

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

WEDNESDAY 16 JULY 2008

PROFESSOR SIR JOHN BELL and PROFESSOR SIR ALEX MARKHAM

Evidence heard in Public

Questions 421 - 474

USE OF THE TRANSCRIPT

1. This is an uncorrected and unpublished transcript of evidence taken in public and reported to the House.
2. The transcript is not yet an approved formal record of these proceedings. Any public use of, or reference to, the contents should make clear that neither Members nor witnesses have had the opportunity to correct the record. If in doubt as to the propriety of using the transcript, please contact the Clerk to the Committee.
3. *Members* who receive this for the purpose of correcting questions addressed by them to witnesses are asked to send corrections to the Clerk to the Committee.
4. *Prospective witnesses* may receive this in preparation for any written or oral evidence they may in due course give to the Committee.

WEDNESDAY 16 JULY 2008

Present

Broers, L
Finlay of Llandaff, B
Krebs, L
O'Neill of Bengarve, L
Patel, L (Chairman)
Taverne, L
Warner, L
Winston, L

Memorandum submitted by Academy of Medical Sciences

Examination of Witnesses

Witnesses: **Professor Sir John Bell**, Chair of the Office for Strategic Coordination of Health Research (OSCHR), President of the Academy of Medical Sciences and Regius Professor of Medicine at Oxford University, and **Professor Sir Alex Markham**, Professor of Medicine at the University of Leeds (Leeds Institute of Molecular Medicine), Chair of the Office for Strategic Coordination of Health Research (OSCHR) Translation Medicine Board, and Chair of NHS Connecting for Health's Research Capability Programme, examined.

Q421 Chairman: Could I welcome you both first of all, Sir John and Sir Alex, and thank you very much for making time to come and see us. We regard this session as really very important; please feel free apart from the questions to comment on any other issues that you may wish. Can I also welcome the public at the back; you will find information relating to the interests of the Members, please help yourself. We are webcast so we have to keep private conversations to the minimum or as quiet as we can, but the best is to avoid it. I will invite you to make any initial comments that you have, either of you, but the first time you

speaking it would be helpful for the record if you would introduce yourselves and, if you do wish to mention who you represent, that is fine.

Professor Sir John Bell: Thank you very much, My Lord Chairman. I am Sir John Bell and I guess I hold three jobs that are relevant to this: one is the Regius Professor of Medicine in Oxford, with a background in genetics, particularly in immunological disease, the second is the President of the Academy of Medical Sciences and the third is the Chairman of OSCHR. Alex, why do you not introduce yourself?

Professor Sir Alex Markham: I am Alex Markham, I am the Chairman of the OSCHR Translational Medicine Board, I am also the senior responsible owner of a programme in the NHS Connecting for Health activity called the Research Capability Programme, and my day job is that I am the Professor of Medicine in the University of Leeds.

Q422 Chairman: Thank you very much. Does either of you have any opening comments you want to make?

Professor Sir John Bell: I just wanted to start by saying that this particular inquiry is extremely timely because we are at one of those inflection points that you get in medicine every so often where there are very significant opportunities to apply this methodology in a patient setting and having a clear strategic view about how one would go about that at this moment in time I think is very timely, so I must say I welcome the inquiry.

Q423 Chairman: Sir Alex, do you have anything to add?

Professor Sir Alex Markham: I would only echo what Sir John has to say but I would also perhaps add a word that modesty prevents him saying himself and that is that this inquiry takes place against a backdrop of one or two years of successful work in changing the landscape in the UK in the way that we do manage significant change in medical research, and OSCHR has had a very successful first year or so of activity. Some of the issues that you

have already had brought to your attention about the challenges in genomic medicine, particularly things like informatics and the way that new discoveries are pulled through in the so-called translational setting to be applied for patient benefit; there is an awful lot of work being done in those areas and it would be good to reassure your Committee that that activity is already taking place. You can have a good look-see at what has been achieved so far that might be of relevance to your deliberations.

Q424 Chairman: Thank you very much. That actually leads into two questions that I have. One is probably more directed to you, Sir John, and the other one is probably more directed to you, Sir Alex, but feel free to comment, both of you, on both questions. The first one to you, Sir John, is we have had a lot of evidence now about the way the science of genetics and genomics is going, particularly in relation to common diseases, and although the progress of science is extraordinarily rapid there is some concern as to how much of this is going to translate into healthcare, particularly the understanding of common diseases. What is the evidence that these advances are important and where do you expect these advances to lead us and in what timescale, particularly the use of these tests in understanding and identifying common diseases.

Professor Sir John Bell: I suppose I should say that I am on record in a paper I published in the *British Medical Journal* in the mid Nineties saying that the timeframe would be five years and that timeframe lapsed about three years ago, so I am on record of getting the timeframe wrong once before – that is a health warning. There have been really dramatic changes in the pace at which the discovery process in this arena has developed, particularly in the last couple of years. We cannot really do anything unless the discovery activity is delivered and you will have heard the information about large whole genome association studies, the abundance of new genetic variants but also the discovery of new technologies that make this much easier to apply in a more routine setting that generate more specific and more substantial data that

could be available to us. In my view, therefore, there is likely to be an incremental growth of its use in common complex traits, but it will not all happen overnight and you have to differentiate the use of these tools for prediction of asymptomatic people early in life, perhaps at birth, which I think may happen but is not going to happen in the short term. There are a whole set of things you have to put into place for that to work, and separate those from some of the applications of genomic technology which can be applied in an active clinical setting, which would involve stratification of patient populations, identifying responders and non-responders to particular types of therapy, monitoring therapies and genetic tools. All those things are likely to happen in a very short timeframe, particularly as the incentive to do it is enormous and I think there will be a huge amount of effort to try and make that deliver in a relatively short timeframe. If you want me to put a number on it, certainly within five years there is going to be a lot of activity in this arena using genomic technologies, broadly defined, for common disease.

Q425 Chairman: Are we investing enough in the big science related to genomics to make this happen?

Professor Sir John Bell: How much is enough and of course scientists could always claim they could always use twice the budget, but the truth is the UK is really, really competitive in international terms. In fact, you might argue that we are now entering an era where we are actually right out in front so if you look at the output of large case control studies there is no doubt that the best data and the most data came out of the UK studies. If you look at studies like the UK Biobank project, which is essentially a large genetic project in common disease, everybody else in the world would die to have a project as good as that. So when it comes to applying genetic technologies in a setting where you have well-characterised patient populations, and people who are willing to participate in research in very large numbers, the

UK is uniquely positioned. Of course I would say we need more money, my job is to say we need more money, but the truth is we are doing really well in the basic sciences.

Q426 Lord Taverne: You are optimistic about this. We have had some more pessimistic views about the short term benefits we are likely to see, really based on two propositions, that either the extra risk in the case of common diseases that you discover is relatively small – it might be a 30 per cent increase but from a very small base – or else in cases where there was a cumulative build-up of risks the actual cohorts affected were very small so that the prospect of early benefits were really not all that great.

Professor Sir John Bell: Let me just go back to a comment I made earlier, and that is I think if you focus your attention on the snips associated that have emerged from whole genome association studies and you say that is genomic medicine, then you would be very badly wrong. That may be genomic medicine but there is a whole set of other tools that are having an impact today. You will have heard about the comparative genome hybridisation arrays – CGH arrays – which are now systematically being applied to a whole range of disorders in clinical genetics laboratories, including all the major leukaemias, many of the common cancers and a number of developmental disorders. It is not being applied to diabetes but it is being applied to a whole range of other diseases and those things are starting to happen in clinical practice, and it will completely replace the whole area of cytogenetics which has historically been a big activity in the NHS. That has gone because no one would sit at a microscope and look for translocations and deletions and duplications when you have the other tools that allow you to do that much more systematically. So there are really good examples of how those things are already impacting. The whole issue of stratification might relate to the snips that are emerging from whole genome association but it might not, you may not need those because a lot of it can be generated from direct sequence data, from transcript profiling data, from all the other tools that are available to this field. I think, therefore, that

the concern about predictive testing and the relevance of the whole genome association data from predictive testing is fair; we do not yet know what that will do if you add up all those very small risks, what it will do in a population to identify people and what you would do if you had that information anyway. That is why I said that predictive testing in asymptomatic people is actually, in my view, the last thing that is likely to play but all the other things are beginning to play now and are likely to continue to play actively, so I guess it really depends on where on the landscape you want to place your bets.

Q427 Chairman: Have you got enough facilities for C-fast sequencing?

Professor Sir John Bell: As you will have been told the revolution of the last two or three years has been the new generation to sequencing and it is truly revolutionary because the capability of the new machines is allowing geneticists to generate data – interesting sequence data – at a rate and in different dimensions that we never dreamed we would be able to do. At the moment there are three common platforms that people are using and some are better for clinical diagnostic use than others but, for example, in Oxford we have just installed two 454 machines with the intent of using them in a purely translational mode to actually facilitate clinical diagnostics of all kinds. One of the crucial issues that that has made available to us is that you can talk about all kinds of surrogates of information which is genetic information that you might like to have which would include snip variation, would include transfer profiling variations, would include all kinds of intermediate measures from which you infer a particular outcome, but the truth is the ultimate sort of data that you can generate is sequence data and if you can get sequence data the chances are you may not need any of the rest of it, so the ability to generate large amounts of sequence data becomes very central. Let me also warn you that this is the first of several waves of new sequencing technology and I am familiar with at least one other platform which is a UK-based platform which will be capable within five years of generating, for around \$1000, a whole genome of an individual in a very short timeframe.

