

HOUSE OF LORDS
MINUTES OF EVIDENCE
TAKEN BEFORE
THE SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY
(SUB-COMMITTEE II)
GENOMIC MEDICINE

WEDNESDAY 2 JULY 2008

SIR JOHN SULSTON, DR FRANCES FLINTER, DR CHRISTINE PATCH,
PROFESSOR ALBERT WEALE and MR STUART HOGARTH

Evidence heard in Public

Questions 287 - 342

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WEDNESDAY 2 JULY 2008

Present

Broers, L
Northesk, E
O'Neill of Bengarve, B
Patel, L (Chairman)
Perry of Southwark, B
Taverne, L
Warner, L
Winston, L

Witnesses: **Sir John Sulston**, Acting Chairman of the Human Genetics Commission, **Dr Frances Flinter**, Clinical Director and Consultant Clinical Geneticist, Genetics Centre, Guy's and St Thomas NHS Foundation Trust and member of the Human Genetics Commission, **Dr Christine Patch**, Genetic Counsellor Manager of the Clinical Genetics Department of Guy's and St Thomas' NHS Foundation Trust, and member of the Human Genetics Commission, **Professor Albert Weale**, Professor of Government at the University of Essex, and Chairman of the Nuffield Council of Bioethics, and **Mr Stuart Hogarth**, Research Associate, Department of Social Sciences, University of Loughborough and member of the Society for Genomics Policy and Population Health (SGPPH), examined.

Q287 Chairman: Good morning, ladies and gentlemen, welcome to all of you, witnesses and members of the public. We look forward to your evidence today as the questions we have for you are pretty crucial. If any one of you wishes to make an opening statement, please do so.

Mr Hogarth: Can I make a brief opening statement about my affiliation, just because it is slightly long-winded and I would rather get it over with now. My name is Stuart Hogarth, I am a research associate at the Department of Social Sciences at the University of Loughborough. I submitted written evidence to the Committee with Professor David Melzer

of the University of Exeter based on research that we have conducted over the last three to four years on the regulation and evaluation of genetic tests. I am also a Council member, as is David Melzer, of the Society for Genomics Policy and Population Health. This is a very new society which provides a forum for those interested in the impact of genetic and molecular science and population health, particularly the ethical, legal and social issues arising from genomic and post-genomic science and technologies. Our members include lawyers, philosophers, social scientists, public health professionals and policy makers as well as geneticists and molecular scientists. At the moment what we are aiming to do is provide a forum for the discussion of the very important policy issues that surround us in the kind of clinical translation of genomic science into clinical practice. As part of that work we recently held a workshop on susceptibility testing into policy implications and Tim Aitman, your scientific adviser, was present at that meeting. I should say that the evidence I give today is my personal views on the regulatory framework for diagnostic tests rather than the views of the society who have not submitted a collective response to the inquiry.

Q288 Chairman: In the evidence that we have had, both written and oral, there is a suggestion that many of the recent advances in genomic science, particularly relating to the management of common diseases, are soon going to be applicable to clinical practice. If that is so, how soon are any of these tests likely to be available in clinical practice?

Dr Patch: I am a member of the Human Genetics Commission and I am a genetic counsellor manager at Guy's Hospital. We need to be very excited about the science but we need to be realistic about the implications of that science. If these possibilities are evaluated properly it may be a long way off before they emerge into clinical practice. The one that is most likely to come into clinical practice is pharmacogenetics and that will probably happen within the short term. In terms of the implication of these advances for the management of common diseases, the benefits will depend on what you can do with the result of the test, for example. If there is

a clinical benefit to the test, i.e. you have the test and you can do something that changes your risk, then those things will come in sooner. Tests just for knowledge in terms of the health service one has to question the actual benefit of that.

Mr Hogarth: From the US' perspective, because I have spent quite a lot of time talking to companies and clinicians in the United States, it might be interesting to make a distinction between tests based on single nucleotide polymorphisms or other heritable variants, and gene expression tests, particularly in the area of oncology. We are now seeing a fairly significant clinical uptake, for instance, of a test like the Oncotype DX test over genomic health in the United States which is for breast cancer patients. Based on the gene expression molecular profile of the tumour, patients will be given a risk assessment of whether their cancer is likely to recur and treatment decisions are made on the basis of that. I think there are different kinds of applications and some of them seem to be being adopted more rapidly and readily than others.

Q289 Lord Winston: Is there the slightest evidence that that actually works?

Mr Hogarth: I am not a clinician and neither am I a scientist, so I am not well qualified to answer that.

Dr Flinter: I will not answer specifically about that particular test but in general the problem we have is that the measurement of particular genetic variation is relatively easy and laboratories can do that well and accurately, but collecting the data about whether what you are measuring is linked to clinical disease takes time and is more difficult to do. The step up to that is actually working out whether if you do the test there is then an intervention that can be made in terms of modifying the treatment or offering screening that will actually affect the outcome of the disease. What is tending to happen is that, as soon as it becomes possible to measure something, there is a tendency to say we now have this test and we should offer it

perhaps sometimes in advance of the knowledge or ability to be able to use that test effectively in clinical practice.

Professor Weale: I am here in my capacity as Chair of the Nuffield Council on Bioethics which some members of your committee will know, at least as well as I do, that we are an independent organisation established by the Nuffield Foundation to look at ethical questions arising from biological and ethical research. We did publish a report in 2003 with a working party chaired by the late Professor Peter Lipton on pharmacogenetics and it is specifically on that point that I would like to come in on. There clearly is a conceptual distinction between genetic testing for disease and genetic testing for variations in the reactions to medicines used to treat those diseases, but in practice they may come together. The example we give in the report is Herceptin targeted at over-expressed proteins for categories of breast cancer patients where the over-expression is itself the product of genetic variation. More generally, in relation to the management of disease, genetic variation may be important. We cite the example of a liver enzyme important in metabolism of about 25 per cent of medicines with variations across both individuals and groups in terms of its underlying genetic profile. We would want to draw attention to the potential importance of the pharmacogenetic component for the safety and efficacy of medicines. The one further point that I would make is that when we were doing our report back in 2002/2003 we were operating in the conditional mode, if I can put it that way. We were trying to think about what the implications would be were pharmacogenetic tests available. I think our sense is that we would still be operating in the conditional mode were we doing that report today, so we would be very interested to see that your committee could take this further.

Sir John Sulston: That has covered the ground very well. One could refer to of course some kind of excitement in RNA, for instance, in the microarrays, the genome-wide association studies. All of this as going through but is rather unpredictable about the efficacy. What we

are here for as the Human Genetics Commission is to keep a watching brief on all of this. I am afraid that is where we have to leave it for those more recent developments.

Q290 Chairman: Moving on to the next question, which leads on very well, about an individual's ability to have genetic testing done for common diseases that may indicate that they might be at a higher risk. First of all, is that so and, if it is, what are the benefits for the individual to know whether they have an increased risk? I have a supplementary to which I will return.

Dr Patch: Reiterating my previous point, for some things there may be a benefit for evaluating what that benefit is and evaluating how people manage what they have to do to reach that benefit is a requirement before those tests are introduced into practice. At the moment for the subsets of common diseases the advice people will be given would be to lose weight, to give up smoking, et cetera, and we know that people do not take those health messages anyway. Where there is an advantage is changing the threshold at which you might offer a proven intervention; for example, we have strategies for offering breast screening to women at a certain risk and we define that risk by their age. If the science should develop so that there is a combination of genetic markers that can move people's risk threshold up and down, then the decision is we have a proven strategy for hopefully diagnosing and treating breast cancer early. We are changing the point at which people enter into that strategy and that is a potential benefit. Today at the moment for these common diseases there are very few interventions that one might say are proven to have benefit. Of course, once a test has benefit then it is a different question.

Q291 Lord Taverne: What would be the risk that you would regard as significant though? If it is an increased risk of 1.5 per cent would that influence your decision?

Dr Patch: That is a very complicated question because of the cost benefit argument. The level of risk which you regard as significant depends on the perspective you are taking. For a public health benefit, the National Screening Committee has various criteria for introducing screening programmes. For an individual that might be different and individuals have a different perception of risk. My personal view is that an odds ratio of 1.2 is meaningless, but that is my personal view.

Q292 Lord Winston: Dr Patch, I am sure you have made a very good point about breast cancer screening. I wonder whether you or anybody might be able to hazard a guess as to the percentage of breast cancer victims which might be susceptible to this kind of screening because this is a very common disease – one in nine, one in ten of the population – and so much of it would appear to be much more epigenetic than genetic in origin. That is going to be a confounding problem.

