

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

WEDNESDAY 25 JUNE 2008

DR ROB ELLES, PROFESSOR RICHARD TREMBATH, MR RON ZIMMERN
and PROFESSOR MARTIN BOBROW

Evidence heard in Public

Questions 235 - 286

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WEDNESDAY 25 JUNE 2008

Present

Broers, L
Colwyn, L
Krebs, L
O'Neill of Bengarve, B
Patel, L (Chairman)
Perry of Southwark, B
Taverne, L

Memoranda submitted by PHG Foundation and British Society for Human Genetics

Examination of Witnesses

Witnesses: **Dr Rob Elles**, Chairman of the British Society of Human Genetics (BSHG), and Director of Molecular Genetics, National Genetics Reference Laboratory and Regional Molecular Genetics Service, **Professor Richard Trembath**, Head, Division of Medical Genetics, King's College London (past president of BSHG), **Mr Ron Zimmern**, Executive Director of PHG Foundation (formerly the Public Health Genetics Unit, Cambridge), and **Professor Martin Bobrow**, Head, Department of Medical Genetics, Cambridge University, examined.

Q235 Chairman: Good morning, gentlemen. Thank you for coming along today to help us with this inquiry. We are hoping very much that you will be able to give us the definitive answers we need in the kinds of areas we need to make key recommendations. Could I also welcome members of the public. For the public, there is some information declaring the interests of Committee members if you wish to see it. I do not know if one of you is going to take the lead position, or if the appropriate person is going to answer each question as it comes, but I would invite you to make an opening comment if you would like to. Otherwise,

please would you introduce yourself and say who you represent the first time you speak.

Does anyone want to make an opening remark?

Professor Trembath: We are happy to respond to the direct questions.

Q236 Chairman: Thank you very much. It is becoming clear to us from a lot of the evidence hitherto presented, both written and oral, that there have been many advances made in genomic science but we are not clear which of these are the most important in managing the common diseases. Most of the inquiry is going to focus on genomics and its implications for health. How soon are they likely to reach mainstream clinical practice?

Professor Bobrow: I am Martin Bobrow, I am listed here as Head of the Department of Medical Genetics in Cambridge. That is no longer true. I am a member of the great unemployed – and delightful it is too. I think that is a very difficult question. I am extremely enthusiastic about the advances in knowledge that have occurred – and we are just beginning to scratch the surface, so a lot more will come. In my view, the results of that will be better understanding of biology and a better understanding of disease and the development of new diagnostic and treatment modalities a long way down the road, many of which will not be genetic at all. I am not myself convinced that there is any serious number of short-term benefits in terms of screening tests (of the sort that are commonly discussed), for reasons I guess we will get into later. I am sure that we will see, as we have already seen, more and more novel treatments beginning to emerge as people understand the biochemistry of disease and health better.

Mr Zimmern: I am Rob Zimmern. I am a public health physician. I am the Director of the PHG Foundation which was formerly the Public Health Genetics Unit. For the last 11 years I have been involved in issues of genomics and public health and the whole translational issues. I wish I could disagree with Martin, because, enthusiastically, I would like these tests to be of some benefit. However, as each year goes on and I learn more and more about it,

I come more and more to the view that, yes, there will be long-term implications when one understands biology better, but as for the direct use of a gene-disease association, there are huge problems. One of the problems is that they are being sold as tests. A test is something normally that you dichotomise: it is either positive or negative, on the whole. By dichotomising you can say, “Well, if you are positive we do this; if you are negative, we do that” but I think this is entirely the wrong way to think about these genetic variants and biomarkers. First, their relative risks are very small: 1.05, 1.1, 1.1, 1.2, and, until you get to relative risks of 30 or 40, they are of absolutely no use in dichotomising and distinguishing populations with the variant and populations without. If there are to be any advances directly from understanding gene-disease association, we have to think about these as items of data which you feed into some form of predictive model, which must start from the age and the sex of the individual for whom you feed these various results. Whether a combination of factors like that fed into such a model will produce predictors, time will tell. Maybe in some cases they will. We already see it with cholesterol, blood pressure, and heart disease. Whether, as some experts might think, adding genetic or protein-type biomarkers on that will improve the risk prediction model, we have yet to see.

Dr Elles: I am Rob Elles. I am currently Chair of the British Society of Human Genetics. My job is in the Regional Molecular Genetics Service in Manchester, which also houses one of the National Genetics Reference Laboratories. For the past ten years in genetics, particularly for familial cancers but also, increasingly, for familial forms of heart disease, we have been identifying classes of patients at high risk, offering predictive tests, and, increasingly, as time goes on, we have helped patients to open up options for themselves and advised on the management of these conditions. If that is our starting point – and that represents a large chunk, perhaps even the majority, of the work of Regional Genetics Centres currently – I have seen changes recently. I have seen changes in terms of demands for tests to

look at the genotype of tumours and to help manage prescription in relation to those conditions. Those tests, in relation to those management options – the subject of your question – are already starting to emerge as a clinical demand on us as regional centres. In fact, in recent months we have been fielding requests for genotyping in relation to clinical trials, again in relation to cancer therapy, so I think we are starting to see the thin end of the wedge in terms of genotyping, genetic testing, and management, and I think this is going to increase as time goes on.

Professor Trembath: Richard Trembath. I am the most recent past Chairman of the British Society of Human Genetics and an academic professor of medical genetics at King's College London. There is essentially consensus amongst the witnesses here – although, as ever, it is in the detail and, having previously attended the seminar that was held as part of this Select Committee, I am aware that many of these issues were highlighted during that seminar. Part of it of course lies in the definition of common disease and what it is that we are seeking to apply to those. That has direct relevance to what Ron has alluded to. In many instances, the current array of genetic tests, as they would apply as potential predictive tests, will, if they have any potential, become part of an amalgam of predictives that will be brought into some kind of model. And we are very used to that in medicine. That is exactly what we do in terms of practice: we take a number of observations and integrate them. It is highly likely that those will continue to be the ways in which current advices have their most common application. As I think Rob was alluding to, we have – because we have seen it already and we will anticipate more examples – the ability to use genomic sequence, the ability to interrogate our genomes to identify specific subgroups that currently are buried within what we might term common disease, for whom alternative approaches of management are pertinent, which might include alternative therapeutic strategies or specific therapeutic strategies. There are some examples. We might use the breast cancer example of that,

because, of course, we are only now identifying the BRCA genes because of access to sequence. We would be saying, "Here's a great example," but we have come to it from a slightly different angle. I have no doubt that there will be an increasing number of examples, within the depth of common disease, of the ability to use genome sequence to identify specific sub-groups within that, for whom direct application and virtually immediate application is pertinent.

Q237 Chairman: Some of the evidence that has come to us about these genomic tests is that they should not enter clinical practice unless they have been validated and tested. Who would do this and where would the funding come from in terms of testing their clinical effectiveness and cost effectiveness?

Mr Zimmern: There are three issues here: (i) who will produce the data that will enable the analysis and evaluation; (ii) who will carry out the analysis and evaluation; (iii) who will set the standards by which after the analysis has been done ----

Q238 Chairman: You have put my questions well. Perhaps you could answer them now.

