professionals who register with the Genetic Counsellor Registration Board. They are skilled in genomic medicine and clinical genetics, but also in care of the family. Their job is to help families to navigate their way through the testing. Who is going to be tested? What does it mean? How do they want to incorporate it into their lives? That is what genetic counselling is.

There is a very large space for genetic education, which is very different. Anybody could do that. You just need to understand what genes do. Any health professional could do that. A website could do it. A chatbot could do it. It is the interaction where you explore what it means for you. Do you want to have your children tested? At what point could they be tested, and why? What screening might they access if they are tested? That kind of holistic care is genetic counselling. As a discipline, that is what should be available when we are talking about serious, life-threatening conditions. There is an opportunity for genetic counsellors to specialise in that, but also to support their other clinical colleagues to have conversations about genetics when they are dealing with the patient in front of them.

Professor Lucassen: I think you mean serious high-risk conditions that are largely determined by genetics.



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Professor Middleton: Yes.

Professor Lucassen: There are lots of serious high-risk conditions where it would not be very predictive.

Professor Middleton: Yes. We are talking about inherited conditions.

Q28 **Martin Whitfield:** What you are doing is granting someone who is thinking about having a test, or undergoing a test, access to a specialist post test results, who can formulate the nuance of the information that is coming in. Is there, or should there be, different levels and steps of counselling, depending on the generic test, or—I am going to use this phrase and regret it immediately—should the gold standard of identified counselling be available for all generic testing, because of the nuance that you are talking about and the change that is happening?

Professor Middleton: No, I don't think genetic counselling per se should be the gatekeeper for the ability to access a genetic test, but it is context specific. For example, if a woman with breast cancer and no variant-inherited genes goes to see her oncologist, has a diagnostic test for one of the breasts and is found to have a mutation in one of those genes, that can be relevant to determining the chemotherapy and surgical options that she has. The oncologist could have a very sophisticated conversation about the fact that they have done the test and that is what they found, but the oncologist will not say to the patient, "Do you have any sisters? Should we test them now? When should we test them? Who else in the family is at risk?" Somebody else doing genetic counselling would be the one picking up the pieces in time.

Q29 **Martin Whitfield:** Rather than a generic test, it is to the individual the counsellor comes across that they can bring their expertise and knowledge to suggest wider review research or other questions that could be prompted. I suppose the question that flows from a lot of the information we were given is that that is a face-to-face discussion. I accept that it may be by telephone, but it requires human interaction with the human who is undergoing it. What are the panel's views on the idea of trying to get away with just written counselling, AI counselling or flow-chart counselling?

Professor Middleton: That would not be counselling; that would be information gathering. Counselling has to be a two-way process; it is a dialogue and it is patient-centred, because it is focused on what the patient needs.

Professor Lucassen: Our recommendation would be that counselling is recommended for the very high-risk conditions, but they are rare. I do not think that you would be calling for counselling for all genetic tests. Certainly the BSGM would not. When we are talking about direct-to-consumer tests, ostensibly most of them will not be for very high-risk conditions. I do not think we are saying that there it is really mandated. What we are saying is that consumers can find themselves getting what



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they think is high-risk information without ever having seen a counsellor, and they might have benefited from seeing a counsellor before they were in a position to get that information.

- Q30 **Bill Grant:** I am being terribly negative this morning. If somebody gets bad news, for want of a better expression, having had genetic tests, and fails to engage with a counsellor properly, might it lead those individuals into some form of depression or an event in their life that makes that counselling almost essential, particularly if their mind runs riot with the news they have had? It might be unexpected or anticipated news, but once they get it they cannot manage it. Would you say it is absolutely essential?

Professor Lucassen: Particularly for conditions you cannot do anything about, it is important that people have the opportunity to discuss them. One of the tests that has been around for the longest in the NHS is for conditions like Huntington's disease for which at the moment there is no treatment. It is incredibly important that people have access to skilled genetic counselling from anyone in the clinical genetics profession, so that they can talk about whether or not they want that test. We know from many years' experience that many people, when they have the opportunity to discuss it, decide that they do not want the test. People say they want it, come forward, talk about it and then most of them fall away.