Dr Patch: That is back to the same point we will be reiterating over and over again. I think what is needed as part of this is good descriptive epidemiology. We probably do not know yet. What is happening is that there is a sort of technology creep. Tests and prognostics are being introduced into the market – the NHS is also a market – prior to really detailed evaluation and they should be introduced in controlled evaluation circumstances, but at the moment there is a funding and policy gap in that area. We would need to do the evaluation studies to answer that question.

Q293 Chairman: Do we have any research-based information about what would be the behaviour of people if such tests were available?

Dr Flinter: There is some research which shows that perhaps almost paradoxically sometimes if you say to people you may have a slightly increased risk of developing, say, coronary artery disease, they may feel somewhat fatalistic and think oh well, I am doomed

anyway, I may as well carry on having a fry-up for breakfast every day because my genes have predetermined that I am going to develop disease. There is some evidence that it may even have a paradoxical effect and in fact be unhelpful to identify those at increased risk. We also need to remember that often lifestyle can have a bigger determining influence on somebody's state of health than their genetic make-up. There is a tendency for people to feel that genetics is very deterministic and if only we knew what was in our genes we would know what was going to happen to us. As a geneticist I have to say that actually for most people what they eat, how much they exercise, whether they smoke, how much they drink will have more of an impact on their health during their lives than their genetic make-up.

Q294 Chairman: Today one of the news items is that you can reduce your cancer risk by 22 per cent if you eat a Mediterranean style diet.

Dr Flinter: Yes.

Mr Hogarth: I think your question points to a significant empirical gap in the evidence base that we really need to plug quite urgently. There have been relatively few studies done on the psychological and clinical consequences of telling people their genetic risk of common diseases. The Reveal Study in the United States which focused on giving people their ApoE4 results for risk of Alzheimer's diseases is one of the few major studies that has been done in that area. This is certainly an area where we require more research and more funding.

Dr Patch: There is a reasonable amount of research in the rare single gene disorder but I am not sure that that translates over necessarily into the common disease world.

Professor Weale: The potential benefits that we saw would be particularly in relation to adverse reactions and if there were pharmacogenetic tests in which it was possible to distinguish between patients who would respond adversely or not. The examples that we cite are schizophrenic patients in relation to Clozapine. That could potentially provide benefit.

Q295 Earl of Northesk: Following on from your point, Professor Weale, in a diagnostic setting rather than using genetic testing as a predictor, what is the possibility that genetic testing will, as a diagnostic tool, determine the most effective and beneficial therapy for an individual patient?

Professor Weale: The question that as a working party we considered was how far would a genetic test give an improved tool over and above, for example, trial and error prescribing which currently goes on with the knowledge of the doctor. I do not think that we felt that we could come to any definite conclusion about that. One of the reasons we thought that there was not the imperative to develop genetic testing for adverse reactions in many cases was that they potentially were not serious enough and the information that you would provide would not necessarily help in the diagnosis and treatment of the individual patient. In particular in relation to Clozapine where we did have evidence that for patients suffering from schizophrenia some of the adverse reactions really were quite serious and if that sort of issue could be dealt with there was then a potential of a targeted intervention in that sense. As a general tool, it is fair to say that when we were reading the evidence the journalists were coming up with very strong statements to the effect that everyone would carry around a chip with their own genome on it which doctors would then just use in their prescribing practice. As we collected more evidence we became much more sceptical at some of those sorts of claims.

Q296 Baroness O'Neill of Bengarve: I would like to move on to the gap that you have identified and that some of the gap may be a regulatory gap. As we know, scientific advances in genomics have produced a new range of genetic tests for a wide range of one would probably say genomic conditions rather than absolute clinical conditions at this point. What mechanisms do we have now for assessing the validity and utility of these tests? Who then

decides whether a particular test should be introduced into clinical practice or left aside and, if there are mechanisms, do you think they are sufficient or do we need additional mechanisms?

Dr Flinter: The NHS has set up a very good system for evaluating tests for single gene disorders. There is an organisation called the UK Genetic Testing Network (UKGTN) which was basically set up by those who commissioned the regional genetic services because they wanted a mechanism whereby tests could be very thoroughly evaluated before they would then agree to purchase them from the regional genetic centres. Laboratories that want to offer a new test have to submit what is called a gene dossier to a committee of the UKGTN and the evaluation process includes looking at the laboratory test, how robust it is, how reliable, how efficient it is and so on, so the technology, but that is only the first stage. They do also look and see whether there is a link between what the test is actually measuring and clinical disease and they ask the question if that link exists, is it actually worth doing the test? Is there something you can do about it? They also look at the ethical, legal and social implications and so on. That is the framework called ACCE which you may have heard about from the UKGTN's submission. They do sometimes have a problem in that the evidence that is submitted to them may have gaps and that it might not be clear in terms of studies having been done in large numbers of patients what the evidence is, but very often for single gene disorders, rare conditions that affect a small number of patients, a gene is found, you can find mutations within the gene and the laboratory can develop a good test for that. Even once a test is approved it is not necessarily appropriate to do it for every family that you see with that particular diagnosis. There are some relatively common genetic conditions, such as neurofibromatosis, for which there is a good test but actually as a clinician we do it very rarely because most of the time you can make a diagnosis clinically by examining the patient; you do not need to do an expensive and time-consuming genetic test to prove your clinical diagnosis. You may only need to do it in a small number of situations if, for example, the

family is likely to request prenatal diagnosis in the future and you want to have a genetic test that you can perform on a sample taken early in a pregnancy. That mechanism exists for the single gene disorders. The question has now been raised by the UKGTN as to whether their role should be expanded so that they look at genes involved in multifactorial disorders and perhaps other biomarkers as well. It clearly would be helpful for somebody to take on that role but at the moment it is not obvious who should do that, although the people who work within the UKGTN clearly have that expertise. The other limitation at the moment of course is that they are evaluating tests for use within the NHS and nobody is evaluating tests that are offered in the private sector particularly direct to the customer.

Q297 Baroness O'Neill of Bengarve: That is extremely interesting. Do you think that UKGTN are well equipped to expand their remit in that way or were you raising it just as a question?

Dr Flinter: I think they have the knowledge and the expertise to do it, but I do not think they currently have the resources to take on a much larger piece of work.

Q298 Baroness O'Neill of Bengarve: What about current bodies such as NICE? Could NICE take on a role here or would they be inappropriately placed to extend their remit into diagnostics?

Dr Flinter: NICE has looked at one or two things like breast cancer screening and patients with inherited breast cancer.

Dr Patch: They have looked at the bigger question of a clinical care pathway. One of the issues with diagnostics is bodies, as they are currently constituted, such as NICE and the Health Technology Assessment people, they are very slow and they are relatively non-responsive although they do commission research on the basis of suggestions that are made to them. If I could use the example of a technology that the HGC were asked to comment on,

which is free foetal DNA testing, which is a non-invasive method for extracting foetal DNA from the mother's blood and then doing various analysis on it, and at the moment that is being enthusiastically developed and is creeping into use in the NHS. The HGC recommend that actually there is a need for evaluation under properly controlled circumstances in particular areas, particularly relating to a prenatal diagnosis of single gene disorders. We made a recommendation to Sally Davies that this should be considered and the response that unsurprisingly came back was that this would fit into existing funding mechanisms through the NIHR or through NEAT (New and Emerging Applications for Technology). However, back to my original point, these mechanisms currently are very slow. I think there is also another issue that this sort of research is not sexy and exciting. It does not drive academic careers; it does not drive publication records; it is not published in the high impact journals and so the drivers for this sort of research are slightly different. Grant awarding bodies – the committees that award grants – are made up of certain types of professionals who might have a different value system in terms of the research they want to see funded. I think there is an issue in relation to the ability to be responsive and also a change is needed in terms of value in this sort of research.

Q299 Chairman: Did I hear you say that Sally Davies was positive about supporting it?

Dr Patch: No, she was positive about the idea of supporting it but suggested that there were existing sources of funding within the NIHR and various programmes.

Sir John Sulston: Christine has said it all really. This was an exchange of letters between me as acting Chairman of HGC and Sally Davies. I was a little surprised, though I gather it was not unexpected, that it somehow was not seen as the responsibility of the NHS or NIHR to actually make sure these things happened in a timely way. I just want to reinforce what Christine has said that it does not seem to me appropriate that when you have had something important coming along moving into practice in an ad hoc way then it is not part of our

system rather than just open to the vagaries of the granting system to do proper clinical trial evaluation as it goes along. Martin Bobrow of course has made this point forcefully as well and indeed brought it to our attention.