Mr Zimmern: There are these three bits. It is in the first that I think there is the greatest problem because nobody is taking responsibility. Doing the science, making the gene-disease association, is taken care of: that is done by scientists; there are lots of research monies. But once a gene-disease association has been shown, doing what might essentially be seen as the equivalent of phase three trials in therapeutics (getting the test performance, getting the sensitivities, the specificities, the positive/negative predictive values) is stuff that serious scientists do not really want to do. It is very mundane; it is very routine. The pharmaceutical companies do it because under the Medicines Act they are obliged to do it. I have talked to a number of biotech companies, and they have sat before me and said, "I've got this wonderful test which predicts autism, why isn't the NHS buying it?" The first thing I say is,

“What’s your evidence?” and out of their briefcase comes a set of papers from *Nature Genetics* or whatever which shows the gene-disease association and shows it very well. Then I say, “What about its predictive value?” and they say, “Oh, we’ve only done it on ten cases and ten controls.” “Why?” “Well, we’re not the big pharmaceutical companies. We can’t afford to run these trials.” I have heard estimates for diagnostics of three to five million euros to do a trial – which is small beer for therapeutics companies but huge amounts of money for a biotech company. My personal view is that there has to be discussion between the private sector and the public sector about who produces these data. Once the data are produced, I think there are many organisations ranging from NICE and others who can analyse such data, but, even then, there is the question of standards. Here we get to value judgments: How high does the predictive value have to be? What does the sensitivity and specificity have to be before the NHS will take that on?

Q239 Lord Krebs: I would like to follow up, if I may, one of the answers to the first question from Professor Bobrow and others. As I understood it, your reservations about the timescale for translating the knowledge of genetic associations into clinical practice came from two sources, and I would like to check that this is a correct interpretation. One is the low predictive power and the second is the lack of understanding of the biochemical pathways that link the genetic difference to a disease. If we go back to the textbook example that we all learned about in first year biology: in phenylketonuria one knows what the genetic pathway is and therefore can devise a very simple intervention to prevent the expression of the genetically determined disease in the phenotype. Am I correct in assuming that it is those two aspects, the low predictive power and the lack of biological knowledge about the pathways, that link the genetic change or genetic difference to a disease?

Professor Bobrow: Yes, that is correct. The second of those will change, because one will learn more about pathways, and that may lead in a variety of very constructive directions.

The first, although there may be a few surprises, will not change. We now know, as we did not know ten years ago, that examples like the breast cancer genes are rarities. There are virtually no high-risk alleles for what we call common diseases waiting to be discovered. People have spent the last 15 years proving that with blood and tears. We are left with a set of alleles of risk factors that have predictive powers of around 1.02, 1.05, and so on, which obviously one at a time make no difference at all worth speaking of. Perhaps I could take a couple of minutes to get something off my chest, which I will then not have to do later. This leads one into a slight paradox which is not being well-described in the literature. The immediate response to saying that these risks are very small and therefore not very interesting is, “Yes, but there are hundreds of them, and as we learn more we will be able to amalgamate them.” And so we will. Clearly, if you have things that give you an extra risk of five or ten per cent and you test 25 or 30 of them, you will eventually define someone who has all the high-risk alleles, and has quite a substantial risk – it might be an absolute risk of 30 or 40 per cent – of whatever the disease is. But each time you multiply risks, you are also multiplying how common that allele is in the population. Although you will define a high-risk group of people, they will be incredibly rare. They will in fact be rather less rare than the rare Mendelian diseases that everyone has been telling us for the past ten years are not very interesting because they are too uncommon. It just does not work. This is something that was delineated by Geoffrey Rose in the 1960s, that, in any disease that has this sort of complex causation, the great bulk of the individuals and the population lies in the middle of the distribution and the bits at the tails are very interesting to very few families but they are extremely unlikely to be a public health issue. However you set these predictive tests up – different from the stuff Rob was talking about – you will land up in a situation where most of the people that you define as being of moderate risk do not get the disease and most of the people who get the disease are not likely to be in your higher risk categories, so it just does

not play out in practical medicine. I think that is a theoretical block. It just will not go away. It is different when you are testing a disease process, which is what happens when you genotype cancers to see what has gone wrong in that cancer and you are defining part of the process that is already underway in that individual. Although you are using genetic technology, it is almost a functional type differentiation.

Q240 Chairman: Dr Elles, did you have any comment about whether these tests are clinically cost-effective and practical or not?

Dr Elles: Taking you back to the current situation, certainly many members of the BSHG perceive a gap currently. I am really talking about the current situation, where genes are still being discovered for rare diseases or the Mendelian sub-sets of common diseases, or where we are starting to unravel the situation, like in eye diseases. In a condition which is relatively common, like retinitis pigmentosa, of genetic cause, there can be 30 different genes, any of which could be mutative and causative of this condition. How do we get these research discoveries into practice? There is a lot of frustration in the community about the translational gap and a feeling that the NIHR as currently constituted is not recognising this gap. It is really, in some ways, quite modest and small scale, where individual laboratories are seeking funding to take the research findings and to do the process which Ron described, which is really in their own laboratory to design and validate a test in a small series of patients but sufficient data to present before the UK Genetic Testing Network as a gene dossier and have the assessment of the test judged as to whether it can go forward for commissioning. It is that piece of work, gathering that data, which it is sometimes very difficult to get funding for and which does fall, we feel, in a gap in the system. It is telling that, in a number of instances, quite commonly, individual patient groups feel so strongly about this that they end up funding this work. In my own laboratory, the British Retinitis Pigmentosa Society – and

that is just one example – stepped in, in order to allow that validation process to occur and to allow a dossier of evidence to be gathered and put forward for commissioning.

Q241 Lord Broers: Could I pursue this a bit further and take Dr Zimmern's view of his first sub-division of the question. Is the problem in getting reliable data or is it expensive?

Mr Zimmern: No one at the moment has the responsibility or the funding to gather the data. It is not a difficult process. It is purely that, as a matter of policy, nobody has decided who bears the responsibility to produce those data. As Rob says, the research funding bodies do not see it as their business because it is past research, and there is no equivalent to the Medicines Act which says the industry has to do it. It falls between stools, and so nobody is doing it.

Q242 Chairman: In a way it is a direct translation, is it not?

Mr Zimmern: Yes.

Q243 Chairman: That is the point Dr Elles made about NIHR not recognising that this is a translational issue and therefore needs to be funded. Am I right? Or am I putting words into your mouth?

Mr Zimmern: Yes, in part you are right. Perhaps I could here make the distinction between translational research, of which this could be considered a part, and the act of translation itself. That distinction has not been appreciated by policymakers. We understand now that more money is going to translational research, as opposed to basic research; but, nevertheless, there is no money going into the process of translation, of ensuring that we get the communities of researchers and the communities of doers and the funders together to ensure that that piece of research gets implemented into practice.

Q244 Lord Broers: From my own point of view of ignorance: there is no problem, if you solve your organisational problems, in getting reliable data.

Mr Zimmern: No. Correct.

Q245 Lord Broers: When you take a sample, you generally do not generate errors. The data is the data.

Mr Zimmern: That is right.

Q246 Lord Taverne: I want to pursue further this question of assessing the value and cost-effectiveness of tests. We have heard evidence about lots of newly emerging genetic tests for a variety of purposes (testing for drug efficacy and side effects; for guiding management in cancer and leukaemia; and for predicting common diseases – although quite a lot of doubt has been thrown on that). Which is the best way of assessing this value and cost-effectiveness? Do we need a new body to do that? Or could an existing body, such as the UK Genetic Testing Network, cover it?

Dr Elles: The UK Genetic Testing Network, as it is currently constituted, is designed and operates very well in the area of single gene disorders and tests for relatively rare conditions. As the NHS starts to grapple with emerging tests for common disease that are put forward as predictive tests, then I think that is a much bigger job. It would require a lot more resource to be put into UK GTN, if it were tasked with that job. The recent summit between the Royal College of Pathologists and the public health geneticists recommended a so-called NICE for Diagnostics. Certainly from the British Society point of view, we would strongly support the need for such a body and for it to be adequately resourced to look at this kind of task. Does that answer your question?

Q247 Lord Taverne: You favour a new body. You think it would be difficult to use the UK GTN?

Dr Elles: As it is constituted, it could not take on board this task.