That is the next wave of technology, so one has to be conscious of the fact that we are going to be at the receiving end of almost unlimited amounts of genetic information and the real questions are what useful information can be gleaned from the basic data and is it useful in a clinical setting, does it have clinical utility. That is a big hurdle and one which we have not been very well-positioned to address up to now, I have to say. Secondly, what is the best structure to generate that data, is it better just to sequence everybody at the beginning and have them carry it around on a chip, or is it better to do it disease by disease, is it better to do it in regional labs, is it better to do it in local labs; there is a whole cascade of issues that emerge once you have the evidence of clinical utility.

Q428 Chairman: Alex, do you have any comments?

Professor Sir Alex Markham: Maybe it would be helpful if I went to other end of the spectrum here and in anticipation of a cascade of development, both technological and scientific, do we have any structures in place that are thinking about how we might handle this? In the cancer world we have been working along these lines since about 2004 and there is a thing called the National Cancer Research Institute Informatics Initiative with all of the funders, including the industrial sector, looking at how we will pull together this massive cascade of data as it emerges, anticipating that it will probably be several orders of magnitude bigger than we envisage today, and also issues like how we integrate it with the USA and other parts of the world. There is some very solid thinking that has gone into that and has all the major research funders engaged in it which gives me a level of confidence that we can deal with the sorts of challenges that John is throwing up for us. The other piece of work again in the cancer arena is that for the first time we are now looking at the data that is collected in cancer registries; that has been a statutory requirement since 1960 and we have wonderful data on everyone who has had cancer in Britain since that time – nobody has ever looked at the data. This work was the source of the news items of two or three weeks ago,

highlighting the difference in death rates in the north of England from lung cancer versus the south of England, and it is really a bit scandalous that that sort of thinking and information was not looked for from the public eye. The cancer world is therefore doing a lot of thinking about this and always the UK clinical research collaboration activity builds on that kind of pioneering work in the cancer sector. All of the efforts that are now going in through OSCHR, through its e-Health Board, and through the Department of Health through the Connecting for Health process with this new programme called the Research Capability Programme, that is all about setting up the systems that will enable us to handle this tidal wave of information under the right limitations of good governance to ensure all of those vital components of this game, that patient confidentiality is maintained, that this is not on the front page of the newspapers on a daily basis when data is lost. That challenge therefore is equally as important as the technical side.

Q429 Chairman: In your role with Connecting for Health do you think the NHS has got the capacity to do that, particularly about confidentiality of patient information?

Professor Sir Alex Markham: If we do not then I guess it will be my fault. The problem with the confidentiality landscape, as you will know from many reports, both from this week with the Walport and Thomas report on data sharing, back through reports of the Academy of Medical Sciences, the reports pile high but the solutions are a bit more elusive. We have so many bodies that see themselves as the ultimate guardian of the patient's best interests that it is actually quite difficult to pick your way through the landscape. You can name the Information Commissioner, the National Information Governance Board, the Patient Information Advisory Group, the General Medical Council, the British Medical Association – all of these bodies consider that they have something fundamental to say about that issue and it might not have escaped your Lordships' notice that actually none of those organisations actually can claim to be the last port of call. One of the biggest workloads for me is at the

moment working very hard with all of those bodies to very simply say “I am not here to do something cavalier with the patient information” but there is nothing more unethical than preventing ethical medical research taking place, and some of your bodies ought to give that just a little more weight in their deliberations. There is a real challenge there and I do not under-estimate it for a moment.

Q430 Baroness O’Neill of Bengarve: I want to put in a very quick supplementary which is just this, who is the last port of call on the model we have put ourselves in on the protection of personal data, could it be Parliament and the particular character of the Data Protection Act 1998?

Professor Sir Alex Markham: I think it is that and, obviously, the owner of patient records is actually I believe – Lord Warner will correct me if I am wrong – the Secretary of State for Health. There is a mechanism, therefore, but I am not sure if this personal view is correct. A lot of structures have come into existence as a result of scandals like Alder Hey, like Bristol, like the Shipman fiasco and they do not fit together coherently. They were all done with best endeavours, with absolutely the right desire to preserve patient confidentiality and hold the medical profession to account, but the result is a very fragmented landscape that somehow we need to pick our way through and I do not pretend to have a complete solution to that. We are going down a route of primarily using anonymised data and of building robust systems to use pseudonomised data, i.e. to remove all identifiers from public clinical records, but there are going to be some cases, particularly in the genetics arena, where it will be important to be able to go back to a patient who is found to have a previously unanticipated problem, and that whole question of how do you get consent for consent to approach somebody who does not know they have a problem at the moment is very difficult.

Q431 Lord Warner: Sir Alex, could I just try and get something clear because it is a very complicated but very significant area. Of what I would call two of the “pillars” on which we have operated so far, pillar one has been that the use of any material which has human cells in it is actually something on which you need to consult and require, in most cases, the approval of the patient from which those cells are extracted. That is underpinned by the legal interpretations that have been made of the European Convention on Human Rights as enshrined in the Human Rights Act in this country; that has been the first pillar. The second pillar has been that for research purposes you need consent but you reassure people by giving some assurances about anonymity in the way it is used. Are you saying that those pillars which have underpinned most of the way we have acted over recent decades – they have been more refined but they have been the basic principles – are a problem or are you saying that the mechanisms which have been used to interpret those principles have got into a mess and it is the mechanism that you need to get right, not the principles themselves?

Professor Sir Alex Markham: Absolutely the latter, the principles are fine but the mechanisms have got bent out of shape. Maybe that is a personal view but I think a lot of people will share that. I think as a consequence of the level of confusion instead of taking, based on those two fundamental pillars, a clear message to the public which says you may be interested to participate in this – I will give you an example if I may, just jumping aside slightly. The experience with UK Biobank was that there was an enormous debate as to whether it was ethical to write to individuals, uninvited, and ask them whether they would consider participating. The question was could you go to general practice records, which are actually very accessible electronically, it is not something the public really realises, just how accessible GP records are – in the most ethical ways – could you write to people and say there is a programme going on and we are trying to recruit 500,000 people to do this thing, and most people we think would think that is a good thing to do. There was a huge debate as to

whether you could get consent for consent in that way, a huge debate, and it was touch and go actually whether that whole Biobank programme crashed and burned or whether it could go ahead at all. Eventually, I believe that the Director-General of Research and Development was the signatory of those letters to individuals and the result of that exercise was that of every 2,500 people who were approached, one said “I don’t want my personal records used in this way” but 200,499 basically said “Fine, how could I possibly object to this.” That is where we are at with the interpretation. The principles are pretty solid but I think most of the community involved in making these decisions is in a defensive mindset and they do not realise what I see in the clinic every day, which is when I ask patients questions like this and say “Look, I cannot ask you to be in a trial because in a way that smacks of coercion, you had better go away and think” and they say, “Doc, what is the matter with you, you have been looking after me for a fortnight.”

Q432 Baroness O’Neill of Bengarve: In some ways this question has already been answered, which is the question about the clinical utility of a lot of these exciting new scientific discoveries. We have been hearing from witnesses already that there is not very much evidence yet that the new genome profiling tests have useful healthcare applications. We have also heard evidence of data in recent publications – for example on screening for breast cancer susceptibility genes – suggesting that the new tests might be used for stratifying the population for breast cancer screening. Where do you think we are on the clinical utility of these advances?