Mr Hogarth: If I could expand on Frances' final comment which was about what happens to tests that are offered outside the National Health Service, so not just direct to consumers but in private clinics and private hospitals, in terms of what mechanisms exist for assessing the validity and utility of these tests, such tests should in theory be subject to Medical Device Regulations and specifically the *In Vitro* Diagnostics Directive part of the Medical Device Regulations. At the moment who decides who carries out that assessment, the answer is the person who is the manufacturer of the test. It is a process of self-assessment for nearly all diagnostic tests because nearly all diagnostic tests are classed as low risk, so you must, as the manufacturer, assure yourself that you have fulfilled the essential requirements of the Directive, and once you have assured yourself that you have done that, then you can place the CE mark on your test. I can tell you that, in general, the CE mark, which is a quality mark that is used in a very wide range of products in Europe, consumer research indicates that in general European consumers assume that a CE mark means that the product has been subject to independent evaluation. In the case of these products they have not been subject to an independent evaluation.

Q300 Lord Winston: You have pre-empted my question but let me put it on record because I think it could be expanded really and it is about the Human Genetics Commission's point that more research studies are required to establish the utility of genetic tests and susceptibility to disease and to assess their long term value if introduced into clinical practice. There are three things: first of all, who should fund this research and carry it out? I think it would be quite helpful if some of you might address what you see as the most valuable nature of the research; what sort of research is really most important to do?

Dr Patch: Commenting on the last one first, in terms of diagnostics and prognostics, what is needed is a research in use and that is why it falls through the gap in that there is a gap between developing the diagnostic in a very controlled circumstance as you do not need such huge patient numbers – you have selected patient populations – and then rolling it out just in the NHS for use or in service for use and then bring it to market use. It is controlled studies of the device in use I think where is the gap. At the moment that evaluation is happening in an ad hoc way funded by the NHS because these tests are being used and paid for, so it is happening but in an ad hoc way, evidence is being lost and I suppose what happened in the past was that it would either work or it would not; it would either continue to be provided or it would not be provided; it would fall out of favour or stay in favour. Possibly what has changed is the complexity of the diagnostics, the complexity of the clinical care pathways and also the cost.

Dr Flinter: In terms of who should fund the research, there are well-organised funding bodies such as the Wellcome and the MRC and so on. Applications can be made to them but, as you know, that is a fairly lengthy and complicated process. I do wonder whether there is perhaps room also for tests which have the potential to be very important within clinical practice for that research to be directly commissioned by somebody like the NHS so that it can ensure that tests that it may consider purchasing in the near future are properly evaluated in the context of the whole clinical pathway before they slip into clinical use.

Q301 Lord Winston: That is a pretty unprecedented suggestion, is it not?

Dr Flinter: Yes.

Sir John Sulston: It would give value for money probably in the sense that you would not be wasting time. You would capture what is going on in different parts of the country.

Q302 Lord Winston: It does seem very difficult, does it not, to imagine that charities like the Wellcome, or the British Heart Foundation, or Cancer Research UK, would take up this kind of baton because it really is not really within the kind of remit of their research that they do so well. It seems therefore that it has to be done probably from a more public angle. Is that fair?

Sir John Sulston: Exactly.

Dr Patch: The NHS at the moment is paying for these if they are introduced prematurely but the actual payer is dissipated around the various commissioning bodies.

Mr Hogarth: There are a number of countries that have experimented with the concept of conditional reimbursement on the basis of systematic data collection for some medical technologies, but it is still something that has only been tried on a few occasions.

Q303 Chairman: You are not saying it, Sir John, but you are implying that in fact the OSCHR and its various health services research grants should be looking at funding this kind of research and commissioning it.

Sir John Sulston: That is why I am saying I would have thought that when you really go through the numbers this would be value for money for the NHS because you would not be wasting time conducting tests which were ineffective; you would not be wasting, as Christine pointed out, scientific data being lost. The disadvantage to short-term accountancy is that you are paying more upfront because you have to set up the trial, but I would have thought that in quite a short period – in a five-year span or something – it must deliver better value for money than this vague ad hoc system.

Q304 Lord Warner: Can we just probe this business about whether the payers do know that they are getting unevaluated tests? The funding mechanisms at the moment in the NHS is money goes to the primary care trusts, they buy care from providers, hospitals are reimbursed

on a tariff basis based on PRGs and, by and large, people then leave it to individual clinicians to do the tests they need to do in relation to the patients they are seeing. Are you suggesting that these tests are such that they need a special treatment of evaluation before they are brought into clinical use? That is what you seem to be suggesting.

Dr Patch: No, I think what has happened in the application of this science as a paradigm for the complexity of the new biomarker testing is it has highlighted a problem in the system which is not unique to genetics. It is similar if one were thinking about immunohistochemistry on tumour samples to look for evidence of loss of expression of mismatch repair genes in bowel cancer which may have a utility in driving treatment. I do not think that genetic tests are special, but I think it is perhaps because of the complexity and the cost to a certain extent that is no longer just absorbed within the costs of a routine biochemistry lab that have highlighted a gap in the system for all complex biomarker tests.

Q305 Lord Winston: With the big disease problem like in heart disease, diabetes and vascular disease, is it not really always going to depend on a much more sophisticated IT system within the NHS anyway? Without that, this kind of research is going to be extraordinarily difficult to do, is it not?

Dr Patch: Yes, and actually without interpreting the results of a genome, and we are already at the limits really of what the NHS IT systems can do in interpreting the results coming out of our cytogenetic and molecular laboratories. We are past that really in the sense that the NHS IT systems cannot cope with the data that is being generated and requires interpreting. It is not just in relation to evidence, but it is in relation to the practicalities of running the kit, as it were.

Q306 Lord Warner: This is a question for the Human Genetics Commission. In your report “More Genes Direct” you highlight the lack of regulation of new genetic tests,

particularly tests sold directly to consumers and to the public. You submit that you have a programme of work in place to encourage and assist this sector to develop guidelines, good practice and ethical conduct. Can you elaborate a bit more on the activities that are going on in response to those issues?

Dr Flinter: We held a meeting last Monday in London to which we invited a wide range of people representing many of the major providers of genetic tests direct to the customer and many other stakeholders, charities, representatives of the patient groups, various regulatory authorities, people from the Department of Health and so on. It was an international meeting with European Council representatives, people coming from America and so on. We spent the whole day discussing the issue of whether or not there was a need for some sort of code of practice to provide a framework for the provision of genetic tests direct to the customer. Perhaps slightly to our surprise there was pretty general agreement that a code of practice would be helpful, particularly the companies that are providing these tests felt that at the moment it was very unclear to them what the framework was in this country, what the rules and regulations were, and they said that they would welcome a code of practice so we then discussed in the broadest sense what should be in that code of practice. I think there was agreement that it needed to cover both the scientific side of things and the quality of the test that has been done, although in a way that bit is already better controlled because there are quality assurance schemes and labs can be accredited and meet various requirements. We also talked of this issue we have referred to many times about the need for evidence to be provided to a customer that actually tells them how useful the test is and of course that is much more difficult to gather and in some situations does not exist yet. Alastair Kent, who was speaking on behalf of the Genetic Interest Group, made it very clear he felt that customers very reasonably should expect to be able to find out whether by looking at the web or looking at the literature that the company provides what the clinical evidence is for the

validity and utility of the test that they were considering taking. Inevitably there is also some discussion as to whether all these tests should be available direct to customer or whether some of them should only be available by going through a clinician. We then had a discussion about what happens when things go wrong because it does seem to be rather unclear as to which regulatory authorities are already there and what their remits are; whether if there is an unreasonable claim made by a particular company this is an issue for the Advertising Standards Authority and I think the Advertising Standards Authority felt it was not always necessarily qualified to be able to deal with those sorts of issues and might prefer the MHRA to take it on. The MHRA I think feel that they are already overwhelmed with the amount of things that they are required to look at and regulate, so at that point it all became rather unclear and we realised that the next piece of work we need to do is to really map out in more detail what is the existing regulatory framework, what areas are covered and where are the gaps. I think we have now identified a useful group of people who would be willing to work with us in developing the outline of the code of practice, which perhaps might be along the lines of the Paternity Code of Practice which was developed by the Department of Health a few years ago and does seem to be working reasonably well.

Q307 Lord Warner: Do you accept then in this work that areas like truth in labelling, claims in advertising, would be covered by this territory for these types of products?

Dr Flinter: I do not know who should have responsibility for doing that but clearly it is very important that somebody does have that oversight because the customer needs to be protected and at the moment they are not. They are advertised and sold tests, many of which actually have very little real scientific validity or utility. The trouble is that they take those tests, they are then confused, they may be falsely reassured, they may be falsely worried, they then go and see their GP and the NHS has to try and pick up the pieces.

