UNIVERSITY OF LIVERPOOL

The Development and Influence of Public Health Genomics

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Published by: Department of Public Health, Policy, and Systems, University of Liverpool, 2022.

ISBN: 9781999920968

Contents

Instructions for Citation

References to these Witness Seminars should follow the format below:

[Witness Name] in *The Development and Influence of Public Health Genomics*, held 8 September and 15 November 2021, published by the Department of Public Health, Policy, and Systems, University of Liverpool, 2022, web details [page number of reference].

Glossary

Clinical Genetics: The study of inherited genetic disorders, their diagnosis and treatment.

Cytogenetics: The study of chromosomes and DNA and their role in inheritance.

ELSI Program: Research into the ethical, legal and social implications of the Human Genome Project.

Epidemiology: The study of the causes and patterns of disease in populations.

Genetics: The study of genes and their role in inherited characteristics.

Genomics: The study of the whole genome – all of an individuals' genes, all the DNA inside each cell – and the interactions between those genes.

Human Genome Project: Collaborative international effort to sequence the entire human genome. Launched in 1990. Completed in 2003.

Population Health: The study of health outcomes, their patterns, and their determinants amongst a group of individuals, often at a national level.

Public Health: A discipline and a practice – the study of, and efforts to improve, the health of the population or populations, as a whole – incorporating elements such as epidemiology, disease prevention and health protection.

Public Health Genomics: Originally **Public Health Genetics** until 2005. A field of study or collective approach which aims facilitate the effective translation and implementation of genetic and genomic knowledge in order to improve population health.

Whole Genome Sequencing: The technological process of constructing an individual or organism's whole genome so that it can be analysed.

Introduction

In April 2005 eighteen delegates from Britain, the US, Canada, France, and Germany, including geneticists, bioethicists, and public health experts, met at the Rockefeller Centre in Bellagio, Italy. Their aim was to share interests, knowledge and experience and agree a collective definition for the developing field of Public Health Genomics. It was unanimously decided to aim for 'The responsible and effective translation of genome-based knowledge and technologies for the benefit of population health'.[1] The approach was broad so as to encompass all disease-causing gene interactions, prevention at different levels, and governmental, economic, legal, and social factors as well as scientific knowledge. This approach has had a significant influence as the possibilities of genomic medicine have expanded and new services have been developed. These witness seminar examined the development and impact of public health genomics, and its place in the wider landscape of genetics and genomics policy in Britain.

Though public health genomics is still a relatively young concept – emerging over the course of the last twenty-five or thirty years – the history that it can draw on goes back further. From the 1960s population-based approaches were inherent in new-born screening programmes for conditions such as phenylketonuria, while the study of gene-environment interactions formed an important part of research in genetic epidemiology. The potential for understanding the genetic contribution to common complex conditions, in addition to established single gene disorders, and the development of new genomic technologies, was exemplified by the Human Genome Project initiated in 1990. Key individuals in Britain, and in the US where the ELSI Research Program – Ethical, Legal and Social Implications – played an important role in shaping debates, began to think about the revolutionary potential of these developments, and how to plan for them.

While genetics had been of interest to British government policymakers – Cedric Carter was appointed as the first Consultant Advisor to the Chief Medical Officer on Genetics in 1972, and civil servants such as Ian Lister Cheese recognised its importance – it remained on a relatively small-scale. It was often geneticists themselves, working through regional NHS structures, academic networks, and representative bodies such as the Royal College of Physicians and the Clinical Genetics Society, who raised the profile of genetics and pushed it up the policy agenda. By the mid-1990s a more detailed consultation and advisory machinery had been developed, and the Department of Health (1988-2018) had its own Genetics Unit which took an interest in the organisation and delivery of expanding genetics services. Bodies such as the Nuffield Council on Bioethics also played an influential role, and in 1996 the Human Genetics Advisory Commission and the Advisory Committee on Genetic Testing were formed in response to a report by the House of Commons Science and Technology Committee.[2]

By the early 2000s there appeared to be a more propitious policymaking landscape for genetics. A new Human Genetics Commission was formed in 2000. In 2001 Health Secretary Alan Milburn announced the creation of six Genetics Knowledge Parks and the UK Genetic Testing Network was formed. The White Paper *Our Inheritance, Our Future* was published in 2003, coinciding with the completion of the Human Genome Project.[3] Further technological advances

[1] *Genome-Based Research and Population Health*, Report of an expert workshop held at the Rockefeller Foundation Study and Conference Centre, Bellagio, Italy, 14–20 April 2005, p.7.
[2] *Human Genetics : The Science and its Consequences* (London, HMSO, 1995).
[3] *Our Inheritance, Our Future* (Department of Health, 2003).

in sequencing, another series of influential reports and advice from bodies including the Human Genomics Strategy Group, subsequently provided the impetus for a gradual, broader shift in focus from genetics to genomics. In 2012 the 100,000 Genomes Project was launched, and a new Genomics Strategy was introduced to support new lines of research. The 2016 annual report by the Chief Medical Officer, Professor Dame Sally Davies, titled *Generation Genome*, helped to shape future priorities, and in 2019 the British government announced a comprehensive new Genomic Medicine Strategy.

A key moment in the wider development of public health genomics was the creation of the Public Health Genetics Unit in Britain in 1997. This was almost simultaneous with the establishment of the Office of Public Health Genomics by the Centers for Disease Control and Prevention [CDC] in the US. The University of Washington also founded an Institute for Public Health Genetics. The International Ethics Committee of the Human Genome Project served as a focal point for important discussions. The Public Health Genetics Unit produced the influential *Genetics and Health* report in 2000 in collaboration with the Nuffield Trust and continued to grow under its new designation as the Cambridge Genetics Knowledge Park between 2002 and 2006, with a distinct interdisciplinary approach. Following the Bellagio conference in 2005 the GRaPH-Int network was formed to foster further collaborations and 'consolidate the position of the discipline'.[4] The PHG Foundation was formed in 2007 and has produced influential reports in areas such as genetic testing, screening, sequencing, and pathogen genomics. The PHG Foundation and other international organisations have sought to develop links between policymakers and professionals, and advocate for the responsible, effective, and equitable translation of genomic knowledge.

The aim of these witness seminars was to bring together those involved in the development of public health genomics and the formation of genetics and genomics policy in Britain, in order to share their experiences and insights.

[4] R. Zimmern and A. Stewart, 'Public Health Genomics: Origins and Concepts', *Italian Journal of Public Health*, Vol. 3, No. 3-4, 2006, p.14.

Areas For Discussion

Origins

- What were the antecedents of public health genetics?
- What was the background and experience of those individuals who were later associated with the development of genetics policies and public health genomics?
- When did the possibilities of genomic medicine become apparent and what influence did this have on the development of public health genomics?
- When and why did British health policymakers first develop an interest in genetics?

Development

- How did the Department of Health respond to advances in genetics science and practice and what was the role of the Genetics Unit?
- What were the key policy developments and initiatives in genetics?
- What led to the establishment in 1997 of the Public Health Genetics Unit in Britain and the CDC Office of Genomics and Public Health in the US?
- What was the nature and impact of international collaborations in public health genomics?

Influence

- Did the early 2000s mark a new phase in genetics policy?
- When did the research and policy focus begin to change from genetics to genomics?
- What were the key milestones in the development of genomic medicine?
- What was the role of public health genomics in helping to shape these dynamics?

Legacy

- What are the most important achievements of public health genomics to date?

- How has interest in and recognition of the importance of these kinds of approaches varied amongst different professional groups?

- Has genomic knowledge and technology been responsibly, effectively, and equitably translated?

- With the continuing development of Precision Public Health and Personalised Medicine has public health genomics as originally conceived now reached its natural conclusion?