Mr Zimmern: You have had Professor Peter Furness presenting evidence on behalf of the Royal College of Pathologists. His take is much wider than genomic medicine, but this is an issue that really faces all forms of pathology tests, whether biochemical, haematological, proteomic. Clearly if one goes that wide, the UK GTN is certainly inappropriate to do it. We are talking about a *sui generis* body that will do diagnostic tests across the board, in which case one then has to decide if that takes on the UK GTN stuff as well. As well as who does the assessment, the other main recommendation that came out of this summit was a very important one: all this evidence should be produced and put in the public domain on a website or something. At the moment, the reality of European legislation is that a lot of these results, if carried out by commercial companies, are “commercial in confidence” and they are not put in the public domain, so we do not know with all these commercial tests what the clinical validity is because there is no obligation to put this evidence in the public domain.

Professor Bobrow: I was going to make very much the same comment. I am very much against treating genetic tests differently from the way in which we treat other tests. Because they are not different. They are simply one way of assessing risk and you can put them in with biochemistry, with imaging, and with all sorts of things. The reality is that the world – and not just the NHS: it is not as though there are great models in other countries, although it is slightly different in the States – does not take the need to produce hard evidence of the real value of tests and diagnosis as seriously as it takes the need to produce hard evidence about the safety and efficacy of medicines. If we look at the treatment side of the world, we do demand lots of data on how safe and efficacious medicines are before they are licensed, but we do not fund it. We expect the drug companies to fund it for us. We then get into

an interesting sort of circle where they do all the science behind closed doors, they produce the data that they want us to see, and they charge us handsomely for the process in the price we pay for the drugs. In diagnostics, it has just been too *laissez faire*?

Q248 Chairman: Is there not a key difference, in that genetic testing has implications for other members of the family which imaging, et cetera, does not have?

Professor Bobrow: That depends what you are imaging. If you are imaging in order to discover an inherited disorder, it is not true. The sorts of genetic tests that apply to Huntington's disease certainly have implications; but if what you are predicting is late-onset type 2 diabetes, the implications for other family members may be – I am guessing – quite modest. I do not think that is a real distinction. I think the problem is that this needs to start from a clinical policy viewpoint. The first question is not: How good is the test? It is: Why would anyone want to take this test? Simply getting information that you are at risk is not very helpful in general. In the very high-risk situations which we have been used to dealing with in the past, people do ask for that information. Not everyone. Remember, most people with Huntington's disease or a high risk of Huntington's disease do not ask to get tested, even today. Most people do not want that knowledge. The people who do, want it because it is a very serious disease, it has a very high risk, and they want to plan their lives and their reproduction and all the rest of it in that knowledge. That does not apply if you are talking about relatively modest differences of getting something like diabetes at the age of 65. Why would you want that information that you are at high risk? The answer is dead simple: Either there is a treatment that you would get, or there is a preventative strategy, and that treatment or that preventative strategy has to have some cost attached to it. Because if the preventative strategy is: "You should really take a bit more exercise," it is just not worth having the test, because you should do that anyway. These rather "Noddy" things which come out of the current range of things offered on the internet do not fulfil the definition of why anyone

should seriously want to get that knowledge for a predictive point of view. If you start off at that level – to get back to your question – you do need a policymaking body that asks the right high level questions and that assesses all of the stuff that Ron has spoken about. In relation to any diagnostic modality that is in practice now, this is a big agenda. It is effectively a NICE-type structure but dealing with diagnostics rather than therapeutics.

Professor Trembath: I think that point has been very well discussed, but I want to go back momentarily to the issue of the role of the NIHR in translational research and its relevance to this particular issue. I also have a role as a director of one of the recently formed Comprehensive Biomedical Research Centres within the NIHR structure, and I think it would be unhelpful for the Committee to have a view that the NIHR is not cognisant of these issues or that they are essentially ignoring them. Quite rightly, resource has been made available and is appropriately targeted at responding to proposals that are looking at the diagnostic utility where the evidence is quite substantial that a test has potential diagnostic utility. Of course what we have been hearing is that that might be true, for example, in genomic profiling, to allow you to better categorise some forms of leukaemia and other forms of cancer, but on the theoretical grounds that Professor Bobrow has very clearly announced, is both unlikely and now factually not going to generate a pure diagnostic test, and so it seems reasonable, within a limited resource that NIHR has, that the targeting of developing those translational programmes is to those that are going to generate real diagnostic utility.

Q249 Lord Broers: Perhaps the question I am going to ask is rather getting ahead of the state of the whole science and technology, but if a new genetic test were to be found useful and cost-effective, how can we ensure that it is introduced into clinical practice in a consistent way across the NHS?

Mr Zimmern: Perhaps I might answer that question, having spent many years as a commissioner of services within the NHS. We mentioned the NIHR but there is another

body that we ought to talk about and that is the Health Technology Assessment. That has a huge budget. I was privileged to Chair the Diagnostics and Screening Panel of the HTA for about six years – I have just stepped down from that. As you know, it is a body that commissions research. They commission this research and a wonderful report comes out, but it is health technology assessment, and, in the technical parlance of Health Technology Assessment, “assessment is the gathering of the evidence” and there is no obligation on HTA, unlike NICE, where the jargon is the word of appraisal, to take the recommendations in that document, called the HTA document, any further. This to me is a major weakness of the UK HTA programme – as distinct from in Canada, where the HTA programme tries to get it into practice as well, so there is this drive. The other thing is the commissioning mechanisms. At the moment, pathology tests are not, except in the field of clinical genetics, separately commissioned. They are in the so-called FCE costs of everything: so someone buys an episode of ophthalmology and all the lab tests are in the costs of that episode. It is very clear to me that if you are talking about haemoglobins and urea and electrolytes and mundane things like that, they can be parcelled up in there, but with modern tests, tests costing £50, £100, upwards, there must be a process for commissioning them individually. Otherwise we do will not understand what is happening. I think these were the recommendations of Lord Carter of Coles’ report on pathology modernisation, of having explicit commissioning of laboratory services. In some form or other that has to come about if we are to drive this process into practice. By just lumping it into a specialty cost, you can see that there will be no levers to do this.

Dr Elles: One aspect of trying to get consistent service provision is to look at the provision of lab services, which at the moment in this area is split between laboratory medicine, pathology disciplines, and genetics (which often stands outside laboratory medicine). I think the moment has come where we should start to open a dialogue between the potential users of

these tests in various specialities (oncology, cardiology, and so on) and the service providers in genetics and the pathology networks. I think the recent reorganisational trend towards aggregating laboratory medicine into pathology networks, typically at strategic health authority level, gives us much more opportunity for dialogue between the relatively few regional centres as they exist and these new pathology aggregates. What is a bit disappointing – not to be critical – is that pathology modernisation has looked very closely at structural issues, hence the pathology networks, and has looked at workforce issues, but it almost nowhere talks about the kind of scientific horizon for pathology over the next ten years. I would like to think that these new developments in genomic science and our experience in genetics and putting them into practice could be a useful input into pathology modernisation and start to talk about what kind of service configurations we are going to need for these new genomic tests, especially when we are considering these exciting new technologies, these next generation technologies, such as these next generation sequencing technologies, which can potentially produce vast amounts of data. How are we going to configure the NHS to make best use of these technologies? My overall point is that we need some kind of structural dialogue between potential genomic medicine and the existing experience in Genetics Centres and the pathology modernisation effort.

Q250 Lord Colwyn: We are having a very useful discussion on genetic testing. I would now like to seek your views on the rapidly growing market of the direct-to-consumer genetic tests. The Regional Genetics Centres and the National Genetics Reference Laboratories have effective mechanisms in place to ensure the quality of the tests they conduct. With this increasing use of genetic testing in other NHS laboratories that perhaps do not have the same specialised genetics expertise, are there concerns about the quality of the tests being offered? Am I correct in thinking that the test itself is relatively straightforward and in fact it is the interpretation of the test which is the vital factor?