- Q31 **Martin Whitfield:** Professor Middleton, in your evidence you said that the situation with regard to genomic counsellors was in dire straits because of the numbers and the retirements that are coming. We have identified a very real need, and an essential part in NHS genetic testing, for this essential counselling to exist, but pressure will come from private companies if they are required to provide counselling. How do we reconcile that problem? We will hit the NHS, which is identifying people who need genetic testing and the support that is needed, but the support will not be there physically because of the lack of numbers. How do we balance that? Should the NHS take priority, but then we have private companies that are making money on the back of it? How do we square the circle?

Professor Middleton: There are so many ways to think about it. Many of the companies have genetic counsellors on their staff to write their customer material, but they are not using them to counsel their customers, which they should be; they should be using those skills.

A big concern is the skills drain from the NHS out to industry, particularly when people are offered three times the salary to go and work in industry. Some of the big companies have enormous teams of genetic counsellors. It is something we are very worried about. We have been pushing consistently over a number of years to increase our training. NHS England and Health Education England have been pushing to increase the number of trainees coming through, but because we have so many senior genetic counsellors retiring over the next five years we need a



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recruitment push to bring more senior people into the profession. That needs resourcing and we have been pushing for that as well. If there is any outcome from this that can help with that, we would be very grateful.

- Q32 **Martin Whitfield:** We have talked about re-evaluating the data second hand and non-medical but medically labelled stuff coming out. Should the companies be responsible for picking up the genomic counselling that at the minute is falling on the NHS once you have got through the barrier of the GP?

Professor Middleton: A few of the companies offer testing for serious conditions: young onset Parkinson's, Alzheimer's and breast and ovarian cancer. If you have those tests, what they offer in terms of counselling is access to a YouTube video that tells you how great it is to be informed of your risk. There is no actual direct link to a genetic counsellor who can support you.

Often, people do not know they will have an emotional reaction until they have it. That is the point when they say, "My goodness, how am I going to tell my parents I might have an increased risk of Alzheimer's? Where has it come from? It must have come from one of them." They start to think about the implications. The commercial companies have a duty of care to their customers to pick up the pieces and not rely on external people, who are not even paid by them, to pick up the pieces.

- Q33 **Martin Whitfield:** If this is occurring in the NHS, all of those discussions are happening at the same time, whereas if it is a private company there is bound to be a space between results coming out, the emotional hit and emotional questions. Let us say that in a brilliant case there is support from counselling, but one then has to go back to the NHS, and that timescale exists. Is there any consideration as to how that can be shortened but with a responsibility so that it does not become a surprise in terms of resources?

Professor Lucassen: I agree with what Anna said, but I also think there is scope for the NHS to inhabit much more the space that is currently inhabited by commercial companies. There are moves afoot to do that. The advanced disease detection cohort will do that to some extent. That is a good move because it will bring together things that feel like polar opposites a bit more than they are currently and allow those mechanisms to be thrashed out a bit more. At the moment, the direct-to-consumer industry is fine for ancestry testing, but by and large it is not helpful for the NHS to stray into health predictions, and the more the public sector can reach out and include that, the less we will have those polarisations.

- Q34 **Martin Whitfield:** The answer is an expansion within the NHS for critical and severe potential genetic identifiers rather than relying on private companies to highlight them.

Professor Lucassen: The critical and severe potential identifiers are already well dealt with by the NHS. There might be some questions about whether the screening to get those people in the NHS picks up absolutely



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everybody—I am sure it does not—but I think the NHS can do much more with the commoner diseases where there is a genetic contribution. I would see that much more as a development in public health than in individual predictions.

Dr Hurles: There is a real challenge around that space. It is great that the Treasury has just invested £70 million or £80 million in the advanced detection of disease cohort. That is a really good thing. The science is advancing very rapidly, and if people want to know what their risk is of common disease X, there will be commercial companies that will provide that information. If the NHS is not sufficiently rapid, there is a risk of reasonably large numbers of people having information that they feel strongly is relevant to their health and it will degrade trust in genomic medicine specifically and more generally in the NHS. There is a time aspect that is quite critical. We are quite well placed with large-scale translational research projects that can gather the evidence that enables us to implement rapidly, but we will need to implement rapidly.

Professor Lucassen: We did a small public engagement exercise where we asked people about direct-to-consumer testing. They thought that might be the responsible thing for them to do because they knew the NHS was cash-strapped; they thought it was something they should be doing to save the NHS money, not realising that it is often unhelpful.