The Development and Influence of Public Health Genomics

Part 1: Genetics and Genomics Policy in Britain

The Transcript of a Witness Seminar held at the Wellcome Collection in London on 8 September 2021

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Dr Paul Atkinson: Senior Research Fellow, University of Liverpool.

Dr Philippa Brice: External Affairs Director, PHG Foundation.

Dr Diana Walford: Director, Public Health Laboratory Service, 1993-2002.

Transcript

Sally Sheard

Good afternoon everybody, and welcome to this witness seminar on the development of public health genomics. Thank you all very much for giving up probably one of the best days of the British summer. The witness seminar is a very rich format. It brings together individuals who have been involved with a particular development or a crisis. In this case it's a very fortunate development – the development of public health genomics. The format is that we will invite you to contribute, and you have all had the circulated briefing paper with the list of suggested items for discussion. We will transcribe what is said, and then you will be sent the transcription to check what you have said.

I think we've interviewed everybody here individually already. Thank you very much for your individual contributions. The benefit of the witness seminar is that you can prompt one another, and we get an opportunity to delve a little bit deeper into some of the issues that have come up in the individual interviews.

I'd like to start, please, with the section on the origins of public health genomics. The first question is really quite a broad one, but I'm hoping it will prompt some interesting discussion. What were the antecedents of public health genetics? I wondered if we could maybe look to the geneticists in the room here to start us on those discussions.

John Burn

Well, we're older than Frances [Flinter] so we have to start. So, when Frances was still at school…

Peter Farndon

Remember, it's being recorded…

John Burn

First of all, I think genomics and genetics have run side by side throughout the twentieth century. Cytogenetics was effectively a genomic technology of looking at the big picture rather than looking at individual, hereditary traits – which of course is what genetics was supposed to mean back at the beginning. In fact, you go back to the beginning of the twentieth century and Boveri was describing abnormal chromosomes in cancer in 1909.[5] So, in a sense, we've been running on a parallel track in a scientific sense, but then the conversion obviously with the Human Genome Project etc.

[5] Theodore Boveri (1862-1915) was a German biologist and the first to recognise cancer as a cellular genetic disorder.

The other thing I'd say is that most of us got involved in birth defects and malformations. Certainly, at Great Ormond Street that was our pre-eminent interest, rather than the monogenic disorders. So, the minute you got into spina bifida and heart defects and so on you were kind of in a genomic space. You were looking at gene/environment interactions as well, and we weren't specifically looking at hereditary traits in the traditional sense. In the 1980s certainly at Newcastle one of my main focuses was the management of malformations. We set up the foetal abnormality survey, which was then morphed into the birth defects records, whereby we collected all the abnormalities both pre-term and post-term to start studying the prevalence of the disease. That was another area that fed in – epidemiology and birth defects were feeding into this space, as well as the clinical geneticists looking for syndromes within that group.

Peter Farndon

And certainly, in the West Midlands we had a lot to do with the public health department at the regional level because of all the population screening programmes and the neonatal screening programme, which were all being developed at the time. We ran the amniocentesis audit, for instance, so we spent a lot of time talking to the public health people backwards and forwards. I agree with what John has said. I think everybody in the old days had this view that we were in it for the day when you could actually offer treatment to people based on molecules. That was a great hope back then.

Frances Flinter

In the 1980s a large part of the work that went on in the clinical genetics department was actually counselling people considering amniocentesis, and the Down's screening programme, ironically, most of which of course aren't inherited. That was the real focus. The other main area that was already part and parcel of standard medical practice, was neonatal screening, because Guthrie cards had been taken and those were all screened for phenylketonuria and not a lot else.[6] That was very much a public health initiative.

Peter Farndon

And even earlier than that, Cedric Carter and Sarah Bundey at Great Ormond Street did all the seminal work on population studies of congenital malformations, and adult disorders as well.[7]

John Burn

We were looking for recurrent risks after one or two. It was all the empiric, recurrence risks, essentially, because we couldn't get into the molecular analysis of it. The Down's screening programme, of course, was very much in the genetics community. We set that up in Newcastle

[6] Guthrie cards were commonly used from the 1960s to collect and store blood samples from the pricked heels of new-borns to facilitate screening for genetic conditions such as phenylketonuria - a metabolic disorder associated with intellectual disability in which damaging levels of the amino acid phenylalanine build up in the brain.

[7] Cedric Carter (1917-1984) was Director of the Clinical Genetics Unit at the Institute of Child Health in London from 1964 to 1982. Sarah Bundey (1936-1998) was a member of the Unit before joining the University of Birmingham in 1974.

for our region. Rather annoyingly, we actually found the HCG [human chorionic gonadotrophin] marker as well, but it all became known as the Bart's Test, which really irritated us.[8] We've got over it now.

Rosalind Skinner

The significance of alpha-feto protein as a marker for neural tube defects and Down's [syndrome] was discovered in Edinburgh.

John Burn

Absolutely. We were setting up regional screening programmes for Down's syndrome. As Frances says, the amniocentesis counselling was a big chunk of our responsibility in managing that.

Ron Zimmern

Can you say something about something developed in those early days by Leo ten Kate, which was this field he called community genetics – and actually a journal was started.[9] That was really about doing clinical genetics, classical clinical genetics in the community. I just wondered what you might have to say about that movement.

John Burn

The Editor of that was my very good friend from Amsterdam, Leo ten Kate. So, Leo and I – back when Cedric [Carter] was still alive, in 1982 – were sent to Portugal to teach the Portuguese genetics as part of a programme. So, there was somebody from Holland and somebody from Great Ormond Street went out. We spent a week giving lectures, and so become lifelong friends. We were stuck in Porto for a week together. Leo, in fact, pioneered the *Community Genetics* journal and in a sense that was, you're right, a public health view.

We were into this space in the 1980s very heavily, because that was, in a sense, the next frontier beyond the monogenic disorders, many of which… one of the misunderstandings of clinical genetics was that we spent almost none of our time in genetics clinics seeing people with monogenic disorders. The single gene defects were mostly dealt with by the biochemists or the haemophilia team or whatever. We got Huntington's disease because that was a big counselling issue, but an awful lot of the stuff that came in the door was things that ran families that didn't quite run in families.

[8] The 'Triple Test' or 'Bart's Test' – from St Bartholemew's Hospital, London – measures levels of alpha-feto protein, unconjugated oestriol, and total human chorionic gonadotrophin in maternal blood to assess the risk of foetal Down's syndrome.

[9] Leo ten Kate (1940-2020) was Professor of Clinical Genetics at VU University Medical Center, Amsterdam from 1993 to 2005.

Frances Flinter

I think what came through the door was largely dictated by the genes as they were found. So, Duchenne muscular dystrophy – suddenly you had all the females from those families wanting carrier testing…

Rosalind Skinner

We were seeing them earlier when we were developing the carrier testing methods...[10]

Frances Flinter

Using linkage, which was a nightmare.

Rosalind Skinner

Yes, and CPK [creatine phosphokinase]. We were also using CPK when looking at the very early diagnosis and even the preclinical diagnosis of Duchenne muscular dystrophy in the 1970s with Guthrie cards.

Frances Flinter

That's why our generation loved Bayes' theorem, but subsequently the trainees haven't really needed to use it.

Rosalind Skinner

In the 1970s, before you get to the 1980s and what you're talking about, there was a lot of work going on trying to develop the methodologies for prenatal diagnosis. We were very active in Edinburgh, for instance, John Scrimgeour looking at the early development of fetoscopy, and also work on prenatal karyotyping.[11] In Glasgow they were doing quite a lot too, with Malcolm's [Ferguson-Smith] lab.[12] There were a lot of epidemiological studies going on, for instance around spina bifida. I remember at one time, golly…counselling patients… I look back in horror, because spina bifida cases were born in the winter months so therefore you discussed the implications of getting pregnant in your summer holiday. Then there was the supposed link

[10] Rosalind Skinner notes: 'Before the Duchenne gene was identified the probability of female members of a family being a carrier of the gene was calculated using a marker such as CPK and the family pedigree information in combination, using Bayes' theorem. This risk value was used as the basis for genetic counselling – i.e. the risk of the woman being a carrier and hence the risk of her sons being affected'.