Dr Elles: The UK has been a leader in developing quality assurance in genetics and has spread that experience to Europe, and through the OECD countries, for example. We know from that experience that the current provision of genetics testing services in the UK in the Regional Genetics Centres is pretty safe from the point of view of quality; whereas in Europe there are some very good examples of best practice but a much more patchy and varied picture. We have a good handle on quality and the question is: As things develop how can we retain that accent and that guarantee of quality? We have the structures in place for laboratory proficiency testing, for example, also called external quality assessment. We have the structures in place in terms of long experience now of laboratory accreditation. The White Paper demanded that genetics laboratories should be accredited by clinical pathology accreditation, and, if not 100 per cent, very close to 100 per cent are now accredited. As the experience spreads, then we must make sure that these mechanisms are brought to bear on other laboratories, other specialties which go into these areas. But I come back to my previous answer. I think it would be foolish for us to allow a completely unstructured and ad hoc development of these technologies through the NHS. The time has come for us to start to discuss what is the best service configuration. If we can do that, then we have much a better handle on retaining quality in this sector. You touched on the private sector provision at the beginning of your question. I think it is essential, if the private sector are coming into this area, that the same kind of quality parameters apply to them as apply to the NHS laboratories. The other part of your question was about interpretation and I think that is a very good point. It is true that the laboratory manipulations are fairly well balanced up now and we have a good handle on quality, but as we generate more and more data, the task will shift away and the emphasis will shift away from the generation of genomic data to its integration and interpretation. We have to start to apply the same kind of quality parameters to the electronically informatics tools that will be brought to bear in that area and to the handling

tasks for information as we apply to the wet lab operations currently. So, yes, there is a need for a new focus on quality on these informational tasks as well as the wet laboratory tests.

Q251 Lord Colwyn: We were in America three or four weeks ago and we were already beginning to hear of genetic testing, the same sample being sent to two different laboratories and coming back with two different answers. I imagine that is inevitable.

Professor Bobrow: It should not be inevitable.

Dr Elles: That is the whole point of external quality assessment. External quality assessment works by sending the same sample and asking the same clinical question of 30 laboratories. The answers that come back should be all the same. We know from experience that two per cent of labs do not get it right.

Chairman: Is it possible that while the tests might be carried out in the same way and you could be fairly confident about the quality of the way the tests are carried out, the interpretation might be different?

Q252 Lord Colwyn: That is what I am getting at.

Dr Elles: External quality assessment can measure interpretation as well as the simple laboratory manipulations. That is a strong emphasis on our external quality assessment schemes. That element of assessment of laboratory quality will need to be developing very strongly.

Q253 Lord Krebs: As I understand it – I hope I have this right – in some parts of the NHS, diagnostic and other testing services are outsourced overseas, for example. Is that either currently or in the future likely to be the case for genetic testing? What are the implications of outsourcing overseas for quality assurance?

Dr Elles: We know from an OECD survey that I was involved with that over 800 laboratories, over 18 different OECD countries, 60 per cent or so either received or exported samples across national boundaries, so there is a huge trade internationally in genetic testing already. That is why the OECD was interested in quality assurance, so that they could start to develop some minimum quality standards and so that the patient could have some reassurance, even if their test was sent overseas, that there would be an equitable expectation of quality. I think we are a long way from achieving that but at least those standards have been derived.

Q254 Lord Krebs: How are they checked? I can see the standards might be expressed in a document but how do you go and check in the remote part of the world where the test is being carried out?

Dr Elles: One answer is that there is starting to be developed an international database where you can go and look at a laboratory and look and see what quality assurance measures it has in place. If you are choosing a laboratory to send a sample to, to refer a patient to, you have a source now of thinking about whether this is a quality assured laboratory or not. But the provision is very patchy. As I said at the beginning, in the UK I think I can say that 100 per cent of laboratories in the Genetics Centres are accredited, and that is a badge of quality. In Europe the number might be more like five per cent.

Q255 Chairman: Does the OECD define terminology and quality standards?

Dr Elles: The OECD has encouraged the adoption of current terminologies. These terminologies are available through, for example, the International Standards Organisation and we should all be working to these terminologies. But terminology is a huge problem. That is one of the things we discovered during this OECD inquiry.

Professor Trembath: I want to be sure that it is clear to the Committee that one of the principal drivers for currently sending a significant proportion of genetic tests to locations outside of the UK is the rarity with which these tests are requested, and, as a consequence, the difficulties of establishing those tests in their entirety within the current UK configuration of laboratories. If you were asking the question, as I believe you were: “Would this be equally true for genetic tests developed in relation to more prominent disease?” de facto, if they are common and frequently requested, it is more likely that those would be established within the UK if it were cost-effective to do so.

Q256 Lord Krebs: I really want to pick up on some of the conversations we have already had about the configuration of the NHS to deliver genetic testing. I notice that in the submission from BSHG, in your first two recommendations, you recommend that the NIHR “supports a programme to evaluate and implement individual genetic diagnostic tests within the NHS and that the Government plans for the resource needs” and you also refer to “links between Pathology Modernisation and Genetics” and that “the NHS should commission a Health Technology Assessment of Next Generation Genome technologies”. If you bring all that together, could you elaborate on what you think the requirements are for a Health Technology Assessment and what outcomes you might expect and by whom that should be delivered?

Dr Elles: We have reached the point where there are some very exciting, perhaps even frightening, technologies which are starting to become available. People are giving a great deal of thought as to whether they should go out and purchase a next generation sequencer which could generate terabytes of data and apply it to health care. Since the initial rush of excitement maybe a year ago, there has been a fall back from that and a feeling that we are still awaiting a generation of instrument which will be more configured towards health care purposes rather than research purposes. But there will come a moment when these machines

come on the market – and it may not be far off – which are configured for health care purposes, and at that moment the NHS will need to take a serious high-level look to see how they could best fit into the kinds of uses we have been discussing. It should not be left to chance and should be not left to local assessments. This is a very fundamental question for the whole for the NHS and so the NHS needs to find a way to do that. We have a core experience of technology assessment in the area of genetics through the National Genetics Reference Laboratories, but they may require some networking and some pump-priming and some additional resources in order to be able to do this job correctly. In answer to your question: “What outcomes would we be looking for?” I think we need to ask the question: “Are these machines configured to answer the clinical questions which are currently on the agenda?” and not go off into science fiction land and start to look for outcomes for tests which do not exist.

Professor Trembath: The response is rather focused around genomic sequencing technologies but in many ways we have more pressing and immediate examples of this. I am sure you have heard of the applications of comparative genome hybridisation: the ability to compare genomes and, through that, rapidly identify levels of changes within the genome that previously were rather hidden to standard approaches, particularly cytogenetics. This technological advance is poised to transform completely the way in which cytogenetics operates. Ron has been involved in developing at least views on what is required in the assessment of this. Essentially, one is then absolutely talking about not only the introduction of the new technology, the utility of which we within the academic sector have amply demonstrated, but it also has immediate consequences for the total configuration of a well-established laboratory service; namely cytogenetics. It remains the case that we do not, I believe, have an appropriate instrument to evaluate that and allow those dramatic changes to be put into practice in a way that can be appropriately validated.