Q35 **Chair:** There is a range of impacts that an individual can feel depending on the outcome of a test, but you do not know the impact until you have had the results of the test. Is it worth considering that, before any test, there should be some form of counselling or input, almost with a health warning, to use the vernacular?

Professor Lucassen: It depends on what the likely predictive value is. If it is a very low predictive value, I am not sure that we would want to recommend counselling. When it is a very highly predictive test that has big implications for either no treatment or drastic treatment, we absolutely should be saying that, but they will be few and far between. Those conditions are rare, so it is not as unmanageable as it may sound to recommend that the more predictive a test, the more we need to give people the opportunity to consider that beforehand.

Q36 **Bill Grant:** I sense that there are great expectations among the public, and indeed the medical profession, in relation to genomic medicine. To what extent does that promise or anticipation depend on access to genomic data from healthy people? How else could we gather that efficiently, and, presumably, ethically, to allow the system to work? I think a lot of it comes from the data.

Professor Lucassen: That is a great question, because so far much of our knowledge about genomics comes from people who have particular genetic conditions. We then find the gene responsible and we think that gene relates to that disease. What we find when we look in healthy populations is that certain gene variants that we thought predicted a



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disease really well do not seem to do so very much, or in an older healthy population either. We need to learn much more about what genetic variation does in a particular context.

There was perhaps a slightly simplistic view that one gene meant this disease. We are now beginning to realise that, even if it is a strong gene, we need to know both the genetic and environmental context around it before we can do the same thing with a healthy person. It is important not to conflate a diagnostic genetic test in a person who has a condition with predicting that a healthy person who has the same variant will get the disease in question. The two are often confused; people often think it is the same thing, but it is far from that.

Professor Middleton: The more research we do on healthy populations, the more we realise that there are people walking around with very serious-looking genes who are not unwell; they are healthy. What is protecting them? Other genes? Environment? That means it is very hard to predict what it is going to do.

Dr Hurles: I agree with everything that has been said. We are in a good position in the UK partly because of the UK Biobank and the fact that it is currently being sequenced. It is of high quality, so you are getting the same kinds of highly predictive variants that we are seeing that you do not necessarily get from an ancestry test. The data have started to flow out from that and we are beginning to identify resilient individuals and disentangle the factors that influence why people are not manifesting the disease that we might expect them to have. We are going to see a big growth in the next five years because of things that are already in the pipes. Part of that is Government investment in things like whole genome sequencing of the UK Biobank, which is a good thing.

Q37 **Bill Grant:** Is that the system that was set up as far back as 2012?

Dr Hurles: For the UK Biobank, the recruitment was set up from 2006 to 2010.

Bill Grant: That far back.

Dr Hurles: The sequencing of all the genes in the genomes has been funded by a pharmaceutical consortium that is putting the data back into the public domain.

Q38 **Bill Grant:** We are now harvesting the good work that was done.

Dr Hurles: Exactly. For example, this year the gene sequences of all the 20,000 genes in the genome were released for researchers for the first 50,000 individuals in the UK Biobank, and I think that by the end of next year we should have all half million. That will be an incredibly useful resource for looking at exactly the thing you mentioned.

Professor Lucassen: It has already been useful in highlighting the discrepancy we talked about earlier between SNP array technology and



sequencing—the false positive rate—and in what we call the penetrance of a condition, which is the chance that, if you have a genetic variant, it will show itself in the form of a disease. Looking at the healthy population, we find that particular variants have a much lower chance of manifesting in disease than we previously thought, so it has been very useful for those two examples already.

Q39 Bill Grant: What are your thoughts on the Government's plans to gather genomic data from asymptomatic individuals? I understand they are individuals who do not show symptoms. You are very supportive of that.

Professor Lucassen: We are very supportive of that. It is also about individuals from around the world. Don't forget that the way we have migrated might well influence the gene we think is important. The genetic background may well influence a particular gene. We find that certain variants in a population from, say, north Africa, behave differently from northern European ancestry, so we need to collect more than just northern European ancestral healthy people; we need to go much wider.

Dr Hurles: The only limitation I can think of with respect to the activities already going on is to do with the accessibility of the available routine clinical data on those individuals. For example, if you are a member of UK Biobank and you live in Wales, your primary care data will definitely be part of that resource. If you live in England, only 40% of the primary care data of those individuals is part of that resource. There are some conditions where the majority of care takes place in primary care, diabetes being one of them, so the benefits of that cohort are not being maximised because of the lack of availability of primary care data for a large fraction of the cohort.