[11] John Scrimgeour (1939-2014) was a Consultant Obstetrician and Gynaecologist at the Western General Hospital, Edinburgh from 1973.

[12] Malcolm Ferguson-Smith (b.1931) was Professor of Medical Genetics at the University of Glasgow from 1973 to 1987.

with potatoes, so there was a lot going on in the 1970s that led into the work that you're talking about in the 1980s.[13]

Frances Flinter

We used to hand out vitamin pills, didn't we?

John Burn

Yes. We started off with Guy's [Hospital, London] and Leeds doing the multivitamin trials. Spina bifida, I remember, was a huge problem back then. It declined in any case, it declined in incidence – prenatal detection took out a large part of the visible burden – but children being born with anencephaly and spina bifida – we had dozens of cases in paediatrics.

Rosalind Skinner

One in 200 births in Scotland. Very high.

John Burn

In fact, it peaked at about one in 50 in some of the northwest corners of the country. It was a real epidemic of neural tube defects in the twentieth century. That was a big challenge for us as geneticists because it ran in families to some extent and because it was an area of interest. Then of course the Smithells study started, and Guy's…in fact I recruited to the Guy's team back in the early 1980s.[14] Then the MRC [Medical Research Council] study started.[15] So, we then had eight years of fighting to say we needed to do it again, but this time with a placebo control. Interestingly, the ethicists in both Guy's and Leeds wouldn't allow the Smithells trial to have a placebo. They said it wasn't fair to not give everyone the vitamins, so the result of the study was made null and void. Nick Wald had to start all over again.[16] It wasn't until 1991 that we established that folic acid would prevent spina bifida. That was very much a public health engagement.

[13] During the early 1970s links were drawn between spina bifida and anencephaly and deprivation and nutrition, particularly with regards to the seasonal and regional quality of potatoes. See for example: J.H. Renwick, A.M. Possamai and M.R. Munday, 'Spina Bifida and Potatoes', *Proceedings of the Royal Society of Medicine*, Vol. 67, No. 5, 1974.

[14] Richard Smithells (1924-2002) was Professor of Paediatrics and Child Health at the University of Leeds from 1968 to 1988. A trial led by Smithells using multivitamins identified a link with reduced frequency of neural tube defects.

[15] A multicentre trial led by the MRC completed in 1991 finally demonstrated a clear link between prevention of neural tube defects and maternal folic acid supplements.

[16] Sir Nicholas Wald (b.1944) was Professor of Environmental and Preventive Medicine at St Bartholomew's Hospital Medical College from 1983 to 2019.

Frances Flinter

The other big MRC trial in the 1980s was the chorionic villus biopsy trial, looking at offering that as an alternative, and particularly trying to pick up the miscarriage rate and establish how it differed compared with people who'd had amniocentesis.[17]

Ron Zimmern

So, when was the neonatal screening programme established? That's something that Paul Polani at Guy's was quite involved with…[18]

Frances Flinter

Guthrie cards would go back to the 1960s….

Rosalind Skinner

We had every card from the babies born in Scotland from – I think it was about 1966 – stored in Yorkhill. But to be fair – and I may be wrong, please say if you think it's wrong – I don't think the neonatal screening programme for PKU [phenylketonuria] started because it was a genetic disease. It started because it was an inborn error of metabolism for which a treatment had been defined, hence it was a screening programme. It just happened to be a genetic disease. The fact the paediatricians would say, 'Well, your other children will be at greater risk, but don't worry, because you will have the same diet for all the family'. It wasn't a genetic problem.

Peter Farndon

That was the reason for all the other screening programmes as well, wasn't it? Thinking about it now, it wasn't a genetic disease that was screened for, it was really because you could do something about it.

Rosalind Skinner

It was a very long time before we actually screened because something had a genetic aetiology. I sat for many years on the National Screening Committee, and it took a very long time to get genetic implications recognised.

[17] Chorionic Villus Sampling – from the cell tissue of the placenta – facilitated earlier first trimester prenatal diagnosis of a number of genetic conditions.
[18] Paul Polani (1914-2006) was Director of the Paediatric Research Unit at Guy's Hospital Medical School from 1960 to 1983.

John Burn

We had big battles with the biochemists on the CF [cystic fibrosis] testing, because they didn't want to move to genetics because that was a dangerous area. They wanted to stick with biochemistry. A key point is that Archibald Garrod picked up the concept of Mendelian inheritance, so the inborn errors were genetics at the beginning.[19] That was the first, and alkaptonuria was the first one. As Ros says, it was a treatable condition, so in sense, before genetics formed as a speciality – which wasn't until the 1950s and the 1960s it really started to take shape – chunks of it had already gone. The biochemistry and inborn errors were taken by the paediatric biochemists, and they went off with that. The haemophilia doctors and the haematologists went off with their chunk, so we kind of never got there. We didn't have…there was an existing infrastructure before the genetics community started to take formal shape.

Frances Flinter

Hypothyroidism was the other early one, wasn't it?

John Burn

Yes.

Rosalind Skinner

Thinking about the interest in Duchenne muscular dystrophy for instance – there were specific areas that the general paediatricians perhaps didn't particularly hook onto, certainly the ongoing management once the diagnosis was made. I think the neuromuscular diseases was one of them. There were specific centres: Great Ormond Street because of Sarah Bundey, the Newcastle group, and ourselves in Edinburgh. We were all particularly interested in neurogenetics and neuromuscular diseases, and so were involved in the ongoing management of cases. A huge amount of hard work certainly went into that area, and I know in Newcastle…

Frances Flinter

Martin [Bobrow] was very involved in the Duchenne muscular dystrophy work.[20]

John Burn

John Walton – Lord Walton – was the pioneer with Duchenne dystrophy.[21] My first tutor, David Gardner Medwin, took that over.[22] The difference with the haemophilia group was that

[19] The British physician Archibald Garrod (1857-1936) first described the nature of a number of inherited metabolic diseases in his 1908 Croonian Lectures to the Royal College of Physicians.
[20] Martin Bobrow (b.1938) was Professor of Medical Genetics at the University of Cambridge from 1995 to 2005.
[21] John Walton (Baron Walton of Detchant) (1922-2016) was Professor of Neurology at Newcastle University from 1968 to 1983.
[22] David Gardner Medwin (1936-2014) was a consultant paediatric neurologist in Newcastle from 1972 to 1996.

haemophilia kept itself apart, whereas the neurologists were more than happy to have the geneticists come and help them out with the X-linking, calculating who the carriers were and doing CPK testing.

Frances Flinter

To some extent that's still the same now.

John Burn

Absolutely. This thing about Bayes' calculation – using probability calculation was a big deal for us. That and spotting syndromes was what made us stand out from the crowd among the genetic clinicians. Of course, that got swept aside once we got the genes, and they said, 'We don't need to do probability calculations anymore'. Except it's come back into fashion now because we have millions of variants that we need to use Bayesian probability to work out which ones map and which ones don't, so we've come full circle. We've lived long enough to become relevant again.

Sally Sheard

We may come back to that. Ron.

Ron Zimmern

Just from the neurological point of view – when I was training as a neurologist at Queen Square there was very little understanding of the genetics.[23] There was this guy Michael Baraitser who did this stuff, and it wasn't until Anita Harding took it over that neurogenetics became a respectable subspeciality of neurology.[24]

John Burn

Yes, so Michael was a South African neurologist. I used to go and be his registrar around there, and we used to sit at a big desk with a big set of wood on it, and the patient sat down there and we talked to them over the top of this piece of wood with all the forms in. It was a very non-genetic counselling environment. But then Anita, who sadly died very young of cancer, took over. She really galvanised the neurology…but that's another story.