Professor Bobrow: It is slightly interrupting that conversation but I wanted to undetribalise now. I want to be able to stand back from what seems to me to be in danger of developing into a discussion of genetics laboratories. I think that the issues that you have on the table here are mostly issues of diagnosis or common disease which really rather transcend what the traditional genetics laboratory went into. I come from the genetics labs. A great bunch of people they are and they do a terrific job, but that does not mean that that is the way that everything that is based on a DNA test is necessarily best done in a genetics laboratory forever. I do not know whether it is or not. The point I wanted to make very briefly is that the same technologies are applicable and are becoming applied, not only in haematology but in microbiology and in virology and, of course, in tissue type ----

Q257 Chairman: I think Professor Bobrow you were in full swing when we were interrupted by the fire alarm. I think you were somewhere between microbiology, haematology and specialised genetic labs.

Professor Bobrow: My view would be that at this stage the technology platforms, the actual bits of test that are being done, are much broader in their potential application than the things that come under genetics in the simple sense of the word, and that their introduction, their management, their appraisal, and all the rest of it, should perhaps be thought of in that rather broader context. I would take it as read that any laboratory delivering clinical services should be properly accredited and properly quality controlled, and there should be no doubt about any of those issues at all, and there should be expertise to deliver a proper interpretation. Just to finish that, the thing that gives me difficulty in thinking about your question, Chairman, is that we are trying to imagine systems for introducing and regulating a set of test parameters which to me at the moment fall into two rather separate categories. There are updated replacements for things we already do, such as arrays in cytogenetics, and there is this imaginary predictive medicine whose form is just beyond me at the moment. I do not know

how many such tests of what value will be introduced and when, and so I have a lot of trouble in answering who should control it and which body should regulate it. I think someone needs to stand back far from laboratory services in the NHS and think about it at a higher level.

Dr Zimmern: I wonder if I might commend to your Lordships the distinction which I found helpful between an assay and a test. The assay is the measurement. Asium(?) sodium is a measurement; creatine phosphokinase is a measurement; what comes out of a sequencer is a measurement; they are all assays, and Rob has already talked about the quality control of that. However, the test in the last few years I have been defining as an assay is in the context of a particular disorder or a particular population and for a particular purpose. That is, if you like, interpretation, so the assay, if you like, is the measurement and the test is the interpretation. When it comes to regulation, although the MHRA say they regulate tests, in fact they cannot regulate tests; they regulate assays. They are there to show that the device is both safe and measures what it purports to measure. I would suggest that in the context of a genetic test we are talking about these things that come out of whole genome studies with relative risks of 1.1. Never mind the utility of it, there may be zero utility, I believe the issue for the MHRA is to ensure that that association, no matter how small, is real because if that association is not real, they are in my view a provider selling a fraudulent test. However, if the association is real then the fact that it is of zero utility is not the remit, I believe, of the MHRA because they regulate devices, so there is therefore a regulatory gap because then who regulates interpretation? I speak of this in the context of these over-the-counter tests or these Internet tests. I have been thinking about this for some months now and it seems to me that we do have a system in clinical practice. It is the professional bodies that regulate interpretation. If Richard gets it wrong and someone makes a complaint, it is the GMC, or if it is a genomic scientist who gets it wrong, it is the appropriate professional body. I am now wondering whether we really need to think about ensuring that for these companies that provide both the

measurement and the interpretation there should be some form of system whereby they are obliged to provide the name and the experience and the professional body of the individual who on behalf of that company is doing the interpretation, and to separate out issues of regulation and interpretation from issues of regulation of the assay.

Chairman: You all seem to nod in agreement. In a way you have answered a later question we have which is about who regulates direct-to-consumer testing and who provides the advice in terms of the interpretation of those tests.

Q258 Lord Taverne: Can I anticipate and go on to a further question which is very much linked and that is the PHG Foundation has written in its evidence that "... advances in genomics are unlikely to enable a person to be given a precise, individually tailored diagnosis or disease risk." As you know, the body I am concerned with - Sense about Science - has been very much concerned about the people who try and commercially produce these tests and which have rather unfortunate results. I cannot remember whether it is the PHG Foundation or BSHG that warns against the danger of over-regulation but the regulation of these kinds of dangerous tests is really quite important, is it not?

Dr Zimmern: I suppose I am less concerned myself than some people because these are really lifestyle tests and at the end not too much damage is going to be done except to wallets. There is a real sense, as I have said, where there is a regulatory gap. When I said advances in genomics are unlikely to enable a person to be given a precise, individually tailored diagnosis or disease risk, it was very much what Martin and others have said about such low relative risk cannot possibly be of any use if you think about it as a test in discriminating. What I have said is that if the gene disease association is real you cannot get away from the fact that if you have that genetic variant you are a member of a sub-population this has five per cent or three per cent or two per cent high risk of asthma. If an individual in this country chooses to have that as a piece of information, provided it is real, I myself have no objection to that. The

issue comes because at the moment we know that a lot of these tests are being done where the gene disease association has not even yet been confirmed so they are fraudulent in that sense, but assuming that they have been confirmed to be real, then the issue is should we be stopping companies from selling this because people might just want to know, and I suspect not, but if they attempt to interpret and give medical advice, that is when I think the dangers start. I see nothing really in a free society to say that we should stop people from having a list of things saying you have a two per cent higher risk of asthma or a four per cent lower risk of heart disease. It is totally useless information ---

Q259 Chairman: Who should regulate so that inappropriate tests are not carried out? It is fine when you have the association but if we do not have the association?

Dr Zimmern: I believe that the MHRA can make that the standard because what the MHRA says and what the European Directive requires them to do is to show evidence of proper test performance. What Dr Suzanne Ludgate, who is the Medical Director, has always said to me is that they are only obliged to provide evidence if they make clinical claims, so if they do not make clinical claims they do not have to provide the evidence. Then when I try to push and say what is the standard of evidence that you require when they make a clinical claim, they do not know. What I am suggesting is that the standard of evidence should be that the gene disease association has been replicated and shown to be a real gene variant disease association according to what science has said. I do not honestly believe that the MHRA can go beyond that because once you go beyond that you are into multiple issues that they cannot possibly control.

Professor Trembath: A very brief comment on that, in actual fact, certainly within the academic sector, it is virtually impossible to publish these associations unless you have replicated them, so in some ways that becomes the entry point.

Q260 Chairman: Our understanding is quite clear that once the science has worked out that there is a gene disease association those are the ones that MHRA or somebody should be involved in regulating.

Professor Trembath: Yes.

Professor Bobrow: It is an Advertising Standards Agency-type comment that it is not only as Rob said but also the interpretation which is given by the company needs to be both accurate and put into some reasonable context.

Chairman: That is the second problem.

Q261 Baroness O'Neill of Bengarve: Lord Chairman, could I ask Professor Bobrow a little bit more about that. What context would one be putting it into? If I discover - and it may be correct - that I am a member of a population which has a five per cent greater risk than the population risk, it seems to me that I know nothing, in that I may of course in fact be a member of that sub-population who if you were to do a variety of further tests would be revealed to have a lower risk than the average member of the total population. The question is: what standard of presentation of these supposed risk levels would be something that would meet advertising standards? I am not at all clear what that would be.

Professor Bobrow: Nor of course, as you know well, is it easy to simply give a tick list. One could relatively easily set out what would happen in a genetics clinic as an example, so you would want to have both a relative risk and an absolute risk in order to put it into a population context, and you would want a clear but brief explanation of what you can do to modify or alleviate that risk and whether it is likely to work. Whether you could seriously regulate at that level of complexity I just do not know, which is why my instinct is that it is more a question of professionals being ready to go for people who make misleading claims in an ASA-type situation rather than trying to set an envelope for regulation. I know that is lily-livered but I cannot think of an easy way out of it. Could I make a distinction. I think the

web companies offer two distinctly different products. If you look at things like deCODEme and the 23andMe website, a lot of their emphasis is on doing your genome so that you can go and find out whether some chap you have met is your second cousin and other things of that nature. It is scientifically valid, it is medically irrelevant and I think it is very much a question of if you want to blow £1,000 on that, it is your business. That needs to be distinguished from people who are making medical claims which is the equivalent of giving medical advice.