Professor Sir John Bell: I think you are seeing just the front edge of what will be quite a significant wave of activity to try and demonstrate clinical utility. I think the sceptics – who I have to say were sceptics 15 years ago when I wrote the article, they are the same guys – will believe that genetics is really only applicable in diseases where the penetration is 100 per cent. It is clearly applicable there and nobody disputes it, it is fine, you can have a little

cottage industry that does that stuff – you know, it is okay, it is not going to have huge effects on the health service but it will help some patients and that is a good thing. The real question is whether these tools – and I am defining genetics very broadly here – will have an application across a much broader swathe of what we are doing in clinical practice. The suggestion that the data that comes out of the whole genome association data, with relatively small but robust odds ratios, can be used to stratify patients in breast cancer screening is an interesting idea but we will need to see the data, so I am the first to say show me the clinical utility, it will be important. There is already though data which is being generated – and we will see the data within a few months – of transcript profiling to separate women with breast cancer into high and low risks groups in a way that you cannot do with other technologies, and that may allow some women who would have been exposed to chemotherapy to be able to avoid chemotherapy, and other women with bad prognosis disease who would not have been treated aggressively to be treated aggressively. Those might be – and I say might because the clinical utility data is not fully complete – in light of the early data a very strong marker and we do know that the starting point is that the way we practise medicine is incredibly inefficient. Only 30 per cent of the people we expose to a new medication respond to the medication, so how does that work; 70 per cent of people are not getting any benefit and yet we cannot identify those 70 per cent when we screen. The whole process of breast cancer screening is unbelievably inefficient – that is not to say we do not support it, it is a good thing to do, but it is really inefficient. Another very good example, which is much more tangible now is cervical cancer screening. Cervical cancer screening has gone for years with cytologists looking at pap smears down microscopes, with about a 50 per cent sensitivity. Jack Cusack has done some nice work to show that actually the sensitivity is about 50 per cent so you identify the problem about 50 per cent of the time. By using genetic tools to look for papilloma virus and the two strains which are oncogenic, which are 16 and 18, you can

rapidly get to a position where (a) you might be able to eliminate the pap smear altogether, which would be a significant benefit, but you also get up to a sensitivity which is nearer 90 per cent, and it is easier and it is more efficient and you do not have all the errors you get in cytology labs and you are not running around chasing what is actually a rather inefficient procedure. That is here today, in fact the labs will be doing it today, but it has not been rolled out on a national screening programme anywhere, but it seems to me inevitable that it is going to happen. I go from caution, therefore – I think justified caution – about predicting how much early prediction you can do to the absolute confidence that some of this will have a big impact on the way we practise a whole variety of bits of medicine. Let me just remind you also – because I think this is a really crucial thing – that the pharmaceutical industry has never really been very interested in stratifying patient populations, because if you can sell a drug to a big population, why would you want to sell it to a small population – in very simple terms that is correct. But the pharmaceutical industry is also realising that it is actually quite difficult in the modern world to discover new innovative medicines that have a very high efficacy signal, which in other words actually have a beneficial impact on 50, 60, 70 per cent of the people who receive it. They can only get from where they are now to where they need to be by stratifying the patient populations. They are not going to be able to stratify it by asking who eats cornflakes in the morning, it is going to have to be something robust and it is going to have to be genetic tools, there is nothing else that will get them there. We already have a hint in Alex's game where a drug which was developed by AstraZeneca called Iressa, which showed promising results in phase two, failed in phase three because there was a subset of the population that had a genetic variation in the target, the EGF receptor, who were highly responsive to the drug, but the people who did not have that genetic variation were non-responsive. That information is make or break for a new agent, so my view is that there will be enormous pressure to use this in those kinds of settings and they may not be the early

prediction of common disease which is, I accept, a goal eventually of this technology but not proved. It will be in a whole host of ways that we use these in the clinic in common everyday diseases and it will, I think, encroach on almost every aspect of medicine.

Q433 Baroness Finlay of Llandaff: I wonder if I might just follow-up on the comments about pharmacogenetic data initially and ask you how soon you think some of these tests are actually going to become available in clinical practice and be rolled out. I am asking you to crystal ball gaze again.

Professor Sir John Bell: There are two types of tests, one type is prevention of adverse effects which largely tests around metabolic function to try and make sure people are on the right dose and also by trying to identify the idiopathic adverse effects that you get with some drugs. We are starting to fill that story in rather more effectively. We know quite a bit about drug metabolism now, we know about variations in the P450 cascade, there are available tests in that arena already that I have to say are not widely used, again for the clinical utility problem that nobody can jump that hurdle, and in terms of idiopathic adverse effects the group in Oxford led by Rory Collins, who has done probably more work on statins than anyone, has done a beautiful piece of work which I believe is now in press. The big adverse effect from statins is a myopathy that can sometimes be fateful, and given that in this country it looks like we are going to put everybody on statins over the age of 50 it would be kind of nice to know if you are going to drop over. It turns out that there is one gene that is responsible for that, they know what it is and they know what the variant is; it is a transporter gene that actually pumps the statins out of the muscle cells and when it has got a mutation in it, you do not pump the statins out and you get a myopathy and then you die. Okay, it is rare but were it cheap would we want to know that information before we prescribed the statin? I think a clinician would want to know that, so a lot of this has got to do with how do you get the clinical utility and then how do you get it out there and used in an efficient way, because

the last thing a GP wants to do is to decide somebody needs to go on a statin and then wait a month to get a result of a test that he cannot interpret anyway. It has to be clean and tidy and easy for practitioners to actually access information that gives them good decision-making tools on a clinical pathway. It seems to me that that piece will come together but there is a series of hurdles around the clinical utility and implementation of the information once you actually have it.

Q434 Baroness Finlay of Llandaff: What about cost? You have not alluded to cost at all.

Professor Sir John Bell: The cost-effectiveness of screening everybody for a statin variant when such a small percentage of people have problems will be pretty suspect. I have never done the analysis, but you can imagine what it would look like. Rory I guess had 150 patients – he looked at 40,000 in trials so that is roughly what you see. In my view the best way to do this will be to bundle it; the great thing about genetics is you can get the answers to all the questions in one test because you answer all the questions on one chip or you answer all the questions on one genome sequence, and then you extract the information you need out of that. If you say there are about 100 things that would be interesting to know, that would be useful in clinical practice, and for 1,000 bucks we could sequence the genome and stick it on a chip and extract the information, then the cost-effectiveness starts to change quite dramatically because basically you are bundling all the information a person might need in their entire lifetime in a single test.

Q435 Baroness Finlay of Llandaff: If we look at the possibility of getting genomic data versus the possibility of having gene expression data, then of those types of tests which do you think is the most mature and which do you think is likely to come into clinical practice soon?

Professor Sir John Bell: The one that is most mature is the gene expression data platforms and that is because they launched early in this guy's business in cancer. There is now a very substantial amount of data and there are a lot of clinical utility studies that are almost ready to report – in fact FDA has actually approved the (?) test for breast cancer based on clinical utility data, so that is mature, but I do not think you need to assume that because it is mature that will be the definitive way to approach this because it may well be that you can infer almost all that genetic expression data from what is present in the germ line. We know that there is an expression, QTLs, which relate expression levels to genetic variations in DNA – germ line genetic variations are well-known in all diseases. In fact, it may well be that the definitive data will come from the DNA and not from the RNA but in the interim it is clear that RNA data is providing people with some rather interesting clinical signals.

Q436 Baroness Finlay of Llandaff: Do you think that DNA data though is always going to need to be backed up by gene expression data?

Professor Sir John Bell: No. Do not forget there is both the germ line data and in cancers there is the somatic data, so one of the reasons you get these strange expression profiles in cancer is because you have all these somatic notations and duplications of lesions and bits and pieces and new variants, so being able to generate that from the tumour itself is actually quite powerful.

Q437 Baroness Finlay of Llandaff: Do you think that that type of information will be coming out of depositaries such as tumour banks or do you think it will all be coming from patient direct data?

Professor Sir John Bell: Alex, I will pass that one over to you.

Professor Sir Alex Markham: Some of it will be coming from tumour banks most definitely, and we have already got cancer genome projects in the UK and your Lordships have been to

see the US equivalent, so there is huge ambition for that. I have to say that so far their output has been a bit disappointing, that you are not finding consistent changes across similar groups of tumours when you start looking for consistent themes, but it will come, so we need tumour banks – and we have those now in the UK – and a lot of work will be done with individual patient samples still, which of course is all that tumour banks are. I think there will be interesting things in pharmacogenetics; some of the stuff that is out there and in process right now are things like testing for malignant hypothermia, people who respond badly to general anaesthetics. We have a big programme looking at polymorphisms for people's metabolism of Azathioprine which we still use quite heavily in rheumatoid arthritis. There is an awful lot of pharmacogenetics going on in the management of epilepsy because there are paradoxical responses to some of the most effective new drugs there, and of course quite a bit of pharmacogenomics in people with HIV, some of whom have paradoxical side effects to some of the better agents there. There is a lot coming, therefore, and in terms of how do you look at value for money and affordability, I think that the NICE process can be applied to this, there is no reason why not. It is much maligned but I think NICE does a very, very valuable job for us in reminding us that there are always other things to spend your money on.

Q438 Lord Taverne: In the light of what Sir John says about the value of a single comprehensive test, if it could be done at a reasonable cost would you see ultimately that every newborn baby would be subjected to tests, as I understand is being envisaged in the United States?

Professor Sir John Bell: I think there is an ethical discussion you have got to have before you start testing newborn babies but the idea is that at some stage during life – the genetic data, until you get a cancer where you have got somatic variations where you have to do it again, the underlying germ line genetic data is basically stable so you can do it at any stage in life and that will give you a set of information that might be varyingly useful at different stages –

if you went on this drug you would look at that variant, if you go on that drug you need that variant, you have got a disease but what sub-type of disease and you would look at the variants that might drive that. My suspicion is that that would be a very efficient way to do it and one can now see for the first time how you might do that in the relatively near future.

Q439 Baroness Finlay of Llandaff: Should we be requiring pharmacogenetic tests in order to optimise efficacy and reduce side effects in terms of drug development, should that be a criteria for licensing?