Mr Hogarth: The code of practice would speak to that. I was participating in the meeting on Monday as well. The code of practice would speak to issues of truth in labelling and informing consumers about the strengths and limitations of what we know about the tests and so forth, insofar as the code of practice would provide a kind of framework for the information that we would expect companies to provide to consumers about their tests, so the categories of information that they should provide to consumers. In terms of ensuring truth in labelling, the More Genes Direct report and the original Genes Direct report from the Human Genetics Commission was very clear that responsibility for that really lies with the MHRA under its kind of responsibility for the IVD Directive. Ultimately the MHRA is the body who, if they feel a medical device, whether it is an in vitro diagnostic device or some other kind of medical device, is unsafe or problematic has the power to either require the manufacturer to change the label, change the claims it is making, or ultimately take the device off the market, but nevertheless I think the code of practice has a very important role to play in promoting good practice and explaining to companies what information they must provide to consumers.

Q308 Lord Warner: Before I ask a further supplementary, I detected from Dr Flintner's remarks that there was a singular lack of enthusiasm on the part of the MHRA for this role in last Monday's meeting.

Dr Patch: I think it is fair to say that Stuart is at one end of the spectrum in his view of what the view of the MHRA's responsibility is but there are other points of view. I think the HGC's position in the original Genes Direct was that there should be a role for the MHRA which at that time was not constituted properly because the IVD Directive was just being introduced and enacted. In More Genes Direct we were perhaps less specific but the thing of More Genes Direct was that this was something that needed to be done and in the current regulatory contracts, as it has been explained to us, the MHRA seemed to be the body that should be taking it on.

Q309 Lord Warner: This is quite an important issue for us so I would like to be clear as to where opinion rests. Would it be fair to say that opinion is divided over the enforcement activity in and around this area?

Dr Patch: I think there are other people on this panel who have a more in-depth understanding of the regulatory framework. It seems to me that it depends on the interpretation of the requirements of the IVD Directive and whether the IVD Directive includes issues like clinical validity and clinical utility and opinion on that varies across Europe.

Mr Hogarth: I do not want to put words in your mouth, Chris, but my understanding from the More Genes Direct report is that HGC does support the view that in terms of the risk classification system in the Directive, genetic tests should be reclassified as moderate or high risk so that they are subject to independent, pre-market review before they come onto the market. To be absolutely clear about the role of the MHRA, it is a competent authority. Each Member State has a competent authority in charge of implementing the Directive and enforcing it in its state, but the people who carry out the evaluation of tests that are in the moderate or high risk categories are not the competent authorities. They are in fact independent third parties called notified bodies.

Q310 Chairman: These tests are international and so a lot of them might be available on the internet. How would this code of practice manage that?

Dr Patch: What was surprising about the meeting on Monday, and we did have representatives there from some of these very major players in this market, was the appetite for a code of practice I think because the companies want to be seen to be acting responsibly. At the moment it is a complete free-for-all and they see it as a mark of their quality if they comply with the code of practice, but that is why, if this is developed, it is absolutely vital that the various stakeholders buy into it.

Q311 Chairman: Will there be a report from this meeting and will it be widely available?

Dr Flinter: Yes. There is a very brief summary going on the HGC website this week and there will be a more detailed report fairly shortly.

Q312 Chairman: We will be able to have sight of it?

Dr Flinter: Yes. I think what has focused the minds of the companies that are providing these tests was the news from California last week that the tests there have been banned, as you are no doubt aware, and in one or two other places. I think they are very conscious that unless they are seen to be behaving responsibly and following a code of practice, there is a risk that the tests will be banned all together.

Q313 Lord Warner: Is there a case for that ban?

Dr Flinter: I do not think so but we are concerned that there is certainly potential for damage to be done if people are sold unevaluated tests in an inappropriate way without the availability of professional counselling and so on. There are undoubtedly risks that need to be managed but banning them all together is not necessarily the best way of dealing with the problem.

Q314 Lord Warner: It is a conditional ban, is it not? You have to have access to medical advice and the tests have got to be done in approved laboratories.

Dr Flinter: That is right.

Q315 Lord Warner: Are you arguing that those conditions are unreasonable?

Dr Flinter: No, I do not think those conditions are unreasonable, although quite what access to medical advice would involve is something of a grey area. Some of the companies may feel that they can achieve that by having a physician as part of their organisation who is available to provide advice. That is very different from actually sitting down and talking to a genetic counsellor before you have a test to understand the limitations of the test, what it does

and does not do, what the implications might be for the extended family and so on. I think that is a very grey area.

Mr Hogarth: The fact is there is a very broad range of business models and delivery models in what we might broadly term as the consumer genetics market and that ranges from companies who will allow you to buy a test at the click of a mouse over the internet with no discussion with anyone and you simply get the results reported at the end of the process that has been churned out of a computer, through to companies who will offer as an inclusive part of the price of the test pre and post-test counselling over the phone or, in some cases, a post-test consultation with a physician, so there is a very broad range of delivery in business models in this market.

Q316 Baroness O'Neill of Bengarve: Can the truth in advertising and consumer protection approaches go beyond providing reassurance on the validity of the tests? Can they also provide any reassurance on the utility and, if so, a utility for what? When we began you were talking about the sorts of trials that would need to be done to take one from an understanding of the validity of a test to an understanding of its clinical utility, or lack of utility, yet I cannot see how these approaches that we have been discussing in the last ten minutes are addressing the clinical validity set of issues.

Dr Flinter: I do not think they are necessarily. On the whole they are sold as tests that give people information, so they tell you something about your risk which is modified in some way and sometimes they are then linked to advice which might be lifestyle advice, but of course there is no way of ensuring that people take that.

Q317 Baroness O'Neill of Bengarve: If I were to try to push a little on what you said at an earlier stage, the lifestyle advice might be to drink more water, smoke less, walk further, might be perfectly safe advice, because it is good for everybody, but it does not necessarily

relate to the particular test that has been paid for and taken, so that this lifestyle advice is a risk-free activity for companies?

Dr Flinter: Relatively, yes. I think sometimes what companies may then offer subsequently would be additional tests – body scans and things like that – at a price and of course with associated risks as well because there may then be exposure to radiation which may or may not be appropriate and may have consequences, and of course screening tests like that can pick up other things in a way which may or may not be helpful, so there are also risks associated with it.

Dr Patch: I think there is also a question of truth in labelling including what is known and what is not known.

Q318 Baroness Perry of Southwark: Going back to the kind of guidance you might offer or regulation that you would set up for these companies, would it not be helpful to have a factual explanation of what the figures mean? If you are told that you have a 30 per cent increased risk of some rather rare disease, that may mean that you go up from, say, seven in 10,000 to nine and half in 10,000. If the regulation said that you have to not only say a 30 per cent increased risk but describe what it was, would that not be a big leap forward? I think people are frightened by a figure like a 30 per cent increased risk and if they do not have the counselling over the phone or in person, then at least it could be explained on the printout.

Dr Flinter: I think it is a very good suggestion; it is extremely difficult to do. On the whole, people are not numerate. They do not understand odds ratios and risk figures and, even if it is well explained in writing, I think many people getting that actually will not understand what the risk really means. As somebody who has spent a lot of time talking to patients in the clinic, you can sometimes spend half an hour or more trying to get somebody to understand what a one chance in four means and what it really means to them. These slight alterations of overall lifetime risk are extremely difficult concepts to explain. I am not sure that even very

good explanations in writing will really ensure that the person who receives them has understood them.

Dr Patch: It is important to use the concept of absolute risk rather than relative risk. As you have rightly said, roughly a 20 per cent increase of breast cancer increases my risk from ten per cent to 12 per cent. If you frame it in that way you can somehow incorporate that increase in risk into your decision-making. I think where some of the website-based companies have done something useful is in the way they have presented the risk figures in terms of the population risk is here on this lozenge. We have graded it from green to red. Your result will move you up to here, which in fact is a very small movement. I think some of them have been very innovative in the way they have interpreted this.

Mr Hogarth: I think that is right. I have heard clinicians and scientists in the US say they have been very impressed with some of the emerging new models of how to convey this information that these companies have come up with. What we have now is some emerging new standards best practice from some of the best players in the industry which I think a code of practice would be very well placed to identify as something people perhaps should follow because it is undoubtedly the case that some companies are doing this a lot better than others.

Q319 Baroness Perry of Southwark: We visited Washington and heard evidence and we were very impressed with the care that they were taking. I think the good companies are very much taking this on board. My question is one that I am particularly interested in. We know that the costs of the DNA sequencing are coming down now as they do and there is no doubt that a lot of people will want to know the sequence of their own genome. Certainly again in the United States it is becoming extremely popular. What do you feel are the risks and the benefits of more and more people knowing this about themselves?

Sir John Sulston: I absolutely agree with your point that it will happen. People are obviously going to start doing this more and more as a trophy to have their DNA sequence.