Dr Zimmern: May I add one thing on Baroness O'Neill's question about labelling. The reality is with a medicinal product the label is on the box and you buy the product and you see it. With a diagnostic product the end user never sees the label and there is a real issue there about this. The other point is that the Global Harmonisation Task Force in the last two years has been looking at medical devices and, in particular, the risk characterisation of medical devices, and they advise that medical devices sold direct to the public should be at one category higher than devices that go to professionals, just by virtue of the fact that being sold direct to the public the scrutiny needs to be greater and the obligation to truth in labelling should be greater.

Q262 Lord Krebs: If I just pick up on this last bit of discussion. It seems to me that what you are both proposing, Professor Bobrow and Ron, is a distinction between regulation by a regulatory authority of the assay and self-regulation of the test or the interpretation. Self-regulation implies transparency by the provider about their own mechanisms of quality assurance and what the qualifications are of the people who provide the interpretation. I think that is the distinction you are drawing but I guess further to that, and I am now thinking of analogies with claims in other areas, particularly one that I used to be involved in, the health claims of the things that are sold by Holland & Barrett where glucosamine sulphate may alleviate joint pains, that will become regulated but previously was unregulated. There was a

voluntary initiative by the industry to present certain evidence and to abide by a certain code. Is that the sort of framework you would envisage? It was called the Joint Health Claims Initiative. It has now been superseded by European regulation. Is it a self-regulatory code like that that that you are envisaging?

Professor Bobrow: It was certainly the sort of direction I was moving in. I think your analogy is a very apt one and I have used it myself in the past. If you are really worried about people being mis-sold on the basis of health claims, genetic testing is not the place to start. There is a whole industry of alternative medicine that is orders of magnitude worse.

Chairman: But our focus is on genetics. Lord Broers?

Q263 Lord Broers: Just to comment but surely this is fertile ground! I am going to get down to technology now. Genomic science needs massive computer storage capacity, high band width and great computing power and expertise in information technology. Where is the need greatest for upgrades in IT, and what are the most urgent priorities?

Professor Trembath: May I just have an initial response to that because I have to say I think this question has to be put into the context of IT within the NHS per se. We are still very far short of having the appropriate instruments to maximise on the information that is currently embedded within the NHS and patient care and this is just a further dimension of it, so I do not really know that there is a specific here that is any greater than the general problem of Connecting for Health which we have failed to deliver at this stage.

Professor Bobrow: I am taking too much air time. You have got more expertise sitting next to you than I know of myself. I thought it was a very interesting question. As I thought about it, I truly am not sure whether we are going to need massive computing power in the NHS. When you are doing research where you are trying to dredge for data amongst these largish data sets there is big computing, although probably not big by some of the physical sciences' standards. Once you get down to defining 5,000 genetic markers which might be relevant in a

variety of disease situations you are dealing with less information than one high resolution photograph, so I am not yet clear whether we are in a diagnostic setting going to need really massive computing power as opposed to image processing power which ---

Q264 Chairman: You might need to do comparisons with large data sets.

Professor Bobrow: It depends what you call a diagnostic setting. I think that once you have got an absolutely established correlation and what you are saying is if we test for this, this, this and this and mix it up in some algorithm that will give us a risk prediction for Bloggs, the lab is actually not handling a vast amount of data in the way that an astronomer would be. I am shooting my mouth off in a field where I am not expert but that was my reaction after some thought reading that question and I would be interested to know whether real experts disagree with me.

Dr Elles: I think what has been said is true. The need for crunching terabytes of data will follow wherever the terabytes of data are generated, so it is a feasible model that huge quantities of data production will be outsourced from the NHS. I think that model needs to be examined and not immediately discounted, in which case the data handling would take place wherever that data is generated. I think a more immediate need, in some ways, which faces us day in and day out, and increasingly, is that we find variants in sequencing the DNA of patients and we are not always sure what that variant means so it is the task of the laboratory scientist to try and interpret that by comparing whether for example that variant has been seen in another laboratory in the UK. That search may need to go much further afield and ask where in the world has that variant been seen; is it associated with the condition; can we produce a sensible clinical report for that patient. To do that the tools which we have are relatively imperfect but the problem is a lot of those tools, a lot of the gene specific data bases have been developed for research use. We have talked about quality assurance, and often there is very little quality assurance in the data that is going into those research repositories.

Yet we are starting to need to use them for healthcare in the patient care pathway, so we have got to start to draw attention to the use of translating these research tools into healthcare and applying the same kind of quality standards as we would expect in other areas of healthcare. Another problem is that often these tools, if they are in the research context, are unstable, by which I mean the research funding ends and the tool disappears off the web and we are left high and dry in terms of not having a tool that is useful for healthcare. The emphasis has got to shift in some ways from the wet lab generation of data to the informatics and to making sure that these tools are quality assured and stable and fit for healthcare purposes. Another area which has not been touched on anywhere here is the question of where are we going to get the expertise in order to be able to access that data, to integrate it, and to interpret it at the laboratory level. We need a whole generation of bioinformatics-trained people, the brightest and the best, if you like, from the world of bioinformatics to come into healthcare and to help us to do that job and to interpret this genomic data. One problem which we perceive is that the current reform of training for healthcare scientists is to an extent making a straitjacket which I hope will not preclude us from being able to employ within the NHS bioinformatics specialists and turn them to the task of using their skills for healthcare. This is of real concern amongst BSHG members.

Dr Zimmern: Two points if I may. One is the way I look at informatics is that there is bioinformatics doing all the science, where multi millions of pounds have been put in, and there is clinical informatics, what the NMS is doing, again multi-million pounds, but there is a gap between the two and I have always felt that nobody has paid any attention to producing an informatics base which is for the evidence, if you like you could call it knowledge informatics, on which not a single pound has been spent, so the two are not being bridged. That is the first point. The second point ties up with what Rob has said about not enough bioinformaticians. I have for some years been concerned by the fact that, unlike doctors or

nurses or physiotherapists where there are institutions responsible for their manpower planning, there is nobody responsible for the manpower planning of genetic epidemiologists, bioinformaticians, biostatisticians, health technology assessment experts and health economists who have an understanding of genomics, and surely someone must take that responsibility. It is not good enough just for the MRC or Wellcome to say “We run fellowship programmes. That is the *crème de la crème* who get through and I am talking about the basic jobbing epidemiologist and bioinformatician and biostatistician for which we do need some idea of how many we need five or ten years down the line, because I genuinely think that without these people and HTA people who understand genomics we are not going to get that translational shift.

Q265 Lord Broers: I guess you have answered one of my questions which I was going to put colloquially; do you need more geeks or more kit, and it seems you need more geeks and that kit is not really the problem. These are rather sophisticated geeks of a new type but they are nonetheless expert.

Professor Bobrow: Yes.

Q266 Lord Broers: My next question is: will we get to a position where sequencing is low in cost enough and easy enough that we will include in everybody’s health record their complete genome sequence?

Professor Bobrow: It will be cheap enough but why bother?

Lord Broers: Why bother, all right.

Q267 Baroness Perry of Southwark: The Americans are talking about doing it, so we were told, they are seriously talking about every baby being sequenced at birth or within a few weeks of birth.

Professor Bobrow: From the viewpoint of someone who is selling the machinery I can entirely see the answer!

Q268 Chairman: This was NIX; it was not somebody selling it.

Professor Bobrow: Serious people have discussed it. I remain unconvinced that it is worth generating three gigabytes of data in order to capture 100 important points.

Q269 Chairman: All right, from a public health point of view, Professor Zimmern?