Professor Sir John Bell: My view is that you are using the market rather effectively to actually make sure that that happens, because the truth is the NICE process says if you do not give us a decent signal in efficacy then we are not going to buy the drug, and one of the only ways to get that signal up would be to start to look at sub-populations. Can I just add something which I think is really important? That is that the one thing we do not do, and we have not done, is that we have not incentivised pharmaceutical companies post-registration to find the subset of people in which they are getting a big signal, so provided they got their ticket, and a lot of drugs of course just get their ticket, so they are there and they are selling it across the piece based on a number of qualities, what you would really like to do is to get those guys to keep working, to say actually guess what, we have found the 30 per cent of patients with pancreatic cancer in whom you get all the beneficial results. If they did that I would put to you it would not be unreasonable to allow the price of the drug to go up for those patients to absorb the full quality benefit that is consolidated in the 30 per cent of the population. We do not do that so I think there are some interesting questions about how you can further incentivise industry to do this more aggressively in the post-registration model. Pre-registration I think you have got them actually because the NICE thing does it for you.

Q440 Lord Winston: How important do you think are the epigenetic and environmental factors in healthcare and healthcare-related research, compared to knowledge of the genome? We tend to think in terms of genes in the environment but we forget, for example, the development.

Professor Sir John Bell: The epigenetic story is fantastic. It is about ten years behind where we are with conventional germ line variations, but again the new tools, particularly the new genetic sequencing tools, are really providing a fantastic window on epigenetic modifications in a way that you can systematically screen them around genome, and you can do it pretty efficiently. I think we are soon going to get maps about where genetic modifications are and how that changes, potentially how that changes in development and certainly how it changes in different types of common disease and what you might do about that because there is an interesting question whether by modifying some of those epigenetic changes you cannot actually have therapeutic opportunities as well. My view is that it is very important but we are not yet at the discovery stage where we actually know how it will apply. We know, for example, the Barker view about metabolic disease, that almost certainly it comes from some intrauterine event that actually sets programmes. Because the germ line stays the same we know it is not that so it has to be epigenetic; the real question is exactly how does that work. We know in a variety of other settings that epigenetic modifications are important, there is great work in animal models showing that rats who suckle infants, those progeny get really profound epigenetic modifications and may go on to have quite a different behavioural phenotype. It would be easy to under-estimate the impact of the epigenetic piece but it is also fair to say it is early.

Q441 Lord Winston: It is not only behavioural of course it is things like diabetes as well.

Professor Sir John Bell: That is right, and hypertension. The whole intrauterine environment story rests around epigenetic changes that dictate your likelihood of developing those phenotypes that we find.

Q442 Lord Winston: I know we keep on asking you to push out the predictive boat but how do you think these could be and how soon could they be related to healthcare? Alex, do you have a view on that?

Professor Sir Alex Markham: We may learn quite a bit from looking carefully at what happens to the first generations of agents that work epigenetically in cancer. Clearly, there are the H-stack inhibitors and a whole raft of therapeutic approaches that are targeted at the fact that in some malignant disease the change is all epigenetic. My take on that work is that there are some of them in mid-phase development, phase two, and I guess there are one or two now in phase three, and what I think we might learn from looking carefully at those patients, should they have a profound effect on the cancers, is whether they go on to have peculiar, unanticipated side effects potentially several years down the track. So if one extrapolates from the baby in utero to the development of type 2 diabetes, I guess epigenetic modifiers used as treatments for cancer might start to turn up some unexpected consequences decades later. People are looking at tools to change the epigenetic signature of the cell and the first evaluation is in cancer and I think it is watch this space. I do not think there is a need for UK Plc to be catalysing more research in this area because we have got some of the most distinguished basic science in Britain in epigenetics and, as I say, we do not have much of an option right now but to look very carefully at what happens to the cancer patients.

Q443 Lord Winston: Are you thinking about the supplies of micro RNAs or do you think that is going to be so complicated – there is a plethora of data presumably. Management of

patients with diseases like haemochromatosis, which again is not all that uncommon, now is reliant on genetic testing.

Professor Sir Alex Markham: Management of haemoglobinopathies is absolutely reliant on genetic testing. It has strayed back into monogenic diseases. Where we will see the next big demand might be unexpected. If you want a prediction, it would be in one of the cancers that has rather escaped notice. There is an enormous amount of investment in the genetics of breast cancer and it is very interesting and controversial. It tends to draw attention away from a big challenge we face in colorectal cancer, a very common disease for which we have just implemented, I am delighted to say, a national screening programme. That national screening programme currently tests faeces for blood. What we need for a patient aged 60 who has a polyp in their colon is some sort of categorisation tool that says, “This 60 year old patient now has absolutely nothing else to worry about. We have removed the polyp. They have had an £800 colonoscopy at the NHS’s expense. We do not need to bring them back in two years’ time for another one, another one two years after that and so on.” We need a tool for colorectal cancer, for the screening programme, that says that we cannot afford to colonoscope every at risk patient who is 60 years old every two years indefinitely. We did not have any of those tools and the genetic studies that are just publishing now on colorectal cancer genetics are giving us unique and unexpected insights that I think are probably an order of magnitude more exciting and important than what we have so far out of the breast cancer screening programme, unexpectedly. The application may not be very high wire/high tech but I think it will have a massive impact on the way we go about delivering a national screening programme. My hope is that we can screen a lot more people a lot more effectively for a lot less money. I would be excited about that. I think the genetic studies that are going on right now in prostate cancer are going to offer us some of those kinds of opportunities too. Breast has been a little bit disappointing after a huge euphoria about the BRCA 1 single

disease mutation story and the breast cancer people are going to have to get their thinking caps on about how all these new genetics work. John's suggestions about sub-segregating breast cancer in terms of what genes are expressed is probably the way to go. I think we are going to get some really exciting things to chew over from some of the other malignancies. I understand there are some very interesting things coming out of melanoma genetics right now. I do not know whether it is interesting or quite amusing but the first genetic studies of predisposition to lung cancer have just published and they all show that what predisposes you to lung cancer is polymorphism in your nicotinic acetylcholine receptor genes. If you are predisposed to rather liking your nicotine, you are predisposed to lung cancer. You might say, "Whoopee do, we could have told you that anyway, Professor", but it does show you that genetics do get things right, I think.

Professor Sir John Bell: To give you two other examples, it is really important not to be narrow about the use of genetic tests. HIV and viral sequencing to detect resistance is very common in HIV. It is the way you manage many of the new medications. People have been using it for five years. It is highly effective. The herceptin test used to be based on the presence of a particular receptor in certain breast cancer cells and is now almost all done by fish, so it is there in a variety of different formats, not always in a chip.

Q444 Lord Krebs: I wanted to ask briefly about the translational gap in genomic medicine. Quoting from the Academy of Medical Science's submission to us, they said, "It is far from evident that the UK environment for translating advance in genomic medicine into health care practice is optimal." We have heard a number of concerns about translation and the perceived lack of funding for evaluating the utility of new genetic tests – for example, the NIHR is not funding research into the evaluation of laboratory tests. I wanted to ask whether you think that is a fair assessment about the translational gap. Given your position, what is OSCHR's vision in relation to this issue?

Professor Sir John Bell: Everybody has this problem. The delivery of a new set of genetic tools into the clinic has proved really difficult in every jurisdiction. The Americans have had a very hard time doing it. The Europeans have had a hard time doing it. We were having a hard time doing it and there are several reasons for that. One is that I do not think you can rely, in this setting, on the diagnostics companies to do what is done in therapeutics, which is to demonstrate clinical utility, because the cost of a clinical utility programme is such that, at the prices paid for diagnostics, they would never get the money back. Diagnostics companies say, “If you want clinical utility, you are going to have to do it yourself because we cannot do it.” That is a really important difference. We do have the advantage that the regulatory framework in Europe is much more attractive for moving diagnostics. The approach to CE marking rather than various forms of FDA approval makes it much more likely that you can move down that road efficiently with all the diagnostics. The real obstacle comes in who is going to do the diagnostic evaluation and who is going to pay for it. If you look at the host of different activities and technologies that you could apply at the moment, you can see why the Department of Health has not jumped immediately in and said, “Yes, we will do it”, because the bill is going to be pretty substantial to deal with that problem. There are things going on funded through the NIHR which are very positive. They funded for many years genetics knowledge parks which did a certain amount of this in the very early days of genetic testing. A number of the biomedical research centres brought genetic teams which are funded to try to implement some of these genetic activities. Where we lack real oomph is setting up large scale prospective studies to try and evaluate for example transcript profiling in breast cancer and prostate cancer. What information does it give you? Does it save lives? Does it save money? What is the real data you get from that? Those are complicated, costly projects and they are probably not the same as randomised phase three studies for therapeutics because you do not have to do the randomisation. You can do it in a cohort fashion, running the new tests

alongside the old tests to see how you differentiate people as they go forward. Clinicians may be blinded to what results you get in the lab but you do not have to do it in a test. My view is that this is a really important thing to get right. I have wondered whether the NHS should not consider itself the laboratory for the world for developing clinical utility in new diagnostics. We have a fantastic setup that would allow us to approach the commercial suppliers and say, “You have the test. We will help you do the clinical utility. If we do it together, we are expecting a pricing on the diagnostic which reflects our partnership in the process.” In the end, the payback is that we, unlike the rest of the world, would get our diagnostics at half the price of everybody else and the clinical utility data which we generated to the benefit of our patients in the NHS would be used worldwide for people to get registration and sell their products internationally. There potentially is a deal to be done there that probably requires a bit of reflection to see whether we might do that. One could do it to the long term financial benefit of the NHS as well as providing clinical utility data.