Our job in the Genetics Commission is to look at the uptake of this and make sure that the process is eased socially and ethically. There is no immediate benefit whatever in doing that and perhaps somebody else could amplify on that point, but I would like to emphasise that I am hugely excited by this from the point of view of scientific research and I think that is where the value is. In the long term scientific research is obviously of benefit to medicine. In the long term we shall understand our whole constitution and origin in very great detail. It may very well come to carrying around our sequence in the way that we were mentioning earlier, but right now it is valueless; one of the many reasons why I have not had my own genome sequence done like certain colleagues. Just understanding the comparisons, the exciting programme that is going forward with the 1000 Genome Project which are pouring out of the Sanger Institute and other places, the comparison of these genomes is very important; the sequencing of specific genomes, like for example, cancer genomes is very important, but it is all at the research level. It fits very well in fact with the HGC's view of the genetic solidarity that we would be contributing to this and in that sense I have no objection to being sequenced at all. It is just that one should not expect personal benefit normally from doing this because it is more appropriate just to have testing. One other thing I would like to say is that, unlike some people, we tend to argue quite a lot about this and I do see benefit in this in that I think it is going to force us into a position of having more genetic data floating around and therefore having to deal with it. You mentioned, for example, the need for IT -- obviously we have to do all that -- but also a matter of ethical handling, as Baroness O'Neill has pointed out for many years is that we cannot use the old ways of dealing with this sort of thing and we will be coming to that later on. The main thing is that it is going to happen, it is going to change our way of life, but I think the statements about short cuts that the value of having your genome sequence are misplaced.

Q320 Baroness Perry of Southwark: I interested that you say it is absolutely valueless. Are there not single gene disease-related information which is an absolute certainty that you are going to get it?

Sir John Sulston: Yes, you will pick up certain things. It is just as a cost benefit. The single genes in any case people will know about in their families. That is why I referred to specific testing.

Q321 Baroness Perry of Southwark: That is surely a major ethical question, is it not? If you tell somebody that they are inevitably going to suffer from Alzheimer's at some time in their sixties or seventies, do you tell them or do you not tell them? Do they want to know or do they not want to know? Would it change the way they behave or would it not change the way they behaved in the meantime? These are the ethical issues, are they not?

Sir John Sulston: I agree. That is why I would like to hand over to my colleagues to discuss that because that is what they deal with every day.

Dr Patch: In a sense we are dealing with those ethical issues now in the context of people that know they are at risk through having a family history. I can see no benefit at all to taking a person from the population. How would we handle it if every single woman knew her BRCA gene status? Individual women might want to know their BRCA gene status and, if it is appropriate, we will offer that testing. In terms of actually promoting the act of going out and doing this for benefit now, I think there is no benefit at all. If you want to know your BRCA gene status because you have a high risk family history of breast cancer, that is an individual decision of whether that is of any personal benefit to you.

Dr Flintner: There is one other issue to bear in mind as well. We tend to think that genetic tests give a definitive result, but in fact when you sequence the BRCA gene very frequently what you find is a variant of uncertain significance. You do not know whether it is pathological or not and that sort of information is not helpful at all because it raises anxieties

and concerns but it tells you absolutely nothing about whether or not that woman is at increased risk of breast cancer and until we are better at actually interpreting sequence variation, the value of having extended lengths of sequence is very little.

Dr Patch: We need to distinguish very clearly, and you will have heard this argument before, between the analysis, between the analyte, between the sequence of letters and between the interpretation of the meaning of those sequence of letters. Those are very different things. You need both to happen to use the information generated.

Q322 Lord Taverne: I understand that in the United States they have some plans for the routine screening of all babies in the future. You do not anticipate that happening in the foreseeable future over here. Would it not be of some potential future use? Presumably there is some reason for doing it?

Sir John Sulston: We wrote a report about this called Profiling the Newborn precisely because we were asked to look into it by ministers. It is looking ahead. To sequence whole genomes, we are not there yet for everybody to have. This is a rich person's hobby to have it done now and for some years to come. It may be the horizon of it being publicly affordable may come forward to ten years from now, I do not know, but what we really went into in Profiling the Newborn were the issues of ethics and whether it is appropriate to produce this data from a child which is not able to give consent. I do come back to my original statement and I believe very strongly in this. I think that inevitably it is not only going to drive the science but it is going to drive the ethics as well. I think we are going to have to get used to having our genome known just as we have credit cards and we have mobile phones and they are intrusions on privacy if misused. In my opinion – this is not HGC opinion – is that the ethical dilemma will actually reduce as a result of doing these things and we may then at some point say what does it matter, yes, sure, sequence at birth, we will do it, but how to get from here to there is a rough road because right now it is going to be unusual, we have

privacy issues and, as we are coming to I hope later in the discussion, we have discrimination issues which are very real and have not been dealt with and until we have dealt with those then the ethical problem stands very starkly.

Q323 Lord Taverne: It may also raise some quite difficult issues within a family, might it not, if one finds that the family relationship is not quite what was expected?

Sir John Sulston: All of that will come out, absolutely. This is what I mean about getting real and getting used to it. There will be no secrets about paternity anymore.

Professor Weale: I am wondering in terms of these ethical issues whether it is worth making a distinction between the sort of ethical issues which arise at the individual family level on the one hand and the sort of ethical issues which might arise at a subgroup level at the other. The technologies we are talking about have implications for both. Clearly in terms of individuals, and leaving aside the whole genome sequencing issue, knowing about your potential adverse effects for a particular medicine is very useful indeed. One of the things that our report was concerned about was much more at the subgroup level that as it became apparent that what symptomatically appeared to be one disease turned out to be a number of different diseases in terms of its underlying biological characteristics, one could be in the situation of identifying groups of people who were susceptible to conditions which were in fact very rare and therefore one would start to think about orphan disease status and the incentives that pharmaceutical companies have to develop products in relation to those groups. It is also worth bearing in mind at this group level that there are ethnic and racial differences in gene frequency profile. That is very important in terms of susceptibility to adverse effects and might well interact in rather complex ways with feelings of discrimination and so on for the members of those groups. It may be helpful in trying to tease out the ethical issues to have in mind a clear distinction between the sorts of problems of confidentiality that arise for individuals and the sorts of broad problems of social solidarity that arise for subgroups.

Q324 Lord Taverne: This is a question for Mr Hogarth: you have already referred to ways in which the EU regulation of genetic tests could be improved in the *In Vitro* Diagnostic Devices Directive and there seems to be general agreement which is also featured in More Genes Direct that the classification of the tests at a lower risk should be reviewed. Are there any other improvements that you think are needed and how would they protect public health?

Mr Hogarth: Let me set this in the context of what I think the primary goal of this particular regulatory mechanism should be. The primary goal of this regulatory mechanism should be to ensure that doctors and patients have comprehensive and accurate information about a test's strengths and weaknesses, its accuracy, its utility, its safety, to be able to make an informed decision about whether or not to use it and that when they get test results they have accurate and comprehensive test results which they can understand and which can guide treatment decisions and preventative actions. I think that should be the primary goal of the regulation. In terms of the weaknesses of the Directive and how we might improve it, we have already talked about the fact that because of the risk classification system genetic tests are treated as low risk and are not subject to pre market review. I think that is a very important reform that needs to be carried out and I am very glad to be able to say that at the moment the European Commission is consulting on the recast of all the Medical Device Directives and in its consultation it specifically asked about whether or not we should change the risk classification system. Secondly, there is the issue of the essential requirements. What must a manufacturer do before they put the test on the market? Christine has already alluded to the fact that there is ambiguity about whether or not a manufacturer has to provide details about the clinical validity of the test as well as its analytic validity. The MHRA's position, which I have heard them express in public a number of times now, is that if a manufacturer makes clinical claims for its tests, so about the relationship between the gene and the disease, then those claims have to be backed up by scientific evidence, but if it does not want to make

clinical claims about its test then it does not have to provide evidence on clinical validity. In fact, a number of European Member States disagree with that. For instance, ASAP, (?) the French regulatory authority, would argue that to fulfil the essential requirements of the Directive you must provide data on clinical validity as well. I would submit that in terms of answering the key essential questions that a patient or a doctor would want to know, which is is this test right and what does it mean, then you have to have data on both the analytic validity and the clinical validity of the test and if you do not have that data then you should not be putting the test on the market because you cannot offer a meaningful result. I think we really need to clarify the ambiguity in Essential Requirement (3) of the Directive which talks about analytic sensitivity and specificity and diagnostic sensitivity and specificity. Next there is the issue of laboratory developed tests. You may have heard this term in the United States which has been used now by the FDA and it means an in-house or a home-brew test; that is to say, a test that has been developed and has been performed in a single clinical laboratory rather than a kit which has been made by a manufacturer and sold to multiple laboratories. These are laboratory developed tests (LDT's). Unlike the United States, in Europe the Directive says that LDT's are covered by the *In Vitro* Diagnostics Directive, except there is an exemption for what they call Healthcare Institutions. In the UK that means there is an exemption for NHS labs if they want to make laboratory-developed tests. Unfortunately there is significant variation in European Member States in how we are applying the Directive to laboratory-developed tests, so there are European Member States who have not given an exemption to any laboratories, public or private sector. There are other European Member States who seem to be not treating laboratory-developed tests as medical devices at all. This lack of harmonisation is a significant concern and another issue that we need to address. The other issue that we need to address is the fact that we now have emerging business models where the laboratory-developed tests, like the Oncotype DX test produced by Genomic Health