Dr Zimmern: I was on the working party that considered this. It was called, rather nicely, the Barcoding Babies Working Party, and I think we were very much against it for exactly all the reasons that you have said. Maybe in 50 years' time.

Q270 Chairman: 50, not ten?

Dr Zimmern: Certainly not ten but at the moment I see absolutely no sign. There are really important ethical issues about consent and stuff so barcoding adults at the age of 16 when they are able to give consent maybe, but certainly not barcoding babies ---

Baroness Perry of Southwark: Meanwhile most of the adults will be in the forensic database to which there is no access!

Chairman: Baroness O'Neill on that point.

Q271 Baroness O'Neill of Bengarve: Not on that point but we have heard quite a lot of evidence from you and from others of the increasing amount of genetic testing, and also it has already come up to today that somebody has to commission all these tests and interpret them. Do we have in the NHS the right skill mix, the right health professionals in other specialisms outside medical genetics to take on responsibility for commissioning and indeed for interpreting where maybe it is not a clinical geneticist who does the clinical interpretation for a particular patient?

Dr Zimmern: Certainly not at the moment and it really is an uphill struggle. I think first of all on the provider side - and my colleagues will be much better placed to comment - we need to think seriously in the context of genomic medicine about subspecialties and the accreditation of whether it is cardiologists, dermatologists, neurologists or dermatologists “with an interest in” because I think that when you deal with medical genomics as opposed to clinical genetics, (and that distinction is important because clinical geneticists deal with inheritance and deal with the families whilst with the medical genomics what we are talking about primarily is using genomic technology from a patient in front of them and treating that patient) we will need to really gear up and make sure that a proportion, and it may be a small proportion, of people in each specialty is appropriately trained now. I have no idea how much training they will need. Martin or Richard will comment: will 12 months be enough or 18 months, but at that provider level in the specialties. In general practice I think that is more about the general practitioner understanding risk and conditional risk and probabilities. They are already doing it with cardiovascular disease so where do we go from there? I do not know. Commissioners have very, very poor understanding. I started public health genomics in 1997 with the word “genomics” blazing but actually it is not about genomics; it is about putting modern biology back into public health, and I think one of the sadnesses about public health in this country is almost the eschewing of the medical model of disease of understanding cellular and molecular biology in favour of a social model of disease. It is important but we must bring the two together again. I think that is something that really needs working on and I have been totally unsuccessful in getting my public health colleagues to focus on all this. I have tried to suggest that we might even just have in every single strategic health authority one public health physician who is skilled in this area. There are other priorities directed at PCTs, at issues of inequality and so on and biology is just not getting onto the radar of service public health. In academic public health it is totally different and there are lots of excellent academic

groups working with geneticists doing the work. They are the people that need to give the input into commissioning and it is just not there at the moment.

Professor Trembath: I think we have already touched on the issue that within laboratory services in the introduction of these technologies - and we would assume this is accepted - they will come with the necessary quality controls. NHS laboratories will not introduce a new approach to something without recognising the need for those quality controls and, as a consequence, the necessary training both in the development of those technologies but then in the context of their interpretation. Within medicine I think the comments that Ron has made are pertinent right across medicine. I do not believe clinical genetics is any better placed to interpret at least those who are in the delivery of clinical genetics because they are better placed to interpret some of these things because they are predominantly outside the sphere in which any training has been provided to a standard clinical geneticist. I think it is really in the context of training across the breadth of the medicine and that is in discussion.

Professor Bobrow: Could I just make add one very brief comment to that with which I entirely agree. The degree of skill that the bedside doctor needs in interpreting is utterly dependent on the kind of report that comes back from the laboratory and the better the latter the less the former is an issue. Of course we want everyone to be fully up-to-date on everything all the time but in the real world it is easier to get to the report issuer.

Q272 Chairman: Would you not expect, particularly for genetics, that the report would have come with the interpretation?

Professor Bobrow: I would absolutely say that is the point at which to make it work properly, so that you do not expect the physician to have to do a lot of complicated stuff for which they were not trained when they qualified 20 years ago.

Dr Elles: Laboratories for a long time have taken this issue very seriously and you can imagine just sending back some string of numbers and letters back to a physician of almost

any type is almost completely useless, so the scientists have to translate that into some information that they get from the referring doctor about the clinical parameters which led to the referral, the gene type and the interpretation of the variant to try and help generate a genetic risk for the patient. That has been what we see as our job for a long time. I think that whether this business grows that should be a focus of what the laboratories do and should continue to be an important facet of what they do. That is why I think we need scientists who can go out there and search databases nationally and internationally and then make best use of that variant data which they generate.

Q273 Baroness Perry of Southwark: Following on from that discussion, within the specialty of medical genetics genetic counsellors are playing a substantial role and are clearly very important. Do you think that that would also carry through to specialisms other than genetics? Would there be counsellors there?

Professor Bobrow: Everyone is being so quiet! There are already specialist nurses playing an enormous role in diabetic clinics and prenatal, all sorts of places. I can see no reason at all not to assume that that is a sensible way to go.

Q274 Baroness Perry of Southwark: It follows very much from your point that the genetics specialists themselves probably do not have the expertise in lung or skin or whatever to give a great deal of detailed counselling to patients, and maybe there is a bridge between the genetic information and the specialism.

Dr Zimmern: I think the key is the distinction between what you do in the context of an inherited disorder and what you do with those complex disorders where it is just risk information. By tradition more than anything else, and there are good reasons why in inherited disorders like Huntington's you need special people called genetic counsellors, but it is this conflation of the word "genetic" in the different spheres. Just because the technology

you use is DNA technology rather than biochemical technology, why you need a special person called a counsellor to interpret your cholesterol level or your blood glucose level if you look at it in those terms, it sounds crazy, and I think in the common complex disorders we are just talking about risk, so to me the issue is about getting all physicians and all nurses better trained in an understanding of risk and delivery of risk information.

Q275 Chairman: How much is it a reality that will happen? Is it ever going to happen?

Professor Bobrow: It is definitely happening. It is not terrific but it is certainly happening. There is no question ---

Q276 Chairman: You are struggling I sense.

Professor Bobrow: There is no question that medics and even the nurses in the wards today are infinitely better informed about genetics than they were when I was a lad when they were not born. There is much more knowledge but it takes a generation for the stuff to seep through.

Dr Elles: There is a role to give them help and assistance, by which I mean desk top access to accredited good information sources, so they may not need to know everything but they need to know where to get the information and where to get information that is reliable. There are some good examples of expert systems which have been put in in a primary care context, for example, to help the nurse make a preliminary assessment of a family history of breast cancer. In many cases they can reassure but in some cases they just need to know the limits of their knowledge and where it is necessary to refer on to the doctor and maybe refer on to a specialist service.

Q277 Chairman: Do you think there ought to be authoritative information available to the public in terms of genetic risks and gene association risks?

Dr Zimmern: This is the idea, Lord Chairman, of the Royal College of Pathologists and we recommended that there should be a publicly accessible database. We used the analogy of a patchwork quilt and we used the Wikipedia analogy because this information is not going to be there on day one, so as information gathers.

Q278 Chairman: So who should be responsible?

Dr Zimmern: At the moment there is nobody responsible for developing such a database and this is exactly what I mean by the fact that we have bioinformatics and clinical informatics but no knowledge informatics in the middle to give that sort of information.

Q279 Baroness O'Neill of Bengarve: To go back for a moment to the quality of the report that interprets the significance of genetics, that would suggest other data for an individual. Should the setting of quality standards there be a professional task? If so, which professions, and should the same standards run across the tests commissioned within a medical setting and tests purchased for non-family history reasons that are sold over the counter or across the Internet?