[23] The National Hospital for Nervous Diseases (1948-1990), now the National Hospital for Neurology and Neurosurgery, Queens Square, London.

[24] Michael Baraitser (b.1936) was clinical geneticist at the National Hospital for Nervous Diseases and then Great Ormond Street Hospital, London. Anita Harding (1952-1995) was Professor of Clinical Neurology at the Institute of Neurology, University of London.

Sally Sheard

OK, we are drifting a little bit, but in a very constructive way, so thank you. Can I just ask if there's anybody who'd like to speak to the contributions of the ELSI programme at this stage? Ron, is that something you would like to make a comment on?

Ron Zimmern

I think only two things. One is that when I set up the Public Health Genetics Unit, I had done so realising that in some way ethics and law and such things were important and had something to do with it. The second point is that with all those various committees in the Department [of Health] – the Human Genetics Commission and so on and so forth – there was always, again, quite a significant ethical element to their discussions. I remember Onora O'Neill was a very prominent member of the Human Genetics Advisory Commission.[25]

Alison Hall

So, can I just ask – when you say, 'at this stage', do you mean the 2000s or do you mean the 1970s?

Sally Sheard

I think the 2000s. If we can keep the conversation focused on that early period.

Alison Hall

It's a shame that Eric [Meslin] isn't here because he would have been able to comment on that ELSI stream within the Human Genome Project, which I think was a really important precedent for entrenching ethics into policymaking in this.[26]

Rosalind Skinner

I don't know the dates, but it will have been around the 2000 mark. I think it's when the Milburn speech and the White Paper came out, and it looked as if the Department of Health was seriously taking forward genetics and the development of genetics services across the NHS.[27] The ESRC set up a network of units to look at specifically the ELSI issues.[28]

[25] Onora O'Neil (Baroness O'Neill of Bengarve) (b.1941) was Principal of Newham College, Cambridge from 1992 to 2006, and a member and then Chair of the Human Genetics Advisory Commission, which ran from 1996 to 1999.

[26] Eric Meslin, now President and CEO of the Council of Canadian Academies, was Bioethics Research Director in the ELSI program at the US National Human Genome Research Institute from 1996 to 1998.

[27] Alan Milburn (b.1958) was Labour MP for Darlington from 1992 to 2010, and Secretary of State for Health from 1999 to 2003. An important speech on genetics policy in April 2001 foreshadowed the White Paper *Our Inheritance, Our Future* in 2003.

[28] The Economic and Social Research Council funded a Genomics Network made up of four academic centres between 2002 and 2013.

John Burn

That was 2003, Alan's speech.

Alison Hall

The White Paper was 2003.

Peter Farndon

Yes, 2001 was his speech.

Naomi Brecker

The speech was earlier, around 2001.

Mark Bale

I can't comment on the 1970s – actually, I was still alive then – but there's something into the mid-1990s – or probably before that, given how long a select committee takes – were there was a big inquiry by the House of Commons Science & Technology Committee that galvanised an awful lot of discussion internally.[29] I think that was largely around some of the ethical issues. I think it was 1995.

Sally Sheard

Thanks, Mark. I'll come to that further on. It's been a challenge to actually put this into some sort of logical order to drive the discussion, because so many of these things are happening in parallel. Having picked up on them we'll come back to them.

Frances Flinter

I think in a large part what was happening clinically was actually driven by what was developing in the laboratories, and as and when it became possible to offer more tests – to improve the screening for Down's syndrome, to increase the number of genetic tests that we could offer that were more accurate and reliable – that then inevitably influenced the sorts of referrals that were coming to the genetics clinics and the awareness of paediatricians and neurologists and others as to what clinical geneticists had to offer. I think always the pull has been the technology.

[29] House of Commons. Science and Technology Committee. *Human Genetics: The Science and its Consequences* (London: HMSO, 1995).

Naomi Brecker

That also led to the focus within policy in the Department of Health on the fact that this had to be systemised, brought together, improved, and make sure there was equal access, and something about the investment in those technologies. So, it wasn't thinking about the wider genomics picture, but it was very much around the commissioning of services to get all these scientific developments to patients as fairly and systematically as possible.

John Burn

I think it's fair to say the Department of Health was a bit late to the table. Ron was very much a pioneer in saying, 'We've got to be talking to public health'. My perception of public health back then was that they really didn't want to know about genetics – the concept that there were differences between people.

Ron Zimmern

And they still don't, John.

John Burn

I know. They liked the idea that we're dealing with a million people and they're all basically like little blocks. The idea that every one of them has got their own personal life story and genetic predisposition just filled them with dread. So, we sort of steered away from them, and most of our focus, as Frances says, was actually about hunting genes and finding causes and writing papers. An awful lot of what we did was influenced by what we were aspiring to do – find the gene for Duchenne dystrophy or polycystic kidney disease or whatever. That slightly distorted the work, but it was very much seen from a clinical perspective, a speciality perspective, not about coming at it from the whole population point of view.

Hilary Burton

I think that's where public health came in, from my point of view, because at that stage public health had a responsibility for the shape of healthcare services, which they don't now. They had a special interest in that. We could see that with the developing technologies and the developing clinical genetics capabilities that you could think about that on a population basis, and you could try and bring the best of that work to the whole of the population. I think as we started to look at it that's what we could see, in a sense, wasn't happening.

Frances Flinter

Another thing that made a really big difference was the fact that because we're a relatively small speciality we all knew each other, and so we started talking to our colleagues in different regions about the way their services were commissioned and funded. What became apparent

in the early 1990s is that there were huge discrepancies. Some people had block contracts, other people had payment by results, and the amount of funding varied enormously from region to region.

We were lucky in that there was a number of very wise commissioners who actually did get very interested in it, and I'm thinking of people like Jacquie Westwood, who made an enormous effort to try and standardise things across the country and help people who were working in the centres that were much less well-resourced have the appropriate conversations with their commissioners.[30] As clinicians we had to learn how to play that game and how to start thinking about money and how to have those conversations, so that we could argue for better resources for our own services. I think that made a big difference.

Hilary Burton

I think often we were thinking about how we would develop patient pathways, for example, that could realistically be provided to a whole population. The work we did on, say, colorectal cancer.[31]

Ron Zimmern

There was one issue which was really the basis of a long argument I had with Leo ten Kate as to the relationship between community genetics and public health genetics, because Leo treated community genetics as doing clinical genetics in the community and working with monogenic disorders and congenital disorders. Whilst, by then, we had started seeing in…I'm using the phrase public health genomics…that there was a huge area of the common polygenic diseases where genetics could input. Therefore, I suggested to Leo that community genetics was a subset of public health genetics, which he never accepted.[32]

John Burn

I'd like to criticise us as well at this point, because it sounds like clinical geneticists were all smart, but actually the truth is we didn't…as a community we shied away from public health genetics because there was too much of it. One of the great failures of our community was to get a grip on familial hypercholesterolemia, which is still a problem. If we were really focused on the maximum benefit to mankind then we should have been focusing on things with a high penetrance and which were common. But there was a fear that if you called all the people with high cholesterol to the genetic clinic they'd just disappear without a trace, so we kept pushing stuff away. In fact, to some extent public health and community genetics was about us saying, 'We don't really want that. We want all the rare stuff'. We were rare disease doctors, and we were equally liable to criticism that we weren't looking at it from a total population perspective as we might have done.

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[30] Jacquie Westwood was part of the London Specialised Commissioning Group and lead commissioner for genetics at South East Thames Regional Health Authority during the 1990s and 2000s.