Q445 Chairman: Who is doing this thinking? What structure will be required?

Professor Sir John Bell: That was my idea. I floated that by the DH and Andrew Dillon at NICE because I thought NICE should be involved in that as well. You could conspire to make sure whatever studies you do are the ones that deliver the health and economic data for NICE to make decisions on. The discussion went rather well, as far as I can see. I think they have gone back to talk within the Department of Health about how they might advance that. There are a variety of ways to play this but it seemed to me that would position us right in the front of this field and this whole issue about how you get innovation delivered to the NHS quickly – nothing does that better than being in a place where you do the utility testing in the first place. I think it has many benefits.

Q446 Lord Winston: Is there a model for that so far in the history of ----?

Professor Sir John Bell: Not that I know of. I do not think there is.

Q447 Lord Winston: I could not think of one.

Professor Sir John Bell: Neither could I. If I come up with one I will let you have it but I cannot think of one.

Q448 Lord Winston: Current genetic tests for single gene disorders are approved for NHS commissioning by the UK Genetic Testing Network. Do you think the role of that network could be expanded to include genetic tests for common disorders?

Professor Sir John Bell: The UKGTN has done a really good job. As you know, it is a voluntary organisation where people participate in the evaluation of single gene testing and have been pretty effective in providing a clear understanding about whether it works or does not. The decision about commissioning does not sit with the UKGTN. It sits with the Genetic Commissioning Advisory Group and then it gets passed down to local commissioners. That process needs another look because the time frame from getting from the top to the bottom is at least three years, so the time frame to get stuff to patients, in my view, is far too long. When you enter the arena of some of these much more complex tests in common disease, I am not sure that the skill base that is housed within the UKGTN is the right skill base. You are talking about often epidemiological data. You require health economic data to work out whether this stuff works or not. I am not persuaded that the structure which I applaud is necessarily transferable into this rather more complicated, complex world where clinical utility testing will have to be done on thousands of patients in large prospective cohorts. The methodology for analysing that may have to be new because some of this is relatively new methodology. My feeling is that the structure that is needed might have to dock with a NICE like agency which has some of those other capabilities to

think about what evidence you would need and how does it work. My view is it might need to move.

Q449 Lord Winston: Effectively you need a new agency?

Professor Sir John Bell: Yes.

Professor Sir Alex Markham: I am always reluctant to start new agencies because they always seem to me to have a tendency to slow everything down. I think the pathologists as a community have to take some ownership of this. The Royal College of Pathologists has to step up to the plate here because they have responsibility first of all for managing the scientists in the genetic testing networks anyway. That is a discipline that the College of Pathologists sees itself as being top of the food chain for. Once you get into the realm of polygenic disease, there was a question in the preamble you sent out to us: does all this genetic advance imply that the profession of medical genetics needs to massively expand? I would argue no. If you have to manage a patient with psoriasis, you have to be a dermatologist. You as a dermatologist have to understand the implications of the new genetic understanding. I would put pathologists on the spot and say, "What are you going to do about this? What do you think of the role of the UK Genetic Testing Network?" which has done a terrific job. What they did successfully was they divvied up the cake and let the whole community develop individual tests that they were good at and then shared that together. The sociology of the thing was good. When you get into looking at updated versions of cytogenetics in whatever form they evolve, when you start looking at profiling expression levels in particular tissue, diseased tissues like tumours, I think you have to be given the pathologists because they are going to have to advise front line clinicians on issues of prognosis. They are going to have to give advice about optimal clinical management routes. This is where multidisciplinary clinical teams have such an important role to play. I would

urge against another body until you have exhausted all the possibilities of making the one we already have do its job a little better.

Q450 Lord Warner: That brings us neatly to an issue that has been raised with us on a number of occasions about the competence and costs of the current pathology labs doing genetic tests. I am interested that you say they should step up to the plate. There has been a bit of nervousness about stepping up to the plate in this area. Should genetic tests be carried out in the specialised regional genetics centres or will most pathology laboratories need to be carrying out these tests in the relatively near future?

Professor Sir Alex Markham: That is a very timely question. The regional laboratories have played an important role. I get the sense that the regional genetics laboratory service is a little uncertain of the future. It feels to me that people in them are intrigued and a little bit worried about what the future holds in terms of all the new advances that can be anticipated and what their place in that world is. I get the impression that it is becoming more difficult to recruit into regional genetics laboratories. That may be incorrect. Lord Winston will probably have his finger even more on the pulse than me on that. The time might be right for moving to a system where they are more integrated into “mainstream pathology”. The time might be right for that to be considered. A lot of the funding streams that have driven the genetic testing laboratories over the period since the White Paper will probably be coming to an end now. A lot of what went on in the genetic testing world was underpinned by things like the genetics knowledge parks and the funding for that cycle is ending. I do think there is scope to look very carefully at how the NHS structures those laboratories and goes about commissioning that activity and paying for it in the context of pathology as a whole. Lord Carter is reporting on pathology and I think he would miss a big trick if he does not address that question of genetic testing and its incorporation into mainstream pathology.

Professor Sir John Bell: Alex and I did not conspire on this question before we came in here but I think we are on the same spot. I would go a little further. We have got ourselves silo-ed in a really unhelpful way in laboratory services generally. One of the things that has emerged in my local domain is that pathologists want to do a little bit of molecular pathology and some genetic stuff but clinical genetics often use the same technology. Haematologists want a ray machine. I would just say, “Forget it; you are not doing that.” Let us have one really good molecular pathology lab and the best facilities in there. When you want DNA sequencing done in the clinical setting, it gets done there. It can go out to the sub-specialties. Moving everybody to a different space I appreciate will be difficult but I think you have to do it because the waste in the system, if you just let everybody fool around, is going to be terrific. I would really urge you to take a serious go at this one. It is not complicated. You just have to break down some of the old barriers.

Q451 Lord Warner: What levers would you use in this area? The two levers you can usually use are money and regulation, money in the sense that you can incentivise people. That becomes the only show in town, which is a bigger grouping and bigger competence. The other is regulation which says to people, “You have to pass certain thresholds of competence to be able to do these tests.” Which combination or use of those levers would you be saying to the Committee we ought to be pushing?

Professor Sir John Bell: There is another piece to this, which is another dimension that I think might be a lever. My suspicion is you will not want to start, even if within a single general hospital you put all the lab services together. I am not sure you will want every little district general hospital to have a DNA sequencing facility in the back room. It is not straightforward technology. Having some significant regional laboratory capacity is going to be part of this. You are going to have to say, “We, the NHS, are going to fund these in a certain number of places”, ideally hooked up to the capacity to move novel developments into

them in an efficient way. There are some good examples out of the White Paper where you spread technology all over the country but they are still using it in the way they were five years ago, which is unhelpful. Being hooked up to a stream of innovation is really crucial and also to have the capacity to provide that set of services at some kind of regional level. You may be able to dictate how many of them there will be and what sort of area they will cover. By doing that you will end up with the right result because you will say, “We are not going to do it unless they have dah-di-dah.” It has to soak up all the activities in those areas and provide services for the surrounding regional hospital arrangements. The Americans have done this really effectively. If you go to the molecular pathology labs in Germany, it would knock your socks off. They are fantastic. They are really slick. They have all the bits of kit. Every record is on an IT system. There is no paper. The big American reference labs are like that too. I would look at those.

Professor Sir Alex Markham: I would just remind us of a model that was used for the genetic testing labs five years ago. Each regional health authority has a genetic testing lab but only two of them are resourced and recognised as the ones that develop the new, special tests for relatively rare diseases. That was done, as I recall, in Salisbury and Manchester. Now, with modern IT and the way this technology is developing, one of your levers is to say to a region, “If you cannot get your act together to deliver an integrated molecular pathology services that covers all these bases, the region down the road can eat your lunch” and get some competition in like that. The history here is that the clinical medical genetics community rather used the regional genetic testing laboratories as part of their empires. That was what came with the turf of being a clinical geneticist. You had the regional clinical genetics lab in your fiefdom. I do not think that is necessary any more. The clinical laboratories need good interaction with the clinical geneticists but they do not necessarily need to be down the corridor any more.

Q452 Lord Winston: Lord Warner mentioned two ways but is not the best way to be getting research done?

Professor Sir John Bell: Exactly. You get certain expertise and if it is hooked up particularly to people who are using these skills in the research environment then they can implement them in the clinical environment and the whole thing should be seamless. It is really important that you do not recommend that we just establish another set of regional genetics labs. What both Alex and I are saying is that this is not a regional genetics lab; this is a regional molecular pathology lab that brings the geneticists in, the haematologists in, and if you give it to the geneticists to own it will cause a lot of trouble. It has to be everybody working together and that means they will probably end up in different places as well.