in the United States, are being offered to patients in the European Union, often through an intermediary in the case of Genomic Health who have partnered with a UK company called Medical Solutions. The position of the MHRA is that if the test is performed in a laboratory outside the European Union then it is not subject to the Directive. This creates a horrendous double standard where there is no way in which the regulations are being applied to a growing number of tests that are available to consumers in the European Union from companies outside the European Union. It also creates a perverse incentive for the UK and European biotech sector to shift off-shore, which I am sure the Committee would agree does not seem very sensible from an economic perspective. Then there is the issue of transparency because if we focus our regulation on the idea that we want to make informed consumers, informed doctors and patients who can understand test results and make informed decisions and intelligent decisions about whether or not to use them, the fact that the company's data on its tests is treated under the Directive as commercially confidential and is not made transparent and open is something that needs, again, urgent review.

Q325 Lord Broers: I would like to turn to some of the discrimination issues and my question relates to insurance. The Association of British Insurers announced two weeks ago the extension until 2014 of the voluntary insurance moratorium on the use of predictive genetic tests for insurance purposes. Is this voluntary extension sufficient to cover all aspects of potential insurance discrimination, or is further attention required? Is there a need for legislation in this area?

Sir John Sulston: The HGC of course welcomes the extension of the moratorium. It is a step on the way. We think it is extremely important that people should not be excluded from being able to obtain insurance and exactly how one achieves this is inevitably a matter for debate. It is not a matter for simple black and white solutions in the headlines. We did recommend that there should be a genetic line in the Single Equality Bill. It is unclear

whether there is appetite to actually do that and it is equally unclear exactly how that would feed through into insurance because you can argue that, where insurance is concerned, it is actually fair discrimination, not unfair discrimination, which is why I said at the beginning the important thing is not to have an excluded class. A couple of details about the moratorium and what it entails: one very problematic aspect, and this is only deferring the problem rather than getting rid of it, is the test now creates a problem, namely that the ABI has understandably, but staunchly, resisted any promises about what will happen after the end of a moratorium, either the previous one or this one. Somebody may well be inhibited, and people are being inhibited, we hear, from our own consultative panel from taking tests now because this will then be on their record and they cannot get into them later, so it is not solved in a temporal sense. Equally important is that it is very limited what the moratorium does is because it applies only to tests on DNA and they are very unusual. The only test which has been approved is for Huntington's at the moment. The companies have been minded to apply for tests on BRCA and I think on colon cancer as well, although I am not sure, but it has not happened as they withdrew. There was a bit of an outcry in the newspapers and they withdrew the preliminary application. The reason that they are content for the moment is that actually they depend much more on family history and they are pretty happy with that. They are also not prohibited from using tests of a metabolic nature, of a proteomic nature or other tests, anything in fact that is not directly looking at the DNA. The moratorium, I am afraid, although we are very pleased that it exists and it is being extended, is a very limited instrument. The answer to your question is no, it is not sufficient, and we have to find ways of ensuring that people are not excluded from full citizens' rights on grounds of their genetic data.

Q326 Lord Broers: What is your prognosis that such regulations might be introduced?

Sir John Sulston: We have to go on pushing for it. We are waiting to see what the outcome of the Single Equalities Bill is right now and we shall just have to continue working to try to ensure that people are equitably treated.

Q327 Chairman: Do you think we should have similar legislation to the USA that has just recently been passed?

Sir John Sulston: The GINA? That is very interesting and it is important and I am sure others will want to comment on this but I will put one or two pennyworth in, if I may. GINA is of course a very different situation in the US in that it is covering health insurance as well and that is an extraordinary thing. It is very surprising that it has gone through. It has gone through because of the dedicated efforts of a group of people, including Francis Collins, who dealt with the matter at NHGRI, for many years now. It sat in Senate for ages and has finally been approved. It is a much bigger thing for them than for us because it is covering an awful lot more resource to prohibit genetic discrimination in health insurance. It is very much bound up with employment because many private health insurance schemes are through the employers. It is a remarkable thing. It will be much easier for us to follow than for them and I personally am excited and dismayed by the fact that I think we are being left behind ethically in this country if we do not take similar but smaller steps on our behalf. I do hope your Lordships will see fit to support the idea that we should make sure that this is equitable in the future. Although your question does not apply to that, we should put employment in there.

Q328 Lord Broers: You would like to see us have a recommendation?

Sir John Sulston: We would. The HGC has recommended that there should be non-discrimination in employment. We are monitoring it but, thus far, we have very little problem in this country. We see potential for problem as genetic tests perhaps become more

diagnostic of lifespan or debilitating disease and so I think it is something we have to be aware of and to implement as needed. One other thing about GINA which I think is important is that it removes the complaint that we have heard from companies when we have been discussing regulation of genetic testing that the business atmosphere is freer in America and in fact there is at least one company that has left the UK and moved to the US because of the easier atmosphere there. GINA and the events in California, of course, now mean that there is no business argument for not having proper antidiscrimination rules in place here as well.

Q329 Lord Broers: In the United States with their legislation with respect to age, they need it more than we do, but we may change our legislation with respect to age which would make all of these issues more important presumably?

Sir John Sulston: I guess.

Q330 Earl of Northesk: In part, Sir John has foreshadowed my question. To state the obvious, personal genetic data must be stored in ways that ensures confidentiality and security, but excessive regulation can be counterproductive and impede progress, for example, in research, or in conferring potential benefit to family members. Does the current system of regulation balance these needs adequately, or does this need further consideration, or perhaps even further legislation?

Dr Flinter: It is an interesting dilemma, is it not? Patients as individuals expect us to look after their information securely. They also expect us to look after their DNA samples securely. In fact, it is far more common for patients to express concern about who else might have access to their DNA sample than to express concern about who else might have access to their medical records. To be more specific, the most usual question is could people like the police get hold of my DNA sample, because we do explain to them that once we have done a test any remaining DNA is usually stored for possible future use unless they expressly ask us

not to do that. There has of course been so much publicity about data loss through human error over the last few months that it has become a very topical issue. Although the Data Protection Act is very clear in laying out what people's responsibilities are, of course it cannot prevent inadvertent loss. It is therefore appropriate to look and say what are the sanctions in place if things do go wrong and if people suffer harm as a result of identity theft or whatever. I am not an expert in this area but my understanding is that the Data Protection Act does not have a lot of teeth. There is not an awful lot that can be done when data is lost or inappropriately accessed. On the other hand, researchers would say that sometimes they now find it difficult to collect the sort of data they need, particularly to do prospective long term studies. At the time we obtain consent from people to do a particular test or to take some DNA or to enrol them in a research project, it is not always possible to know what the potential uses of that information might be in the future, so it is not really possible to get consent in a specific sense for all the possible ways that that data could be used in future research. I think that is an issue that we need to look at more carefully so that we can make sure that we do not hamper long term large prospective epidemiological studies, but at the same time do protect individuals' data and samples which they have a right to expect us to do.

Professor Weale: Over a number of reports this is an issue on which the Nuffield Council has been concerned. The Council has always set its face against too strong a doctrine of informed consent if that is understood to mean that you have to consent to each and every subsequent use of a sample that you are given, precisely I think for the reasons that Frances has just referred to, namely that it is very difficult in terms of research to anticipate what possible uses samples might have. This is me rather than the Council, but I think although the Council tends to take a broad interpretation of consent rather than a narrow interpretation of consent, perhaps the way to think about this is that individuals do need some assurance when they are giving a sample that it will not be misused, and just as we cannot anticipate valuable

uses in the future, so by definition it is difficult to anticipate misuse in the future. Therefore the crucial principle in the design of the regulatory framework for this is one which gives sufficient assurance to reasonable citizens that their data will be protected and will be used for the purposes that satisfy some threshold of ethical integrity of research, but there clearly is a difficult balance to be struck.

Q331 Baroness O'Neill of Bengarve: Dr Flinter, you electrified me by uttering the only words of praise for our current data protection legislation that I have ever heard in recent years and that is exciting, but at the same time this crunch between the issue of confidentiality for the individual and, on the other hand, the availability of information for epidemiological public health purposes and research is, I would have thought, something that is bubbling pretty hard now. Do you have any views on how it might be resolved? Would clearer expression by the Information Commissioner and/or others of the difference between anonymised – I do not mean de-identified – data and data that are not anonymised and differential treatment of the two categories go some way to helping matters?