[31] *Biomarkers in Familial Colorectal Cancer Screening* (Public Health Genetics Unit, 2006).

[32] See for example, R.L. Zimmern, 'A Reply to Community Genetics: 1998-2009…and Beyond', *Journal of Community Genetics*, Vol. 1, No. 4, 2010.

Hilary Burton

I think there was a slight addition to that though, John. I felt at the time that clinical geneticists were absolute perfectionists – 'therefore I have to see everybody that could possibly have links to a syndrome, because they might have this or they might have that' – whereas I think Public Health was able to bring, 'Okay, how do we get the best bang for our buck for the whole population?' They lived with the fact that somebody with a very, very rare manifestation might get missed, and I think that clinical genetics found that very hard to do. A lot of it was actually letting go of some of it and letting the less specialist nurse in the cancer clinic deal with it, if you like, on the basis of getting something there for the population. That was what I thought public health could bring.

John Burn

Yes, and being intrinsic…sorry, go on.

Peter Farndon

I'm just going to take issue with you a bit about the hypercholesterolemia, because I think we all knew about it but there was absolutely no central mechanism for bringing it all together. That developed later in the 1990s, into the 2000s. I found a quote actually, in 1993, from Kenneth Calman and Yvonne Moores, because they produced a guide called *Population Needs And Genetics* to support the executive letter through which regional managers the previous year had been asked to review genetics services.[33] But said Kenneth Calman in his letter, 'The purchasers should assume that these services, including any new developments, must be funded from existing resources'. So, all the time we were saying, 'This is the demand,' and actually there wasn't any mechanism. So, what you had to do was go and batter your regional commissioners…

John Burn

We were massively under-resourced, living in corners of buildings.

Rosalind Skinner

I think all round the UK there was the same problem in getting the issue of hypercholesterolemia addressed, because I was quite central to this in Scotland. I had to do a lot of networking and a lot of negotiations all around, selling it to people in the health department that this was actually quite a meaningful thing to do when they were writing the cardiac strategy for Scotland, because cardiac deaths had come down and were plateauing. Diet was having an effect, and public health promotion was having a certain effect, but it wasn't going to go any further. I said, 'You have a major cause – it's genetics'. It was really difficult,

[33] Population Needs and Genetic Services: An Outline Guide (Department of Health, 1993). Sir Kenneth Calman (b.1941) was Chief Medical Officer from 1991 to 1997. Dame Yvonne Moores (b.1941) was Chief Nursing Officer from 1992 to 1999.

to sell it even to the outside world…the geneticists – not so bad, I managed to convince them…but the biochemists, the lipid doctors – 'Our clinics will be flooded'. A chap in Glasgow actually said to me, 'But if you tackle the one with hypercholesterolemia, the rest of the family are eating poor stuff anyway, there is not really much point'. I couldn't believe it. It took a long time, but we managed to get funding to set up a demonstration project for a screening programme and show that you could actually do it successfully by employing nurses to work with the lipid specialists in clinics, and the geneticists ran it from Aberdeen. It was very successful. But you're right, every corner, all of us – the geneticists were pulling back a bit, the public health people too. They were a bit worried about it, and certainly the lipid people were not dead keen to start with because it was a huge workload.

Ron Zimmern

If Muin Khoury was here he would reflect that this was happening in the States as well, because he had trouble getting the state medical directors to get involved in this, which was why he set out classifying all these things as Tier 1, Tier 2, and Tier 3.[34] Tier 1 was the stuff that had so much evidence that no sensible public health doctor could possibly…and the three disorders that were in Tier 1 were BRCA, Lynch syndrome, and familial hypercholesterolemia.

Rosalind Skinner

It was still happening in London when I was with you in Cambridge [at the PHG Foundation] because I remember Tim [Aitman] setting up a meeting in London - do you remember?[35] We had dinner in the House of Lords afterwards, trying to persuade or make the case for screening for hypercholesterolemia.

John Burn

I had dinner with Sally Davies…same thing.[36] The other thing, coming back to this negotiating contracts – we had sixteen district health authorities in my region, and I had to get them all to agree to actually have a single contract for the three million people. That's when the cytogenetics was hugely valuable because we said 'It's one. If you get one, you get them all'. So, they wanted to break off amniocentesis and Down's screening into separate places, but I kept…I hugged them all together, which carried the monogenic stuff through, because they weren't really interested in the rare diseases. That was 'Somebody else can deal with that', but we forced all of them to create a single contract on the strength of amniocentesis and Down's syndrome, which was the one thing they could get their head round.

Frances Flinter

Some of the regional genetics centres were having to negotiate contracts with each individual PCT [Primary Care Trust] in the 1990s. It was ridiculous.

[34] Dr Muin Khoury has been Director of the Office of Genomics and Precision Public Health, formally the Office for Public Health Genomics, at the US Centers for Disease Control and Prevention since 1997.
[35] Tim Aitman (b.1958) is Professor of Molecular Pathology and Genetics at the University of Edinburgh.
[36] Dame Sally Davies (b.1949) was Chief Medical Officer between 2010 and 2019.

John Burn

Yes. We didn't have a contract. Back at the end of the 1980s, my predecessor actually let our hospital not be made a Foundation Trust or whatever it was called back then, just because there was nobody putting any proper money into genetics, which was just taking off. So, there was a point around about the end of the 1980s, early 1990s, when people started getting their head around genetic services, but that still wasn't public health genomics. That was a super-specialty in the specialty centres, dealing with the rare stuff.

Peter Farndon

Most of the research, as I'm sure people have said, came from funding from patient groups – to get a new gene up and running and all the mutations found. Then, armed with that, you've created a service, so you then have to go to the commissioners and say, 'We need to fund this'. But then what would happen is one region would say, 'We'll provide this service for the whole country'. So, I think one of the great things about this whole period, as Frances said, was the way that all the individual services…everybody in all the different genetic specialties actually communicated with each other. In fact, a lot of things that happened wouldn't have happened if there hadn't been a national view, completely by cooperation, of the professionals involved.

Frances Flinter

Because they never competed did they? Because we all had our own region to provide services to, we never really felt we were in competition with each other.

Peter Farndon

No. The only time we were told to compete was when the government changed its policy and the hospitals had to fight against each other.[37] I remember going to a meeting with all the leads of the clinical genetics units, and Bob Mueller was in the depths of despair.[38] Then the light dawned, and somebody said, 'Hang on a minute. If we already have one centre providing sufficient services for this rare genetic disease, why do we have to set it up in every centre and compete? If together we say to the government, "The genetics services in the UK work together to provide a complete national service, so it would be better to buy us as a block" then they can't make us fight against each other'. The policy of competition was better suited to other larger specialities for instance to 'Bring down the cost of hip replacements'. This was in the era of competition. It would have destroyed the genetics services. The genetic services said, 'We've got something special here. Let's just clump together', but that was a pretty dangerous time, because the hospitals were telling us we had got to compete.

[37] Reference to the NHS Internal Market introduced in 1991 and foreshadowed in the 1989 White Paper *Working for Patients*.
[38] Robert Mueller was Professor of Clinical Genetics at St. James's Hospital, Leeds.

Sally Sheard

That's a really important point. I'd like to move us on a little bit to talk about some of the individuals and the background of the individuals who've been associated with the development of genetics policies and public health genomics. First of all, those with public health backgrounds. Ron, would you like to perhaps start us off on this and talk about your inspiration for moving into this territory?

Ron Zimmern

Well, I had no inspiration. I knew absolutely nothing about genetics when I decided to move into this territory. I had to go to lectures and read textbooks and things. I remember I went round, and I saw every regional genetic centre, and actually people were very helpful. People like Rodney Harris, they were all very encouraging and helpful.[39] My public health colleagues didn't care. It was really the geneticists who somehow felt that having some form of structure would be a good thing. It was really people like John and Peter and your predecessors who were the ones that really encouraged me.