Q453 Baroness Finlay of Llandaff: With the philosophy of devolution of the NHS and non-central control, picking up Lord Warner's point, where do you think an obligation to participate in research and provide research led data should sit in terms of supplying and having central labs? I am picking up Alex's comment that it is unethical perhaps to treat patients without considering the research information and the knowledge that you gain from it.

Professor Sir John Bell: It is really helpful that the NHS constitution is going to have within it a commitment to making research a major pillar of what we do. We have said this time and time again. Patients do not dislike research. In fact, patients like research a lot. In a sense, one of the opportunities we have within the NHS is to make it available to patients in the same way you make other things available to patients. My view is you can do the distributive model, although I am not a great fan of it. There are a few things where you will have to say, "You are going to have to do this" and it relates to quality, what patients want, and most sensible people will implement it anyway, but I think there needs to be central management to make sure that it is a main pillar of the whole organisation.

Q454 Lord Broers: You have talked about the potentially very competitive position that the UK is in. Perhaps this question relates to that. UK Biobank and Generation Scotland are studying very large numbers of individuals to understand more about their propensity to develop common diseases. How will genome technologies and genomic information be useful in studying these populations? Are these study populations large enough? Could there be a need for a larger, Europe-wide study?

Professor Sir John Bell: I was very involved in the initial stages of conceiving the Biobank study. When we set it up, we felt that the major argument for doing it was the likely availability of genetic tools and technologies to allow you to interrogate large numbers of people for their genetic susceptibility factors, for genetic factors that relate to disease and ultimately potentially their response to therapy. The numbers we chose to recruit were to some extent defined by the budget, but they did provide the sort of numbers that you see in a variety of other genetic studies that have been emerging recently. They will probably be just enough to start to interrogate some of these interactions between genes and environment which is obviously the fundamental thing that we want to try to deliver. We could have done a million but 500,000 is not bad. We are now five years ahead of everybody because everybody said they were going to do it and nobody did. The Germans and the Canadians have just announced one. They are 300,000 each so each one of those is smaller than us. Obviously we are trying to align their protocols with ours so we could add the results together over time. I would put this to you: one of the great powers of the structure that is being set up and one of the reasons that Biobank will be successful is because of our ability to manage and handle data in large numbers of people, which really relates to the Connected for Health programme, and the research capability programme analysis alluded to. If it evolves as we all hope it will, given the ready access to that kind of data, I am not sure why we would not expand the Biobank concept much more widely in the UK, where one gave all patients an

opportunity to deposit a bit of DNA that would be used in an anonymised fashion, to link the data system. When you say to people, “Would you like to be part of a system that will allow you (a) to inform the next generation about their diseases much more effectively and (b) would you not want to know about the opportunities that you have for understanding disease in a much clearer way and understanding your response to therapy in a much clearer way?” I think you will find that, if it is no imposition in time terms and it really just involves a sampling of blood, you might find that you could expand Biobank using largely a DNA sample across a much larger population in the UK. I see Biobank as phase one, a pilot study. We may end up eventually with ten million people who are all participating in the programme. The IT makes it possible.

Q455 Lord Broers: Surely, if you included particularly southern European countries, you might reveal some of the environmental factors more clearly than a monolithic, northern European population?

Professor Sir John Bell: You are right. You will also get diversity of genetic inputs. There are two other studies which are under way, which are already contributing to that. One is the Kaduro Study, being run by Richard Peto in China. They have already ascertained 500,000 people and have biological material, including DNA, on half a million people with health records. There is also a Mexican study which again is led out of the UK but which is being done by the Department of Public Health in Mexico, which was greatly advocated by Julio Frank and others to develop essentially the same bio-repository. My view is: let us get as many of these as we can. I am sorry to say that I do not think in Europe southern Europe is likely to be the place where that will happen. It will happen in Scandinavia and Germany.

Q456 Chairman: In the context of the UK and maybe the rest of Europe, who will fund such large population studies? We are talking about £60 million or £70 million.

Professor Sir John Bell: UK Biobank kicked off with £65 million. That came, as you know, from a number of funders including the Department of Health, the MRC and the Wellcome Trust, who were the founder contributors. My view is that this gets easier over time because the availability of IT records which come as part of the overall system makes the acquisition of data on patients that you are following a great deal easier. Genetic technologies are now a tenth the price of what we anticipated they were going to be when we started the study. The price of doing the analytical side is falling. The price of getting access to the information of patients is falling. I am not pretending we will get this for nothing, but I think it is well within the reach of national governments now to fund this pretty effectively. If we had five national governments each of whom put half a million people into the system, it would be impressive. It would be a good start.

Q457 Chairman: Who from the UK would coordinate this to make it happen?

Professor Sir John Bell: Not me. That is for sure.

Q458 Chairman: OSCHR?

Professor Sir Alex Markham: No. I fear something coming by me here. The answer is no. Rory Collins and Richard Peto would be seen as the head of the food chain I think by most of their international peers. The British leadership of this would be welcomed in most other countries.

Q459 Chairman: In the United States, as you well know, the National Human Genome Research Institute coordinates all the activities related to genomic science and genomic medicine, including ethical, legal and social issues, not just the genomic technologies and research and its implications. Do you think we should have such a body to coordinate all of the activities related to this, because again we have all kinds of different bodies involved.

Professor Sir Alex Markham: Your Lordships may not know this but the director of the NIH Human Genome Research Centre has recently resigned.

Q460 Chairman: We do not know why.

Professor Sir Alex Markham: We do not know why. In a world where NIH funding of grants is currently running at, I believe, eight per cent of applications, I do wonder whether spending \$1 billion on what was proposed for that body in the United States is going to materialise. They talk a good game but we have yet to see the fruits of it. I think we are starting to see a few cracks in it. I deal with quite a few of the American organisations and organisations like the major suppliers, Kaiser Permanente and so on, have very impressive data sets on their customers, mostly of course driven by the need to send them a bill. You cannot send somebody a bill unless you have pretty good records of what you did to them. In the UK, because of some of the changes in the way the NHS is funded, we have fantastic records about many aspects of how we pay for care. We have superb data now about waiting times for treatment in the NHS, which is very interesting. I do not think we need another body for me to persuade about the ethics of what I am trying to do. We can do these things with the structures we already have quite effectively.

Professor Sir John Bell: You need to look at where we are in this field. I have huge respect for Francis and what he has done at the NIH but the reality is that, in terms of delivery, our structures deliver considerably more. We had an equal share of the sequencing of the genome, thanks to the Wellcome Trust. The Wellcome case control consortium is a million miles better than anything. If you look at the new genome sequencing methodologies and technologies, one was invented in the UK and the other was invented in Scandinavia. They were not invented in America. I can tell you, because I have just met with them, they would die to have a Biobank project. They do not have one and they are not going to get one. I think we are doing pretty well. I would be very concerned about upsetting the apple cart.

Q461 Lord Broers: We have heard in evidence that the storage, transfer and interpretation of genetic tests requires sophisticated IT systems and expertise in bioinformatics. Will present IT systems and expertise need to be expanded? If so, how should this be done? How should it be funded and what are the priorities?

Professor Sir John Bell: I will first of all refer to Alex's very positive comments about the Connected for Health programme which I think are going to take us into a new era as it relates to research activities. Even research labs that have a hold of the new sequencing technologies are finding it almost impossible to manage the data. We have only just begun. We have not really used it in earnest for epigenetic analysis or across large populations. There are two problems. One is that there is a hardware issue about having the kit to store the information on. There is also a human capacity problem. Despite the fact that we all sat around 15 years ago and said that the really crucial thing to train in the UK will be bio-informaticians – people who can handle data – the truth is we have now hit the wall in terms of data handling and management. We do not have that cadre of people. We are in real trouble and I am not quite sure how we get from where we are now to where we need to be, but there does need to be a much more concerted and systematic approach to making sure that bright young people are brought into this arena and trained up at a variety of different levels. That is something that we will be discussing at OSCHR in relation to the human capital programme because it is a really serious problem.

Q462 Lord Broers: Have the key industrial players been talked to or involved? People at Google or even small companies in this country like Autonomy have people with phenomenal skills using absolutely vast volumes of data and searching through them in a very sophisticated way.

Professor Sir John Bell: I have not directly approached people but I know Google has been involved in discussions at the Department of Health. That, it seemed to me, was a very

welcome interaction. You are absolutely right. Google does have capabilities for dealing with that kind of data in a way that many of the public sector participants probably do not. There is expertise out there but I suspect that, taking some of the technical aspects of churn through very large amounts of little bitsy sequence data, getting it all to align and getting the information you want out of it, I still think we are going to be overwhelmed by a wave of data. I think that remains a big problem.

Q463 Lord Broers: Do you think in the long run it is going to be possible to combine personal health care records with genetic data?