Dr Elles: For many years the Clinical Molecular Genetics Society and parallel societies in Europe have been developing best practice guidelines and they focus very strongly on the interpretation of genetic variants. That is considered to be professional best practice and is integrated into the training of scientists. So why should the same standards not apply to tests produced in the commercial sector? I think if the professional standards are there and they can be referred to, yes, they should be apply.

Q280 Chairman: Anybody else? In the earlier questions, Professor Zimmern, you inadvertently began to drift when you were talking about gene disease association into environment. We have had some comments that it is not just genes and disease and gene

disease association, it is the environment, so-called envirogenetics which are more important and we are not putting enough weight on that side.

Dr Zimmern: I think that is absolutely right. When public health genomics started as a specialty in 1997 I used to say the holy grail and that this subject was nothing to do with, as I put it, mucking around with the genome; it was nothing to do with dealing with DNA; it was understanding the concept there could be sub-populations based on genes on which you could apply absolutely bog-standard public health interventions. My colleague, Dr Paul Pharoah, has got a very good example of this and he says that within a very few years one might be able to understand the biological genetic risk of women with breast cancer, and one might be able to segment the female population into four segments, and one might then be able to give more defined advice for mammography depending on in which segment you were. He uses as an illustration that at the moment the absolute risk for a woman of 50-55 of getting breast cancer in the subsequent ten years is something like 1.9 per cent. He has done modelling on this and you can segment into four risk groups. I cannot remember the exact risk, but if you were in the lowest risk group you would not be at that same 1.9 per cent absolute risk until you got to the age of about 70 whilst if you were in the highest risk group you would be at the same 1.9 per cent ten year risk at the earlier age of 40. This is very crude stuff and it does not take into account the difficulties of mammography and the younger breast and all that, but it does show that if we are going to be rational about it there are ways fairly soon where one might say, well, it is surely rational to give the intervention at the same absolute risk rather than willy-nilly age 55 you enter into that programme. It may even be that for those at the lowest risk you might not recommend mammography because the risks outweigh the benefits. This is one very small example of how in the public health as distinct from the individual clinical context where we are agreed that paradoxically in the public health population context there might be a greater potential for some real action rather than at the individual.

Professor Bobrow: As a matter of clarification, is Dr Pharoah talking of making a risk assessment for each individual based upon a variety of genetic and non-genetic factors?

Dr Zimmern: No, in this case the modelling was done on the genetic factors based on all these moderately low relative risk genes. He has known that there is six-fold difference between the highest five per cent and the bottom five per cent in that curve in risk and therefore he models that it is possible to segment the population and give different preventative advice so that they get the interventions at the same absolute risk.

Q281 Chairman: It is very interesting that you are answering the question about how you interpret different risks in different groups but my question was more related to the effect of the environment and other issues on the genome or even genetics, for example markers for disease.

Dr Zimmern: In public health terms there is no doubt that smoking and nutrition are going to be much bigger so you start off with these risk prediction models, you start off with age and sex and you start off with smoking, and then you start adding these other bio-markers in, and what we do not know but we suspect is that adding these biomarkers in will not improve the risk prediction that much but it might improve them significantly enough that in certain circumstances you might, I just do not know, if you had definite hypertension you would take the pills but if you were borderline hypertensive, 145 over 90, is it possible I just ask myself that if you just happened to have a set of genes you might decide to take the pills but if you did not, you would not; I do not know. It is that sort of level.

Professor Bobrow: For me this is a matter of assessing risk in order to lead people down one of a number of defined choices and I can see no logic in assessing the risk due to genetic factors separately from the often much greater risk implications of non-genetic factors which seems to me part of the package, rather like in screening for Downs where there is an awful lot of biochemistry but age is still the dominant factor.

Q282 Chairman: Are we linking the two here? In terms of implications to the Health Service we have to link the two together; are we doing that?

Professor Trembath: I would argue that that remains an academic activity at this stage because we are only just now getting the insight into the genetic determinants of what has to happen, but it is at an academic level in the first instance the integration of any information we might have with regards to environmental exposure. The problem of course is that in many instances our data sets are incomplete in both domains. It is an academic exercise at this stage. We do not have that information for the majority of our common complex diseases to allow us to create models on direct implications for the NHS.

Q283 Chairman: So until we have that knowledge a devil's advocate might say we should not make too much investment in genetic sequencing or genetic marker identification?

Professor Trembath: We need investment in to generate that knowledge but in the context of the delivery of service then we have to await the acquisition of that knowledge.

Professor Bobrow: With the exception that there are some well-defined genetic conditions where Rob will tell us that you do not want to stop investment because we are still not that fantastic at doing ordinary genetics.

Q284 Chairman: Okay, my closing question, if you were asked what would be your three key strong recommendations or areas of recommendation, what would you like to see in our report as three key strong recommendations? No promises they will be there!

Dr Elles: Lord Chairman, the message from the BSHG is that the White Paper investment was a great boost in recognition of the strength of genetics in the UK. That is five years ago now and if we are to realise the benefits that have rolled on since then for knowledge of the human genome sequence then we need to continue that investment stream. Genetics is not a box that has been ticked. The ambition in the White Paper of rolling genetics out to

mainstream medicine is increasingly a reality, and genetics is no longer confined to specialist genetics, and so that is a theme which has become a reality. The second thing I would suggest, which is perhaps more detailed, is that the volumes of information which can potentially be generated will lead us to, as we have discussed, focus some investment in bioinformatics, and as has been said, at this stage we would like to see more geeks, more bioinformaticians coming into the area and for us not to develop policies which preclude the recruitment of specialist bioinformaticians into the health service to help directly in patient care.

Q285 Chairman: You do not have to cover all three. I was hoping you were going to assist us.

Dr Elles: That is probably enough.

Dr Zimmern: My three would be that first of all we need to set up mechanisms for getting the data for test performance and setting up systems or institutions that will do their analysis, as we have discussed. My second is really to pay attention to the distinction between translational research, which I think we are now actually through NIHR doing much of, and the need to fund the actual nitty-gritty act of translation and getting research into practice through working with commissioners and so on. I think my third is really a very general thing of avoiding genetics exceptionalism. We have this working party called genomic medicine but really it would be helpful if your Lordships could emphasise that this is really an iconographic name for modern biology and there is nothing about the genome nothing that could be said that should require genetic tests to be regulated in a different way to other forms of predictive testing or anything else.

Professor Bobrow: I think I would start with the need to formalise the place of diagnostics in medicine, and that includes both the appraisal of diagnostics, the commissioning of diagnostics, the whole bundle of taking diagnostics as seriously as we have taken therapeutics

in terms of setting objective standards and monitoring them properly. That would inevitably, in my view, lead us to consider a much greater degree of integration of the laboratory disciplines and break down this now century old division into haematology and histopathology and so forth and start bringing the processes together because they are inherently similar and becoming more so. I would keep the research going because we are talking as though we have learned what there is to learn but we are really at the beginning of the road. I would definitely find some much more structured way of that research including pragmatic trials of diagnostics, which is the point that has been made several times. It is almost impossible to get diagnostic trials funded and unless you do it that way you never get real evidence of the thing that Ron has talked about. My third one is to keep training everyone because in the end educated professionals answer many of the questions that you are grappling with and an educated public is by far the best defence against charlatans.

Q286 Chairman: Do you want to add anything, Professor Trembath?

Professor Trembath: Being the last it makes it very difficult, particularly following Martin Bobrow and as an academic, but whilst I certainly do not advocate the notion and I cannot see the benefit of barcode sequencing every baby born, I think the issue of maintaining the research component is exceptionally important, but thinking much more about that in the context of patient populations which are within the NHS, and I think that overlaps very much with what Martin is alluding to that this has to be established as its utility for diagnostics and that means its utility within an NHS service.

Chairman: Gentlemen, thank you very much indeed, you have been most helpful in helping us with our inquiry and we appreciate you coming in. Thank you.