And then the other main thing, I suppose, was meeting Muin Khoury, who in the same year [1997] set up his centre at CDC [Centres for Diseases Control and Prevention]. I tell this story – I remember going to the first meeting in 1998 of public health genomics in the world, and it was held in Atlanta, in some grotty hotel in some suburb called Decatur. There were about 100 people there. Bartha [Knoppers] was one of the keynote speakers, and the American public health service were all a part of the Forces, so they all had uniforms and things, and the Surgeon General came out.[40] But the thing that struck me was I was the only attendee, of 120-odd people, from this side of the Atlantic. The others were all from Canada and America, mainly America. It was really Muin and I working together that gave me…you know, you need to have at least one person to talk to.

Sally Sheard

Thank you.

John Burn

The other thing to remember about the comparison with the US is that genetics never really took off as a speciality. It was largely this side of the Atlantic that it was recognised that you could specialise in genetics.

[39] Rodney Harris (1932-2017) was Professor of Medical Genetics at the University of Manchester from 1980 to 1997.

[40] Bartha Knoppers (b.1951) is Canada Research Chair in Law and Medicine at McGill University. From 1985 to 2009 she was Professor of Law at the University of Montreal.

Frances Flinter

Well, they don't have regional centres. A lot of hospitals have one lone geneticist who's a paediatrician with an interest in genetics.

John Burn

Well, that's right. You have to be a paediatrician or an obstetrician or a physician. The idea that you could be a clinical geneticist and not any of the others still surprises colleagues in America. I always used to upset them and tell them I also get paid the same as the neurosurgeons, which really upset them. Basically, we had a slightly unusual development. I guess Europe generally had clinical geneticists, although I think probably…

Frances Flinter

Not every country, because the Clinical Genetics Society did some work with the EU to try and define what a clinical genetics training would look like, and even in countries like, I think Germany at the time we looked at it, it wasn't a recognised speciality for them.

Mark Bale

It's not that many.

Rosalind Skinner

What about Holland?

Frances Flinter

Holland did.

John Burn

Holland was the best.

Frances Flinter

But the Czech Republic, certainly did not.

Mark Bale

The further you go south and east the less likely it is.

John Burn

The Eastern European countries did rather better than the West, actually. Also, when I was President of the European Society [of Human Genetics] I discovered that one of the very first things that happened was that Romania cancelled genetics because they were sorting out their healthcare system and they decided they didn't need genetics, because it wasn't recognised as a European speciality. I happened to have a Romanian PhD student, so we managed to write a letter in Romanian from the President of the European Society to say, 'Hang on, you can't do that'.

There was actually a long-running effort to try and get the European recognition. There were three countries that blocked it. Spain didn't want too many specialities, in Greece the scientists didn't want doctors involved, and Belgium were blocking it because they had a control of all the clinical posts from the universities and they didn't want a European ticket which would allow people to cross borders. But eventually we got it through.

Frances Flinter

Milan Macek.[41]

John Burn

Milan Macek, yes. We managed to get it onto the European…Arnold Munnich, who was then an advisor to President Sarkozy, got us into the Ministry of Health to allow us to have a breakfast meeting.[42] Then Milan Macek ran it, and it turned out you only ever got anything through the European Union if it was put forward by two successive Presidencies. So, we got it on the table in France, and then it went to Milan, who was Czech Republic?

Frances Flinter

Czech, yes.

John Burn

Yes, and he was very well connected in the Czech Republic, so then they carried it through. I still have a photograph of the breakfast in the Ministry of Health, which actually was a silver service with things over your arm, not a grotty cup of coffee like we used to get from Mark [Bale]. [laughter]

[41] Professor Milan Macek (b.1961) is Head of the Department of Biology and Medical Genetics at Charles University.

[42] Professor Arnold Munnich (b.1949) was Advisor to the President for Biomedical Research and Health from 2007 to 2012.

Sally Sheard

That's going in the transcript, you know.

John Burn

I was being generous. I imagine we didn't even get a coffee, actually, did we?

Sally Sheard

Is there anything else we need to record about the background of the key individuals – whether they're coming from public health backgrounds, bioethics backgrounds, medical backgrounds? Any other key determinants on an individual level that you think has driven some of this development?

Mark Bale

It's a question more than…because others might know better. I'm interested in a comment made about the Chief Medical Officer's role, because of course it's gone in peaks and troughs in my time, in my involvement. I don't know whether that's something that's visible from their reports, because certainly the later ones like Sally Davies and Liam Donaldson have done these advocacy reports as well as the state of the nation's health one.[43] I don't know whether there's anything you can pick up from those themes.

Peter Farndon

In the 1970s, Cedric Carter was the first advisor [Consultant Advisor to the Chief Medical Officer on Genetics].[44] In the Clinical Genetics Society [CGS] minutes for 1972 Cedric Carter reports that the Minister of Health asked him if the CGS would keep a register of families with Huntington's chorea – not disease, Huntington's chorea in those days. Then Sir Henry Yellowlees asked some questions again in 1976, so there was obviously a dialogue going on, certainly into the Clinical Genetics Society.[45] The people that I remember before Ian Lister Cheese…there was Jeremy Metters, who was an obstetrician, I think.[46] I think the way that we used to communicate was through the Chief Medical Officer's advisor on genetics – who was Cedric Carter, then Rodney Harris, then Marcus Pembrey, then Dian Donnai.[47]

[43] Sir Liam Donaldson (b.1949) was Chief Medical Officer from 1998 to 2010. The importance of genomics was highlighted by Davies in *Annual Report of the Chief Medical Officer 2016: Generation Genome* (Department of Health, 2017).
[44] Cedric Carter was Consultant Advisor to the Chief Medical Officer on Genetics from 1972 to 1982.
[45] Sir Henry Yellowlees (1919-2006) was Chief Medical Officer from 1973 to 1984.
[46] Dr Ian Lister Cheese (1936-2020) was a civil servant in the Department of Health from 1983 and Secretary of the Standing Medical Advisory Committee. Dr Jeremy Metters (1939-2020) was Deputy Chief Medical Officer from 1989 to 1999.
[47] Professor Rodney Harris was Consultant Advisor to the Chief Medical Officer on Genetics from 1982 to 1989. He was followed by Professor Marcus Pembrey from 1989 to 1998 and Professor Dian Donnai from 1998 to 2004.

Mark Bale

Yes, that's right.

Frances Flinter

And the National Screening Committee was involved in parallel with all of this as well, particularly people like Muir Gray.[48]

Ron Zimmern

I sat on the National Screening Committee for about five or six years, and I don't think anything specifically genetics came up.

Rosalind Skinner

It took a very long time. I was on it from its very first meeting until I retired.

Ron Zimmern

They were very reticent.

Frances Flinter

I was on the antenatal sub-group, and we did spend quite…maybe that would have been more in the 1990s by then, but there were quite a few proposals coming in. There were long discussions about people wanting a national screening programme for Turner syndrome, a neonatal screening programme and things like that.

Ron Zimmern

I remember people in public health interested in genetics. There were several papers written…someone called Darren Shickle writing papers on modifying the Wilson and Junger criteria for screening, to modify it so it was fit for purpose for genetics.[49]

Rosalind Skinner

That all started when…there were two sub-groups of the National Screening Committee, to start with. The antenatal one was the most active one, and the one that really looked at genetics.

[48] Sir Muir Gray (b.1944) was Programme Director of the National Screening Committee from 1995 to 2008.
[49] Darren Shickle is Professor of Public Health at the Leeds Institute of Health Sciences. See for example, D. Schickle and R. Chadwick, 'The Ethics of Screening: Is 'Screeningitis' an Incurable Disease?', *Journal of Medical Ethics*, Vol. 20, No. 1, 1994.