Professor Sir Alex Markham: Yes. Right now, in the first phase of the pilot studies for our NHS research capability programme, we are working with Biobank to link the Biobank data with data that currently they do not have. For example, at the moment Biobank is not linked to the death records in the UK. That is job one in our set of pilot studies. Biobank is not linked to hospital episode statistics, HES data so-called, which is an incredibly rich source of data from the hospital sector. Biobank is not linked formally to GP research databases, so we are going to be linking Biobank to GPRD and others. There are some interesting challenges that we are going to take on in very short order there. Can we combine that with the tidal wave of genetics information that John and I have mentioned? Yes, I think we can, because in the governance process of this programme, which is overseen by an OSCHR committee, some of the key members of that are the likes of the senior scientists at the Sanger Centre who are, I guess, the world leaders in dealing with massive amounts of genomic information. We have representatives from the European Bio-informatics Institute in Cambridge, who are world leaders in pulling together bio-informatics information of every kind including the sorts of things that you get in the public literature. We have the British Library involved in the process to bring their expertise to bear in how to align published information to make sure that links into these databases. All the time, how do you keep out wicked people who would

want to do something mischievous with people's confidential material? How do we keep the firewalls up? Yes, it is a problem. Yes, through OSCHR, we have right at the front of our minds the need in training the so-called human capital programmes to make sure that this agenda gets fed with the sort of workforce it is going to need. Is the UK in a place where we are miles behind the rest of the world and on the starting blocks without any planning in place? No, I do not think we are. I think we are in reasonably good shape.

Q464 Lord Krebs: Can I go back to your comments on bio-informatics? You said that there had been a discussion about a decade ago to recruit more people to this field. What went wrong with that?

Professor Sir John Bell: It was one of those things that everybody said because everybody realised they would look clever if they said it, but nobody did anything about it. Everybody nodded wisely and then nothing happened. I cannot think of any significant, single initiative that produced even a dozen. People recruited a few of those interested in IT and computing but I do not think there has been a systematic push to generate a whole new generation of people who have those various sets of skills. It has happened a bit but it certainly has not happened in a systematic way. Nobody really grabbed it. OSCHR is very cognisant of the fact that we do have a capacity programme and we will be working together with the two big agencies to see how they propose to deal with these problems.

Q465 Lord Warner: Can I ask about the national programme for IT? My scars have now healed in this particular area. One of the intractable problems of that which is very relevant to this inquiry is the electronic patient record. That has been bedevilled by a couple of problems. One is the issue of people giving consent to their records actually going on the system in the first place. The other has been the wish of many people in the National Health Service to have their own version of the electronic patient record. This is largely clinically

led. The problem of standardisation, which helps the kind of research that you enjoy that Alex and John have been talking about, is under threat to some extent perversely from within the health professions themselves. What is your advice on this issue of consent and standardisation around the electronic patient record, to make the best use of the emerging amount of genetic data?

Professor Sir Alex Markham: If you ever require me to come and rub some salving balm on your wounds, I would be willing to. The problems you highlight are very real ones. As a complete newcomer to this whole world, I have been pleasantly surprised by how effectively primary care has adopted e-health records. To my utter amazement, effectively 100 per cent of NHS patients in primary care have their records held electronically. Those systems are supplied by three separate commercial suppliers. One has 60 per cent of the market; one has 20 and the other has 20. Of those three data sources, the 60 per cent market leader is available for research purposes because it will provide completely anonymised data. That is done through a body called Q Research within the University of Nottingham. One of the 20 per cent suppliers supplies the GP research database, which is reason by the MHRA, a government body. That can provide pseudonymised data so that if there is ever a need to go back to the patients that can be done through GPs. The other supplier is involved in research activities in a slightly more fragmented way. Primary care is in good shape. The problem you allude to for the hospital sector is very severe, but the first pilot studies for the care record are now ongoing. I believe there is one into the Somerset/Avon region which is going very well. The other one is the whole north Manchester, Bolton, Blackburn, Burnley, Bury conurbation, which is running an electronic hospital record. Again, that sounds as if it has been very successful. There is a huge amount of work that has gone on led by the Royal College of Physicians. Professor John Williams from Wales has been at the heart of that, developing the template for an electronic case patient recording. What does a doctor have to

tap into the computer for each patient and agreeing the sorts of descriptors like snowmen that will be used for that. It is at quite an advanced stage. Although the scars from NPFIT and the people who have been close to it, I am sure, are still there, I am now on the board of the National Programme for IT. I went along to the first board meetings expecting to go to something that was in a state of melt down and actually I found it an extremely well managed programme. I have worked in some very well run organisations in my time and I have not seen a better one than the National Programme for IT right now, which astonished me. If there is one lesson to learn, it is that the National Programme for IT and the Department of Health have a lot to learn about telling the British public just what a great job they do. I think we are missing a huge trick nationally because that would provide people with an enormous level of reassurance that what they are being asked to participate in is not some disaster waiting to happen but is really something that we can take an enormous amount of pride in as a nation. I think we are on track to introduce the electronic patient record. Yes, I am sure it is four years late. Yes, I am sure there have been all sorts of problems along the way but we are introducing one of the biggest IT schemes ever in the history of the world. You only have to look at how quickly IT changes and how ridiculous it makes you look when today's IT insoluble problem is tomorrow's trivial issue. I think we can be very pleased with where we are with the National Programme for IT and I would be very optimistic about it. The roll out nationally I think should go ahead in a measured way. There was a bit of a furore in the press again a month ago when Fujitsu were ejected from the programme. The immediate response to that was that the National Programme had screwed up again and Fujitsu are walking away from it. The truth of the matter was that the government body got rid of a supplier that could not deliver and took a very serious line on not wasting public money. NPFIT needs to hire a decent media team frankly because we have a great story to tell.

Q466 Chairman: That is a rare endorsement for national IT.

Professor Sir Alex Markham: Yes, but why does not everybody say that?

Q467 Baroness Finlay of Llandaff: Can I change the area a little towards education and training? Given that it seems likely that there will be growth in medical genetic tests and health care professionals maybe applying these, do you think that medical genetics need to be expanded to meet this need or do you think it should be training across other health care professionals so that they have education in genetics? Linked to that, if it was, would that be mainly confined to secondary care or would it be general practitioners as well or would it be beyond medicine?

Professor Sir John Bell: This is not a domain for medical geneticists any more. Some of the examples we have given you today show clearly how it is going to permeate all areas of therapeutics and most specialties. As a result, I think it has to be part of the core knowledge base that all doctors have, none more so than general practitioners. The patient will come to the general practitioner and it will all have to be explained in that environment. The results will have to emanate down to that level. They are going to have to start to understand this. If you say to me, “How far are we along that road?” we are not very far at all. In medical school curricula in some of our most distinguished academic centres have precious little of this. I think people have not realised quite how rapidly some of this technology is now descending on us. It has important implications but it has implications much wider than that within the NHS. For example, we probably have 1,000, maybe 2,000, cyto-geneticists. We have a variety of cyto-pathologists. There may be 3,000 or 4,000 people in the NHS who are doing jobs today that, within a very few years, may be completely redundant. How do you take those people and retrain that workforce? What you do not want to do is run to the end and say, “Oh well, now we are going to have to hire a lot of other people.” You have to think about how you can take that workforce and get them used to doing something else. There is a real workforce training issue that needs to be thought through aggressively now, because if

you start a process like that it is going to take a number of years to get to the end. You want to embrace these people and move their skills to where they need to be five years from now, it seems to me. It covers not just the medical profession but a lot of these paramedical areas as well.

Q468 Baroness Finlay of Llandaff: We are talking about laboratory scientists. What about nurses, because there is almost nothing in nursing at the moment.

Professor Sir John Bell: I agree. It probably has to be across the piece. The medical school curriculum has not done so well either.

Q469 Baroness Finlay of Llandaff: You said earlier that we are world leaders at the moment in developing this technology and so on. I just wonder how you think we would be able to maintain the economic benefit from that knowledge capital for the UK in the long term, because these developments are happening here. What will happen in the future in a very much share led, banking led, type of financial world environment?

Professor Sir John Bell: I am innately an optimist. I think it would be okay. If you ask me to explain exactly how it will be okay, it is difficult. As a crucial ingredient you have to have smart people. You have to resource them to do innovative, unconstrained science. Then you have to have a structure to take the discoveries that emerge from that and put them into some translational mode that allows you to turn something that is useful to people out at the far end. If you look at where we have got to through the OSCHR process in the last few years, I think we have had a very significant impact on transforming that landscape with the ability to take basic discovery and trying to establish decent structures that will facilitate it going into something that is useful. There is a whole set of issues that makes it complicated. There is much less risk capital around. The venture capital sector for biotechnology in the UK is not in robust shape. The availability of resources for small companies is limited. There is a

limited number of big players in the diagnostics industry based in the UK so that has some issues associated with it. We need to work our way through how we deal with those things, but the fundamentals, which are the people, the support for discovery science and the support for the translational component of that discovery science, are in place.

Q470 Chairman: Do you want to comment on education and training, Alex?