Dr Flinter: I think it would help. I think the other thing that would help is a general public discussion to try and help people understand how in an altruistic way use of their personal medical data could benefit medical research and science in general. If we can reassure them and give them the confidence that their data will not be misused and that they will be protected from individual harm, then on the whole I think people are very willing to allow their samples to be used for research and for long term data about their medical conditions as they progress to be used.

Q332 Baroness O'Neill of Bengarve: Just as they rather expect their doctors to use information obtained in treating prior patients in the course of their treatment.

Dr Flinter: Precisely.

Q333 Earl of Northesk: Do you think there is a case against the generality of data in the way in which the Data Protection Act is framed in treating medical data generally, and genetic data specifically, as a separate subset of the generality of data, in the sense that there is potentially quite a strong argument for the individual's interest in that data to be treated from an opt out process rather than opt in?

Dr Flinter: In general we need to be careful about always saying genetic data is different and should be treated differently. In many senses it is not different but the one sense in which it is different is that knowledge about an individual's genetic make-up can also have implications for their relatives and there can be very important ethical consequences of that. If we know that a woman who has a son with Duchenne muscular dystrophy, for example, is a carrier of Duchenne muscular dystrophy, then there is a high risk that her sister could also be a carrier and, if her sister were pregnant, then obviously there are important and urgent potential implications for that pregnancy. In clinical practice the way we handle it, certainly in the department where I work, is when we obtain consent from people to do a genetic test on them at that time we explicitly discuss the fact that information generated from that test result could benefit other members of the family and we seek their consent to give that information to clinicians looking after their relatives if it would be appropriate. If you have that discussion at the beginning and explain the potential value people are happy to give that consent, but it does mean thinking ahead at the time you are doing the genetic testing rather than finding yourself in a situation of having to contact them out of the blue some years down the line in order to request permission to pass that information on.

Q334 Lord Warner: Could I ask about access to these what will be growing genetic databanks of the police and prosecuting authorities. Is that an issue which has concerned either the Nuffield or the HGC?

Dr Flinter: The HGC is planning to do some work on genetic research databases generally and there will be a working party looking at that. There are members of the HGC who sit on the ethical committee that oversees the police DNA database. It is a question that worries patients. They not infrequently ask will the police be able to get hold of my DNA and our answer is generally no, the data is held securely within the NHS facility or research facility where that sample is taken. My understanding is that it would be highly exceptional for the courts to order that a sample of DNA were given to the police and I do not know of any situation where that has happened.

Professor Weale: The Nuffield published a report on the forensic use of that information at the end of last year. This question of how data is held does arise in a variety of institutional contexts. As you will know, proportionately the number of DNA samples held on the UK population is the highest in the world. We thought that that did not reflect an adequate balance between the interests of public security on the one hand and the legitimate interests of individuals who may have given samples, for example, because they wanted to be excluded as a suspect from a scene of crime or they had been questioned but not charged with a crime, we did not feel that holding the samples indefinitely without those giving the samples being able to withdraw them did respect adequately rights of privacy, confidentiality and civil rights. One of the guiding principles that we made in trying to strike that balance between confidentiality on the one hand and public security on the other was to say that there ought to be evidence that police authorities should have that holding these samples actually would contribute towards public security. I think our current understanding is that the authorities in this respect may be moving in a direction which we would find more sympathetic in recent weeks, but there clearly are very serious issues there which arise about both the utility of holding this forensic information and about the implications for individual rights.

Q335 Earl of Northesk: What ethical implications arise from large population databases such as UK Biobank and the potential for these databases to be linked in the future to other databases, for example, to electronic health records? Linked with that, and possibly one of the more important questions of all, who is, or indeed who should be, ultimately responsible for ensuring confidentiality and security of individuals' details?

Sir John Sulston: This is very important and very worrying. Can I hark back for a moment and this is going to overlap with some of the remarks that have already been made, and although it is quite right to talk about the forensic databases, I think we should make it clear that these are two different sorts of database entirely: the one that is held for medical reasons and the ones held for forensic reasons. The same is not of course true of the samples. It is a very much more sensitive issue that the police database is hanging on to the DNA samples because they could, in principle, be misused by looking at other things, but so long as you have the microsatellite data then you really are not looking at any medical, and the reverse is true that only by getting the DNA sample and running the microsatellite test will the police be able to use a biological sample forensically. I think we can be reasonably happy about keeping those two things apart, so long as the rules about transfer of physical DNA are observed. As far as these new population databases, I am not going to get a clear answer because there is not one. Frances has already alluded to the fact that there is a piece of work going forward, one of our biggest pieces of work just being initiated under the lead of Sarah Cunningham-Burley, Professor of Sociology at Edinburgh, to consider this. There is also quite a lot of work going on both in America already. There is an ethical committee, as you are aware, for the Biobank. There is work going on in connection with the 1000 Genome Project that I have already referred to in these individual genomes. The issue with all of this is that of course we do not know what will happen when we start linking databases together. Each individual genome is unique and people can, in principle, by putting queries into

different databases that are linked together, acquire the identity of an allegedly anonymised subject. There are issues about this and they have to be dealt with in the end probably in a statutory way, but we need to define exactly what the right way of doing that is. The HGC's position is as always that we must balance the principle of solidarity – the research value of the linked databases and the collective data to all of us in finding out how we work and how we improve medicine – with the right to privacy. As Baroness O'Neill has pointed out for many, many years, we cannot do it by informed consent. You have made it very clear and it is obviously right. The HGC is following in your footsteps here in that we are much more talking in these terms now than we were when we put out informed consent information. The reason is, of course that you cannot have complete information about what is going to happen to data either on the part of the subject or on the part of the practitioner or researcher who is collecting the data. The future is uncertain. We have to have a different sort of consent. We cannot promise to remove people's data from these databases as it gets spread around into different ones as it moves from one computer to another. We cannot go backwards on that – I do not think that is feasible in research terms – so what we have to do, and it really comes back to this idea of having statutory rights of people. Although we hate the idea of genetic exceptionalism, there is this propagatory nature of this sort of information that means that we do have to learn to treat it separately and to legislate. We cannot in the end prevent data being picked up and used wrongly, perhaps to somebody's disadvantage, so what we have to do is to have proper sanctions against that happening. In particular, and we have already referred to the fact that there must be a robust recovery procedure so that if somebody does run into disadvantage as the result of being incorporated into one of these schemes that they can be properly reimbursed, or if it is a real case of identity theft, for example, in an extreme case then their lives can be somehow put back in order. We should not neglect the minority of

people who will suffer. It is going to be rare. I do not think many people will suffer but it could happen and so we must have a procedure in place for looking after them.

Professor Weale: In terms of Biobank, in the forensic use of bioinformation report, Nuffield was actually quite impressed by the ethics and governance framework that had been put into place and indeed I think gave a very generous pat on the back for that, not just because participation was voluntary and participants could withdraw at any time, but the framework had established this ethics and governance council which, if you like, could act as a watchdog on behalf of the connectivity of those giving samples, an independent body who is transparent and had access to committee proceedings and standard operating procedures and so on, so that might be a possible model. How one deals with this more complicated question of putting different databanks together does raise difficult institutional issues.

Q336 Lord Broers: Genetic tests for diagnosing and managing common diseases are increasingly being performed outside the Regional Genetic Centres across the whole range of medical specialities. The Committee has received evidence that more education is needed for physicians, nurses and laboratory scientists and that more genetic counsellors are required. How urgent is the need for more education, what is the scale of this need and where are the priorities?