Professor Lucassen: That is a really good point.

Professor Middleton: Another point along the same lines is that for healthy volunteers, who in an altruistic sense want to contribute their data to this enormous mapping exercise to try to understand human health, there is an expectation that they might like to have something in return for the data in terms of results in some form. As we have already said, when you are looking at potential genetic disease in a healthy population, it is very difficult to predict whether or not the genes are going to play out and cause disease. If we are looking at sequencing tens or hundreds of thousands of healthy volunteers, we would argue that it is perhaps a bit premature to be choosing at this point what to give back to them in terms of results, never mind who would be explaining those results and picking up the pieces.

Professor Lucassen: The desire to want information from something you have donated is understandable, but it is partly a result of the whole discourse about genetics being so clearcut. If we could introduce a bit more of the idea that it is not quite as clearcut, people might not want it so much.



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Q40 **Bill Grant:** It is often referred to as the Government's genomic volunteer service. I am hearing from you that it should be expanded on as broad a base as possible, covering different nations and cultures.

Professor Lucassen: Absolutely.

Q41 **Bill Grant:** How do you achieve that?

Professor Lucassen: We need to think very carefully about what information we give them as a result of that testing. We might want to recognise their altruism, but we might not want to recognise it by saying, "Here's your result and your risk," until we have some very good evidence that that is robust.

Bill Grant: Is there time for a wee supplementary?

Chair: Briefly.

Q42 **Bill Grant:** The word that enters my mind is "dormant". Inasmuch as the system can detect a risk, can that same test or system tell you it will be an active risk, or will it remain a dormant risk? It is not meant to be a wicked question.

Professor Lucassen: It is a really good question, because the more we look at healthy people, the more we will realise that it is a risk based on previous information but it is unlikely ever to manifest. It is very difficult. You will be screening a lot of people, because you have identified them as high risk, who will never go on to develop the condition in question.

Q43 **Bill Grant:** The system cannot tell yet.

Professor Lucassen: No, not at the moment.

Q44 **Chair:** Following up on that, therefore, have advances in machine learning and AI helped to improve that spotting of patterns? Should we broaden the number of people in the system, so that you can better predict whether or not genes, and how they interact with other genes, will manifest in disease?

Professor Middleton: That will be resolved in time, but we need access to enormous datasets from people willing to donate their data. Millions of people need to be willing to donate their data.

Dr Hurles: There is a real opportunity for the UK. Because of the national health service, we have the capability of aggregating data across a large number of people. The US has challenges around its privacy laws, and Scandinavian countries do things very well but have smaller populations. It is a real opportunity for us, but there are barriers to being able to share data across the NHS and aggregate it together. The most benefits will only accrue by bringing very large datasets together. Genetics as a whole has used data analytics technologies that are entering other spaces for many years—indeed, decades—and will continue to do so.



Professor Lucassen: I do not need to remind this Committee that Care.data did not quite succeed in that aim, but it is really important. We have a national health service, but sometimes it does not feel national, because individual trusts are worried about sharing data outside their trust. Privacy concerns enter into this, sometimes apparently unnecessarily; but they need to be taken into consideration. There is much greater opportunity for sharing access to currently available data, as well as expanding it beyond that.

Dr Hurles: My main area of work is on rare genetic diseases and developmental disorders in children. Families often cannot understand why we cannot access the data that they would like us to be able to access as researchers. One thing we ought to think a bit more clearly about as a society is how we enable people to participate in research in the way they want to participate in research. We have quite 20th-century routes for people participating in research.

Professor Lucassen: Yes. Whether it is clinical practice or whether it is research, rather than recognising that they are entwined.

Q45 **Vicky Ford:** My question is about regulation and the in vitro diagnosis regulation that I understand is coming into force in 2022, and whether it will bring in place minimum requirements for clinical validity and counselling. To what extent does the new regulation address the concerns you have about direct-to-consumer testing?

Professor Middleton: The regulation does not actually define clearly what counselling is. Sometimes the word “counselling” is used on its own, and sometimes it is “genetic counselling”. If we think about genetic counselling as a service offered pre and post test for serious, life-threatening, inherited conditions, yes, the regulation will be incredibly helpful, and it would really tighten up what is happening in the commercial sector. But if it is genetic counselling broadly, and anybody can do it, because they are assuming it is a conversation about genetics, it is not going to be terribly helpful. That is where we are at the minute.