Then there was a childhood screening sub-committee too. They did look at things like Duchenne [muscular dystrophy], but for the main committee to look at starting a new screening programme for a genetic disease…it was a long time before we even had a clinical geneticist as a member of the National Screening Committee. The first one was, I'm sure, a lady who used to work in your [Peter Farndon] department. Fair-haired. Christine? I'm sure she worked in your department, Peter.

Peter Farndon

Not Tessa Webb?

Rosalind Skinner

No…anyway, eventually we got a clinical geneticist, and the committee started to look at genetic things really when the BRCA discussion started. No, I'm sorry, prior to that it looked at Tay-Sachs disease and whether or not there should be screening for a Jewish family for genes.

John Burn

And sickle cell disease, presumably as well was also…

Rosalind Skinner

That was later.

John Burn

That was later, OK.

Rosalind Skinner

You [Hilary Burton] did a needs assessment, didn't you?

Frances Flinter

But that was years after the debate started because the Tay-Sachs biochemical screening programme was run out of the lab at Guy's [Hospital], and then there was also some done in Manchester, but the anomaly was it was all paid for by a charity called Jewish Care. I remember going to the Department of Health several times saying, 'Look, this is an anomaly. You've got other screening programmes which are funded by the NHS, and yet for the Jewish community they have to raise the funds themselves'. They were very uncomfortable about that, but it took a very long time before anything happened.

Hilary Burton

We did the Tay-Sachs work in 2009.[50]

Frances Flinter

Yes, that was about 10 years after we first started raising everything.

John Burn

We haven't mentioned Paul Polani of course, who was a massively influential figure in getting Guy's into such a prominent position.

Sally Sheard

Thank you, I'm glad you brought him up now.

Frances Flinter

Well, he set up what was originally called – it's interesting – the Paediatric Research Unit at Guy's, which actually then became the Genetics Department, but when I joined it was called the Paediatric Research Unit.

John Burn

Marcus Pembrey trained with him before moving on to join Cedric Carter.

Yes, so I think the big areas were undoubtedly FAP [Familial Adenomatous Polyposis] screening and hCG [Human chorionic gonadotropin] and Bart's test for Down's [syndrome]. That was the area where I guess we as geneticists sort of were in contact with the screening committee. That was an area of common interest.

Rosalind Skinner

Antenatal screening tests offered to pregnant women for Down's syndrome and neural tube defects were already up and running, but run by departments in various parts of the UK. The antenatal sub-group tried to pull it together as a national screening programme and set quality standards and standards for patient information and so on.

[50] *Tay Sachs Disease Carrier Screening in the Ashkenazi Jewish Population: A Needs Assessment and Review of Current Services* (PHG Foundation, 2009).

Ron Zimmern

On that score, Malcolm Ferguson-Smith, when he came down to be a Professor at Cambridge, I remember I was Director of Public Health at the time.[51] I had huge arguments with him, because he wanted to set up what was essentially a screening programme for Down's [syndrome] before all the evidence was in place. I, being very public health, said, 'No, you can't do that'. To give him his credit, this interaction was one of the things which really taught me that maybe evidence-based medicine isn't everything, that Malcolm was right to have pushed through one of the first regional programmes before all the evidence was ready.

Rosalind Skinner

This is exactly the problem that existed on a bigger scale with the National Screening Committee as it was, because it was largely public health doctors who didn't know too much about genetics, didn't rate genetics, and it was an eye-opener to them because screening programmes were run according to the WHO [World Health Organisation] criteria, and that's it. It took us a long time to start debating widening the criteria to allow consideration of diseases that had a genetic aetiology. There was considerable concern about the identification of carriers and the implications of this when we started trying to talk about CF [cystic fibrosis] screening. It was very, very difficult.

Frances Flinter

The WHO criteria required an intervention, and there were many people on the antenatal sub-group of the National Screening Committee who were uncomfortable with the idea that the intervention might be termination of pregnancy, because they didn't feel that that was an intervention...

John Burn

Well, it might be of benefit to other family members. It's a little analogous to vaccinating children now, isn't it? It has to be of benefit to this child to do the screening test.

Hilary Burton

I think the same was true for neonatal screening, because for new-born screening they very much wanted it to be the advantage to that child, and the fact that screening might mean that the parents might be able to find out that a subsequent pregnancy might be at risk – they couldn't accept that as a reason. I don't think they have yet, have they?

[51] Malcolm Ferguson-Smith (b.1931) was Professor of Pathology at the University of Cambridge from 1987 to 1998. Ron Zimmern (b.1947) was Director of Public Health for Cambridge and Huntingdon Health Authority from 1991 to 1997.

John Burn

No.

It might be worth mentioning Angus Clarke in Cardiff because he was very active with new-born screening for Duchenne [muscular dystrophy], where this conversation became very focused.[52] So, we had to try and make an argument that it was a benefit to the child to have an early diagnosis, so they didn't spend a year and a half getting diagnosed and not getting the right care, but also, of course, it meant there wasn't a second child born in the family before you made the diagnosis of the first one. But that…it never quite got off the ground…

Peter Farndon

It ran for a while didn't it, and then it was stopped.

Rosalind Skinner

It did. It was on research funding, and I remember having a conversation with the Welsh CMO [Chief Medical Officer] – we were on the train together – who was unaware that the programme had started.[53] She was a public health physician.

John Burn

The other resistance with cystic fibrosis, which was mentioned…I can't remember the exact timing of this, but I ended up in lots of heated conversations with a biochemist from somewhere in the Nottingham area, who was absolutely, hugely resistant to using molecular testing, delta f508 testing and so on – it had to be done by biochemical means. And the idea of using carrier testing…they wanted to restrict us to only testing for the four [biomarkers], because they didn't want to make a diagnosis of heterozygous carriers of cystic fibrosis, and so they wanted us to do a test for four markers and then go back around and do a test for fifty-nine markers. We shocked them by saying, 'Well, we'll just test for fifty-nine, but we'll only read four of them', which, of course, was entirely possible…but that seemed a shocking concept. And we did. We actually set it up so you could only see the four and, if one of them was positive…but again, that was resistance from a biochemist.

Rosalind Skinner

That was new-born screening wasn't it.

To try to introduce antenatal screening for CF carriers, again, was a huge debate in the NSC [National Screening Committee]. I happened to sit on the NSC and the HGC [Human Genetics

[52] Angus Clarke (b.1954) is a Clinical Professor at the Institute of Cancer & Genetics, Cardiff University.
[53] Dame Deirdre Hine (b.1937) was Chief Medical Officer for Wales from 1990 to 1997.

Commission], and I remember offering to negotiate between…we got one of the moral philosophers from the HGC – John Harris, from Manchester – who came to one of the National Screening Committee meetings to try and persuade them that people had a right to their information.[54] So, if you did the screening and identified a carrier, they had the right to be told.

Frances Flinter

There was a lot of paternalistic baggage, wasn't there.

Rosalind Skinner

There was a lot, and it took a long time to work through it. There is a great difference between the outlook of a lot of public-health physicians and the geneticists, who are in there primarily to treat, if possible, but prevent too, and offer families information to help them. It came up again in the HGC – do you [Mark Bale] remember – soon after sequencing of the genome really became a possibility, the HGC began to think about its uses or applications for new-borns. I think there was an announcement, unexpectedly, from the Department of Health that all children would have their genotype done at birth, on their Guthrie card.

Mark Bale

That was one of the first things that came out from the White Paper, in a headline…it was just supposed to be a proposal.