Dr Flinter: I might change slightly your first statement in that more and more genetic tests are being requested by physicians outside of genetic centres, but the vast majority of the tests are still actually being done within the laboratories in the Regional Genetic Centres, so increasingly cardiologists and neurologists and so on are requesting genetic tests, but the samples are sent to the Regional Genetic Centres for analysis. It is very clear that clinical geneticists cannot control all the genetic testing that takes place in this country. We are a small number of clinicians, we work in a very specialised area and we concentrate on the management of single gene disorders, but what we can do is work with our colleagues in

other specialities to help them develop clear guidelines or protocols which identify the subgroup of their patients for whom genetic testing may be indicated. We can explain to them and teach them the sorts of processes we normally go through before we embark on a genetic test, talk about obtaining a family history, finding out if anybody in the family is pregnant, for example, being aware of the implications to the extended family and we can help them decide on a protocol-driven basis which genetic tests to request for which patient and we can make sure that when they get the report they are written in such a way that they can understand and it helps them with their future management. I think clinical geneticists and genetic counsellors will have a role in working with colleagues as genetics becomes more and more part of mainstream general medicine and even surgery in some cases. That does of course mean that there is a need to educate a much wider group of healthcare professionals in other specialties so that they can use genetics appropriately. As a practising clinician and a consultant geneticist, I welcome the work of people like the Genetic Education Centre in Birmingham which was set up with funds following the Genetics White Paper which is doing a lot of very useful work in terms of identifying which are the skills which other professionals need to acquire in order to use genetic tests sensibly and which are the ones that they actually do not need to worry about, because there are still some things which it will be appropriate to do in the Regional Genetics Centres. If somebody is found to have a genetic condition and wants to consider all the reproductive options and possibly prenatal diagnosis, pre-implantation genetic diagnosis, it is probably best that they come and see a consultant geneticist or a genetic counsellor, but there will be many other things that our colleagues can do. In terms of how great is this need for educating other professionals, the Human Genetics Commission has not formally counted that. We are aware that there is a very great need and I suspect at the moment that we are not quite meeting it in that some of our colleagues are beginning to request to use genetic tests perhaps not always appropriately, perhaps sometimes

requesting a very great long list of tests all at once when it might be more appropriate to go through a staged process, sometimes asking for a genetic test when actually a simple x-ray might give them the same answer much more cheaply and much more quickly.

Mr Hogarth: This may be a case where genetics is again pointing to where the weakness is and certainly I have heard evidence from a number of people I have interviewed that they feel that there is a broader lack of education on the part of many physicians to properly, effectively and safely use diagnostics to understand the difference, for instance, between absolute and relative risk to understand the significance of negative and positive predictive values that they might be given in test results.

Professor Weale: The only thing I would add from the pharmacogenetics point of view is that when the working party was doing its work it was very conscious of the fact that if pharmacogenetic testing would be introduced into prescribing behaviour, that would carry quite substantial implications for the understanding that primary care professionals and others had about the significance of those tests, some of which may be carried in the licensing requirements, but would still pose difficulties in communication and interpretation.

Dr Patch: I would like to raise one other point as a nurse and genetic counsellor. You raised the issues of genetic counsellors but I am not sure whether you are aware that there is no statutory professional regulation for genetic counsellors. Those of us who have been in the field for a long time, most of us are nurses, midwives or health visitors, so I maintain my nursing registration. We have a voluntary registration board set up and about half the profession are now registered, but given that we are only 300 in the country and that we are doing this basically unpaid and as volunteers, we have done remarkably well. We are probably going to be in a position to submit an application to the Health Professions Council by the end of this year, we hope, and that will go through the process however long that takes and hopefully it will be met with enthusiasm. I think this is of relevance as earlier discussions

related to the provision of genetic testing services and the fallback position of well if you have a bit of genetic counselling you will be fine. I think it is about the appropriately qualified health professional and whereas most of us are currently employed within the NHS within the governance arrangements of being an NHS employee, anybody can set themselves up as a genetic counsellor and there is no protection for the public.

Q337 Lord Broers: I am troubled by this relative versus absolute risk in the point that Baroness Perry brought up. Having lived half of my life in America and half here I am aware that what will work in America may not work here and vice versa. We are a verbal nation, they tend to be a numerate nation, and you only have to think of weather forecasting in that we are told whether it is going to be hot or cold and whether it is going to rain, whereas Americans just want the temperature and the probability of precipitation and the wind index. It is a different society. It might be a good idea to develop a set of categories or rank risk so that physicians and people can know whether it is serious, very serious or not serious rather than give them a number which they will not know how to handle.

Dr Patch: We spend our working lives interpreting risk to people and it is very difficult.

Lord Broers: That is my point. If you could rank it, as one does rank things, it might be useful.

Q338 Baroness O'Neill of Bengarve: The HGC has submitted that in research in the processing of genomic information and in translation to clinical practice there are opportunities for private sector/public sector collaboration. What are the opportunities and how might they best be developed?

Sir John Sulston: We need to clarify our position here. It was in our written submission of course but there was a very important sentence in there that said we consider it very important to have an independent evaluation and of course this harks back to our comments about the

way new treatments of any kind should be trialled and dealt with. We do not see the idea that more is always better; that we should be pushing the NHS to take up always the latest wheeze, always the latest drug; we think that is quite wrong. Obviously there is benefit though in having good interactions, good horizon scanning so that people are aware of what is going on, what is coming to market, what may be available, what may be useful, so that the evaluation can take place in good time. I am not an expert on the specific barriers and I would pass that to others. I really think it is very important that we do not intend to be saying we must take up faster; it is not as simple as that.

Professor Weale: I was rather intrigued by this question. I noticed in our pharmacogenetics report that we did cite the example of the meningitis C vaccine where the NHS had actually said to industry if you can come up with this vaccine then we will purchase it. The inference that I would draw from that is that if there were a clear and distinct advance where one could see very considerable benefits following from that, then there are these precedents where one could imagine public/private partnerships of varying forms being useful.

Mr Hogarth: When we have been doing our research and regulation which can be construed as unkind to industry, we have also been trying to think of ways to be kind to industry, so we have been asking the question not just how do you evaluate clinical data, but how do you create the incentives and the infrastructure for the generation of clinical data? It has been quite clear in our research talking to people in the *in vitro* diagnostics industry that because the industry's traditional business model is that it has intellectual property in testing platforms, not in biomarkers, it is very poorly incentivised to do clinical studies that develop the clinical evidence base for the clinical validity or the clinical utility of new biomarkers because any single company that puts the investment into such a study will immediately have multiple other companies riding on that investment by putting out a similar test unless it has intellectual property in the biomarker and can have some kind of monopoly. I think it is very

important to address these issues. Some companies are going down the route of taking intellectual property in biomarkers and on the basis of that investing in clinical studies, but there are a whole range in this area of genes which the IP is in the public sector or that have not been patented where that kind of business model is definitely not going to work. We do not even know if it is a sustainable business model anyway, so I think the need for public/private collaboration to build the clinical evidence base is actually overwhelming and it is simply a question of how we can go about it.

Q339 Baroness O'Neill of Bengarve: Would that not mean putting into the public domain the very information that companies in many cases wish to keep to themselves?

Mr Hogarth: Yes, but if you look at the regulation of pharmaceuticals then clearly the whole drift is towards greater transparency in the sharing of data. I think we already have some emerging models where companies such as Celera and Decode are already involved in extensive international public collaboration with public sector researchers in a variety of countries.

Q340 Baroness O'Neill of Bengarve: I cannot resist asking whether Sir John would agree with that or whether he thinks they are involved in competition rather than collaboration?

Sir John Sulston: That is why we say there has to be independent evaluation. We should not have the provider of a test being both judge and jury in this situation, but of course communication is essential otherwise we stymie everything, so we have to find ways through but it is important that you put resource into the independent oversight of what is going on.

Q341 Baroness O'Neill of Bengarve: And conditionality of meeting those independent standards is necessary for marketing.

Sir John Sulston: Yes, absolutely.

Q342 Chairman: What are the two recommendations that you would like to see? You have answered one of them which is something to be addressed around discrimination, but what would be your other one?

Dr Patch: Our first bullet point when we are thinking about a collective effort in relation to this evidence giving was essentially that the scientific developments are incredibly exciting but we should not get too excited and it is important to remain realistic about translation into genuine healthcare benefits. That was our major point.

Professor Weale: From the pharmacogenetics point of view, the specific recommendation that we made was that the regulatory authorities responsible for licensing medicines ought to be developing their thinking about whether a pharmacogenetic test ought to be part of the licensing conditions. We understand that some work is going on ahead of that but if there are useful tests then it would be helpful for the regulatory authorities to be anticipating these rather than just reacting to them.

Mr Hogarth: In terms of a regulatory reform agenda then risk classification would be the one that I would put at the top of the list.

Sir John Sulston: The NHS Clinical Genetic Service is generally acknowledged to be a world leader. It has very good processes and it really is a model which could be extended. More than that, the entire NHS, which is a free at point of care service, and a very well liked vehicle for people to obtain their medical treatment, when we have done surveys, and this is true of other surveys too, people actually say they want genetic testing and counselling through their practitioner. They only go to the web or whatever as a last resort if they feel they cannot get it under the NHS. We have always said it is very important that the NHS is resourced, but the thing to be aware is that we have a very valuable way of dealing with exactly this kind of very difficult information involving not only individuals but families, confidentiality and very different costs of treatment may be coming out about very different

worries. It is extremely important to protect the NHS and drive it as the vehicle for dealing with all the things we are discussing today.

Chairman: Thank you very much. If you have any further points to raise or if you wish to submit further evidence, then please do so. It has been very helpful.