Professor Lucassen: I do not think it is terribly helpful in the movement between different tests, for example—reanalysing data and that sort of movement. I do not think it will have any teeth on that, as far as I understand.

Dr Hurles: I do not have more to add.

Q46 **Vicky Ford:** Anneke, in your evidence from the British Society for Genetic Medicine, you listed five areas where you thought regulation could be improved. I want to ask the others if they agree that those are the right five. They were greater transparency of the sensitivity and specificity of tests; greater transparency of their clinical validity and utility; better measures to detect and correct hype and mis-selling; measures to highlight the possibility of familial inferences; and an obligation to ensure access to clinical services to discuss genetics or offer



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genetic counselling. Is the panel agreed that those are the five areas where regulation needs to focus?

Professor Middleton: Absolutely. The key one for me is partnership between the commercial company where they give a result that has an emotional fallout, and knowing exactly how to pick up the pieces. Expecting the NHS to do that is not appropriate, but there could be more of a partnership whereby we work out who will pick up those pieces and how that will be done.

Professor Lucassen: One of the points we listed there, which we have not really talked about yet, is the one on familial inferences. Of course, when you have a genetic test that is only very mildly predictive, that is not relevant. But if you have a strongly predictive test result, you need to think about sisters of somebody who has breast cancer, for example, as Anna mentioned. We need to think more widely about how we let people know, and how we let them know respecting their possible wishes not to know, and how that information might flow in a health service that at the moment is very much about individual practitioner and individual patient. That is an area that I think the direct-to-consumer companies have not looked at, at all.

Dr Hurles: As a general principle, genetics should follow the same kind of rules and modes as other medical tests. The area where it departs is in the value of information for family members, which is something that is particularly unusual about genetics, compared with other tests. The counselling needs to be targeted to particular issues, either relating to family or to the highly predictive areas. Given the challenges and the limited resources, we should focus on targeting it on where it needs to happen and maybe less on areas that are more akin to either ancestry or tests that are not so predictive and are more akin to things that you would get from your GP about your cardiovascular risk, for example, from your lipid profile.

Q47 **Vicky Ford:** To go back to the IV diagnostics regulation, are you saying that it is a good first step and not going far enough, or that we should not have done it that way altogether?

Professor Middleton: It is a great first step, and it needs to go further. Consent is a very big issue in the commercial genetic testing set-up. It does not really exist, so anybody can send in a saliva sample from as many members of their family as they like, including their children. They just spit in a tube and send it off, and the results come back to the person whose account is with the commercial company. So much tightening up is needed about the process, the management of samples and the way results are given, even to be sure that it is a human sample that has been submitted. There are cases where someone has sent in tap water, or a sample from their dog, and a report has come back giving cardiovascular risks. There are quite a lot of quality control issues that need to be tightened up.



Q48 **Vicky Ford:** And that is covered by the regulation.

Professor Middleton: I hope it would be, yes.

Q49 **Vicky Ford:** I understand that the regulation specifically says that counselling is needed when tests relate to predisposition for currently untreatable conditions. What about when it relates to a predisposition for a condition that is treatable—the other side of that?

Professor Middleton: That is quite an unhelpful distinction, because there are very many very strongly inherited conditions. I am thinking of some of the young onset bowel cancers. You can have children with bowel cancer, and it is treatable, in that you can offer colonoscopy screening and remove sections of bowels and potentially save children's lives. With having a test early to pick up a predisposition to bowel cancer, and having screening, the condition can end up being treatable. But the whole process of having that testing requires an awful lot of thought and consideration of the family dynamics and the moment when you need to test, and loads of counselling can go with that. I find it a little unhelpful that a distinction is being made between treatable and untreatable. Also, this is a moving target: what was not treatable a few years ago is now changing.

Professor Lucassen: Just defining what a treatment is is quite a difficult one.

Q50 **Vicky Ford:** Yes. Good point. Do you think that 2022 is too far in the future for that to come into force? Should we be implementing it sooner?

Professor Middleton: It is really interesting. Certainly, in my field, it feels like it is not even on the radar at all. Genetic counsellors in the UK have not heard of this regulation; they are not concerned about it or thinking of implementing it. The communication about this has been way off the sphere for the clinical genetics community.