Professor Sir Alex Markham: Yes. I think it is going to have to become a core component of the medical and the nursing curriculum. When you teach the students this stuff, this is what really excites them. Properly and well taught, this is the hottest story in medicine. The fact that what we used to be shown in a book as a big mystery, disease X, now has all these mechanistic bases to it is incredibly stimulating. We are going to have to incorporate this in the great scheme of things. There was an earlier question about the whole translational research piece here and how do we build the UK capability and commercialisation, particularly of the more diagnostic aspects of this. It is difficult. The UK has never had an internationally competitive diagnostics and devices industry. I was responsible for trying to start one in the old ICI Pharmaceuticals. Now that is an industry which is very consolidated with a small number of international players that make it very difficult to break into the mainstream. If UK plc is determined to go there, the way is going to be to take very radical approaches. It will be paradigm shifts that allow us to get in, not trying to do the same as the big battalions but a little better. I would like to reassure your Lordships about the translational elements of this. In the last 12 months we have put some funding schemes in place that are there for people to take inventions and knock them into things that will do something for a patient. That never has existed very well at the interface between MRC and the NHS and NIHR before. Those schemes are in place. The question earlier said, "We are told that there is no funding available to do this stuff." Rubbish. The money is there. If people are coming to the system with ideas that are good enough, the money is there

redoubled in spades, both through that development funding pathway, through the experimental medicines and the evaluation pathway that runs in NIHR through the technology assessment programme. That comment is not fair. There is money available.

Q471 Baroness O'Neill of Bengarve: The public, as we are told, has a suspicion of genetics because of the potential for abuse of the data and because of poor publicity and, I suppose also, because of the case history of what happened with the attempted introduction of genetically modified crops in 1999. Do you think this suspicion is in any cases well placed and, if it is or even if it is not, what can be done to allay public mistrust and to ensure that it does not impede progress in health care and health care research?

Professor Sir John Bell: There may be public mistrust, but I am not sure that public mistrust is of genetics. A lot of public mistrust relates to what might be perceived to be the bad outcomes of misusing genetic information. The public are very anxious about the insurance industry because everybody relies on it for their mortgage and all the rest of it, so they are very anxious that their genetic susceptibility or data might be used in a way to prevent them getting access to that. They are also anxious because, in fairness, the government has not been perfect in protecting their data held in other settings and preventing it reaching the public domain. We should all accept that. It has not been the finest hour of government departments in keeping public data private, as it were. I think they have concerns about those things but what is interesting is that almost all patients innately understand that health is genetic. Although we have all these complicated tests to tell you what you are going to die from, the truth is when most patients walk in your office for the first time they have a view of what they are going to die from and it is largely related to what their parents died from. They say, "My mum died of breast cancer. My sister died of breast cancer. Am I going to get breast cancer?" There is an innate understanding that health transmits in families and that certain sorts of operations are more of a risk than others. If you are providing people with a

tool that allows you to dissect that in a more precise way to their benefit, I do not think there is going to be much anxiety about that at all. We have introduced a whole set of things in health care over many years that have often produced a flurry in the press. IVF was a pretty good example of that, but the truth is that, when people realised that there were considerable benefits to be had and that it was there without any of the dangers that had been speculated about, people came to accept it pretty readily. Biobank had recruited a very large number of people by the time the disk from the Treasury with all the data of the 22 million women on child support got lost in the post or whatever happened. I immediately called and I said, "Trouble coming. Let us watch the pace at which people pull out of this study because they will say we just cannot trust you guys." We did not have a single person withdraw. People treat medicine differently than they treat the rest of this. That is not to say I am complacent. We have to communicate better. We certainly have to communicate better than the genetically modified food gang who did not do such a good job, but I think you can manage this by really open communication about what we are trying to do.

Lord Taverne: I would like to put the question rather differently. What can be done to stop the government believing in what I regard largely as a myth, namely this public suspicion of genetics, a point which you seem to agree with? Essentially, as was shown for example over the concern with hybrid cells, the government got off to the wrong start. There is no public worry really about stem cell research. What the government seems consistently to do is to listen to a very vocal minority and regard that as the strength of public opinion. Again, there is this very widespread concern that Sir Alex referred to about ethical issues. I almost feel when people mention ethics I want to reach for my gun because it is nearly always counterproductive. What can be done to make sure that the government does not proliferate the ethical dogmas and concerns and does not take public concerns very seriously that do not

exist? Sir Alex mentioned the concern about registration. One out of 2,500 objected to their record being used.

Chairman: Perhaps Baroness O'Neill would like to intervene at this point.

Q472 Baroness O'Neill of Bengarve: I have to plead guilty. I do not think Lord Taverne will reach for his gun, but it seems to me that there is a great tendency to believe that self-appointed spokesmen for the public are indeed representative of what the public thinks. One always has to go behind the opinion polls to ask what do the public do. That is the real evidence of what they think and whom they trust when they go to their doctors, which is not to say one takes it lightly.

Professor Sir John Bell: That is correct. I think this comes out of the hybrid embryo discussion. It is right that government should enter these areas and consider them but you have to get good evidence about what are the facts, what we know and what we do not know. The hybrid embryo thing kicked off with a lot of hearsay, again from vocal minorities, without a substantial understanding even of what the definitions were of what a hybrid embryo was; what have we done before? What does it look like? Just to put a plug in here, the Academy of Medical Science has spent a lot of time putting together a really authoritative report which I hope informed the government as it got closer to the stage of legislation. You have to use the independent bodies, the British Academy, the Royal Society, Academy of Medical Science, to put together people who can give you the best view about what the science is telling you today, what is real and what is not. That is really important because otherwise you end up on a wild goose chase when you do not need to.

Q473 Lord Broers: I am interested in large IT systems and their success or failure. Sir Alex, you seem quite optimistic but what went wrong? Why was an incompetent contractor appointed in the first place?

Professor Sir Alex Markham: Looking back as an outsider, the problem was this: we were trying to develop in Britain something bigger and more complicated than had ever been done anywhere before. We were perhaps too optimistic. What we have not done well is to say, “Let us build something that works for this corner of Britain because if it works there it will probably work almost everywhere else.” We tried to implement this big bang solution. When you do that and you are putting in front of IT suppliers potentially the biggest contract that they will ever see, they have to get them. There is not going to be another one of these come along any time in the foreseeable future. If they do not get the contract and their competitor does, they are effectively out of existence. I suspect that the companies were complicit because they said, “We will tell you we can make you one of these even though we are pretty sure we cannot because we cannot afford to admit that we are going to struggle.” I think there was a bit of an unholy interaction, the Department of Health wanting to do something from a completely zero base in IT terms and suppliers being desperately keen not to be excluded from the party. One hears lots of anecdotes about the attempted renegotiation of contracts when it becomes clear that the company cannot deliver what they have contracted to do for the amounts of money that they have contracted to do it for. Everybody is in a blame culture then. There is not really someone to blame. It is a failure to recognise that the challenge being taken on was beyond both parties. We are just not very grown up about the way we do those things, I do not think. You can make the commercial world behave in really bizarre, unacceptable ways but I think we are past that. The relationship that Connecting for Health has with suppliers is pretty positive. I am optimistic. You are perfectly right and at liberty to say, “I think your optimism is misguided”, but I do not think it is right now. The way that the technology is developing will get us out of one or two holes that we have dug for ourselves.

Lord Broers: In my experience of these systems, success or failure depends almost solely on whether you have defined the system properly in the first place. That generally does not

happen. When the supplier comes back and says, “That is not a reasonable thing to do” then you start churning and changing the specification for the system and then you have chaos. That is very difficult. You are right; it is an interaction that should take place before the contract is placed.

Q474 Chairman: We have had longer than our normally planned session because both of you were full of information that we needed. Before I finish, if you have any other issues that you feel you would like to submit further evidence to us about, please feel free to do so. It will be regarded as the official evidence. I always ask this question to all witnesses at the end and I will ask you the same question. What two recommendations would you like to see in our report?

Professor Sir John Bell: I would like to see you encourage this idea that the UK becomes the laboratory for clinical utility testing and diagnostics because I think that has all kinds of benefits, from the private sector to the public sector, for patients and doctors. That would be interesting. The other one relates to the question around what does the future of a molecular pathology lab look like. I think this is really pivotal. For cost effectiveness reasons, that really needs some very careful deliberation. If you get that right, it will help drive this agenda and get it much more used in the clinical arena.

Professor Sir Alex Markham: Sir David Cooksey’s recommendations about OSCHR and the integrated working of MRC and NIHR have, possibly inadvertently, provided the nation with a structure that ought to enable us to think strategically about some of the new developments that we have discussed today in real time. Rather than your Lordships having to convene every five years with a sense of impending doom and disaster, OSCHR should be charged to make sure that there is some strategic thinking going on constantly about genetics and its place in the health system. The structures that have been built over the last 12/18 months in and around OSCHR are well designed to do that. Of course I am conflicted because I have

been part of that, but I think we have an oversight capacity now that we have never had in this country before to take the hot science into the clinic when appropriate. All of that crystal ball gazing we have tried to do for you this morning you cannot do and make a policy. You have to push that into a body that is looking at that all of the time and making changes as appropriate when the technology matures. I would, on his behalf, put in a good word for him. Maybe you should give him a bit more power.

Chairman: Thank you both very much indeed. You have been very helpful.