Professor Lucassen: That is right. Also, when it has been communicated, it feels like it will not do everything. It will be very good at dealing with the technical aspects perhaps, but not the bits around it. It will be great if it does, but I feel it would be good at regulating some aspects of direct-to-consumer tests, but that does not do anything about the misunderstandings that people come into those tests with and, therefore, how they carry those misunderstandings on.

Q51 **Vicky Ford:** Given that the UK has committed that it will implement this regulation in two and a bit years' time, are you suggesting that the interim period should be used to look at how we use that to broaden and clarify its scope?

Professor Middleton: Absolutely, and to pad out exactly what it means in terms of the delivery of care.

Q52 **Vicky Ford:** Do you agree?



Dr Hurles: I am not sure whether this is so germane, but it is worth thinking more generally about genomic medicine and what legislation ought to be in place to get to where we want to get to. The regulation of commercial testing is one particular area. There are other areas that may need some help. I am thinking of it in the round, in this period.

One particular area is insurance companies' use of genetic information. If we talk to people about genetic information and want to have large numbers of people signing up for, for example, the advanced detection of disease cohort, that is 5 million people—10% of the population. Are insurers going to be able to access those data, and what for? The US has had a genetic non-discrimination Act for 11 years, and it clearly has not harmed them. Why don't we have something like that?

The second thing that people often have big concerns around is the potential for forensic use of that genetic information. Having clarity from the Government about what the Home Office can and cannot do would, again, help to build trust with the large numbers of people we are anticipating participating in these large-scale research projects to enable us to get to where we want to get to. I see in vitro diagnostics as a piece of the puzzle but not the whole, and it may help for this Committee to think about the whole.

Professor Lucassen: To expand on that a bit, if we say that we are going to regulate something without also telling people why in a way that they can understand, they are just going to find another way around it. People will feel that they cannot access something that is rightfully theirs or that they could have bought before. If they do not understand what the limitations of it are, they will buy an online kit from the States, or from somewhere else. What you said earlier about expanding the work around it so that people understand what a test might show them and, more importantly, what it might not show them, is a really important piece of work to go alongside that, so that it does not feel as if you are not allowed to have this thing that you feel you might have a right of access to.

Q53 **Vicky Ford:** That is a really important point. It has to be done with patient organisations.

Professor Lucassen: Yes, and with public discussions about genetics in the media. Every article about genetics is accompanied by a nice, glossy, clear, technical picture, so it is no wonder that people think it is nice and clearcut and straightforward.

Dr Hurles: When you are expecting 10% of the population to participate in a genetic study, you have to talk to everyone.

Q54 **Chair:** Thank you. Further to that, and taking all the comments you have made today as a whole, what advice would you give to a member of the public considering purchasing a commercial genomic test? What would be your key statement to them?



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Professor Lucassen: I would ask why. What do you want to get from it? I would gear the conversation there. I would say that it might be an interesting sport to find out how your ancestors have migrated across the globe, but at the moment do not use it for anything else, with the exceptions perhaps that Matt has identified, where the NHS really does not provide something. Pre-conceptually and during pregnancy, there might be opportunities that are not available through the public sector at the moment.

Dr Hurles: The one area I forgot to mention when you asked the question about what the NHS does not do was pharmacogenetics. That is a key area; it has been robust science for many years, and very few health systems have worked out how to do it.

Professor Middleton: It is starting though.

Dr Hurles: It is starting, but it is challenging. It would be quite reasonable for a member of the public to want to know whether they are likely to have a very severe response to drug X or not. Those kinds of traits, of having a severe response, are common; many people in this room will respond unusually to standard drugs at standard doses. That is one particular area that we need to keep a close eye on. The gap is not science but implementation.

Professor Middleton: My advice to a member of the public wanting to buy one of the commercial tests is to read the small print. In the small print, it will often clearly say, "We sell your data to other companies." That is not immediately obvious in the marketing, and it is often the business model for those companies.

Professor Lucassen: And more is not always better. There is a tendency for companies to offer more and more either pharmacogenetic tests or disease-risk tests, and there is a sense as a consumer that the one that offers the most might be the best. But the predictor value goes down so much. It might be a pharmacogenetic test about a drug that you are unlikely ever to need. Those sorts of issues need much more clarification.

Chair: Excellent. Thank you very much indeed for your evidence this morning. It will help us to develop our inquiry, so I am very grateful.