Rosalind Skinner

John Sulston chaired the HGC sub-group set up to explore this proposal, and I remember the clash of cultures.[55] John was such a lovely man. He could not understand the clash of cultures between the public-health physicians, the paediatric epidemiologists from Great Ormond Street – the way they perceived screening for children, information for children, consent for children, and the pure geneticists like John – 'You can do the sequence. What's the problem? We can give you all this information'. So yes, it's a different professional way of looking at things. There was a culture difference, I think, and it's taken a long time. You in Cambridge [PHG Foundation] have been pioneers in Britain. There was no one for a long time in Scotland in the public-health fraternity at all. In fact, I found them quite antagonistic when I trained in public health, having been a geneticist. I found it very, very strange.

Naomi Brecker

Ros, I think you're underplaying your own contributions. I can remember, in the very early days of my time at the Department of Health there were very few people, there was very little understanding. There was Ron [Zimmern] knocking at the door and offering advice and

[54] John Harris (b.1945) is Lord Alliance Professor of Bioethics at The University of Manchester.
[55] Professor Sir John Sulston (1942-2018) was Director of the Sanger Centre, Cambridge from 1992 to 2000.

information and the PHGU [Public Health Genetics Unit] inputs and things, and I always remember looking across the border to Scotland, and you seemed to have a calm and careful control over what was going on. You had fingers in lots of pies. You understood the brief. You were spotting the opportunities, and I really think you are underlying your own contribution and the lead you brought to all this.

Ron Zimmern

Talking of Scotland, it leads me to think of another name – Neva Haites.[56]

Rosaland Skinner

She was Professor in Aberdeen. Neva did everything, but she always had time and she was a wonderful communicator. She gave the very first talk that the NSC ever asked anyone to come and give them on a genetic issue to try and inform them. I remember there was an Oxford meeting and I said to her, 'It's got to be you and you've got to talk about BRCA and cancer genetics and explain the benefits of genetic testing'. She was brilliant, and that's when the NSC began to think more widely about genetics, when we were just putting out feelers for genetic issues.

Frances Flinter

Thinking about the route that people of our generation took into clinical genetics, it was mostly from a paediatric background in the 1970s and 1980s. That's where most of the patients being seen in the genetics departments came from, and in fact you had to have paediatric membership, if you remember, to be able to start training in genetics. I'm just trying to remember when that changed, and we started to allow people in who'd only done the adult membership.

John Burn

I did adult membership.

Peter Farndon

So did I.

Frances Flinter

But you did have to do a stint in paediatrics?

[56] Neva Haites (b.1947) was Professor of Medical Genetics at the University of Aberdeen from 1996.

John Burn

No – I did do paediatrics, but I didn't have to.

Rosalind Skinner

We were talking before – Frances is much younger…before that a lot of people came in from pathology, like Malcolm Ferguson-Smith and Michael Laurence in Cardiff.[57]

John Burn

It was whoever turned up in the room, really.

Frances Flinter

There was a period when I know the requirement was that you had to have done some paediatrics; most people training when I was a registrar had a background in paediatrics.

John Burn

I think you certainly had to have a year of paediatrics or something in your training. The role of course of paediatrics in child health wasn't actually formed until the mid-1990s, so you couldn't get membership...

Sally Sheard

I'm going to move us on because we've got a lot to get through. I'm fascinated by the college politics as well. We might have to have a separate session on that. Can we briefly – and I mean very briefly – just cover the impact of the Human Genome Project and the ongoing discovery of more disease genes on the potential for public health genomics. Who would like to speak to that?

John Burn

I would start by saying we almost didn't see it [the Human Genome Project] when it started. Certainly, in my world, my colleagues in clinical genetics…John Sulston and the guys at the Sanger [Centre] were just somewhere else, and it didn't really impinge on my consciousness early on how important it was.

[57] K.M. Laurence (1924-2018) was Professor of Paediatric Research at the Welsh National School of Medicine from 1976 to 1989.

Frances Flinter

Except that most people, when they were doing their training, took three years out to study a particular disease and try and map the relevant genes, so we developed a whole generation of clinical geneticists who had a particular interest in one or two diseases. That then tended to determine which laboratories then set up the testing service for that disease – it was determined by where the former Registrar had done their MD or PhD in that particular gene, so I think it had a big impact.

John Burn

Yes, it had a huge impact, but not the actual planned human genome. In other words, the generation of markers and the fact that we were getting more and more markers…we started with thirty-two in the 1970s and we were trying to map diseases....

Ron Zimmern

We're now getting too much of a clinical geneticist's view on this, because there was another group that, during the 1990s and 2000s I think….a group of academic physicians developed who were very good at genomics but who hadn't been anywhere near a clinical genetics training programme – people like Stephen O'Rahilly and Stephen Holgate.[58]

Just last week, I was speaking to Keith Peters on the phone, and I said, 'Keith, why did I set up the PHGU? I can't remember'.[59] And basically, what Keith said was very interesting. He said, 'Because you were in an environment in Cambridge where there was genetics all around you, genomics all around you, genetic science all around you', and maybe that was it. At a subconscious level, we were surrounded by all this genomic science in Cambridge.

Hilary Burton

Yes. I think I noticed the impact of the genetic epidemiology that was going on and the early work on cancer.

Ron Zimmern

It was Bruce Ponder initially, and then taken up by Paul Pharoah.[60] All that cancer genetic epidemiology was really interesting.

[58] Sir Stephen O'Rahilly (b.1958) has been Professor of Clinical Biochemistry and Medicine at the University of Cambridge since 2002. Sir Stephen Holgate (b.1947) has been Professor of Immunopharmacology at the University of Southampton since 1987

[59] Sir Keith Peters (b.1938) was Regius Professor of Physic at the University of Cambridge from 1987 to 2005.

[60] Sir Bruce Ponder (b.1944) was Professor of Human Cancer Genetics and then Professor of Oncology in Cambridge from 1992 to 2011. Paul Pharoah has been Professor of Cancer Epidemiology at the University of Cambridge since 2012.

John Burn

We haven't mentioned cancer genetics. Cancer genetics was a massive influence, wasn't it?

Ron Zimmern

Huge.

John Burn

That convergence of the genome project and finding the genes for cancer changed our world, because suddenly we stopped getting hung up on prenatal testing and termination...

Peter Farndon

Can I just wind back a bit, Ron, to take up something you've just said? The generation before us were adult physicians or pathologists who had a real interest in genetics. We had a real interest in genetics. I think, if we had been given the opportunity, we may well have stayed in our own specialty and done genetics as part of the specialty, but you could not do that, because the other specialties thought you were completely bonkers to think about doing genetics. The only place where you could do any genetics at all was with one of the people who had been idiosyncratic in the first place in setting a unit up. So, in our generation we had no choice.

Ron Zimmern

And that's coming together now, because the next generation of trainees have to do genomics as well as clinical genetics.

Peter Farndon

Which is what we wanted to do in the first place. Do you agree, John?

John Burn

Yes, absolutely.

Rosalind Skinner

There was no training when I wanted to be a geneticist.

John Burn

We didn't have our own training programme. It was recognised as a specialty in 1976, but you're right – the whole GWAS [Genome Wide Associations Studies] world and the whole chasing of complex traits and so on, came in from another track.

Peter Farndon

It's interesting – the only way that we could do genetics was unlike the people who are in the specialties now doing genetics, because they're surrounded by it in a wider area. We could only do it in the areas that were available then. I hadn't thought of that before. That's true.

Ron Zimmern

Because I remember there were all sorts of arguments at one time about – 'Who's this guy O'Rahilly? He's not trained in genetics'.

Sally Sheard

Can we move on, please – if there's nothing else that people wish to add at this point on the Human Genome Project. Any final comments?

John Burn

It was massively influential. It came up like floodwater, and we were all sitting around doing our own things and suddenly we realised this is getting bigger and bigger and it started to change the whole conversation. It's difficult to pinpoint when that was. It was because it became more and more obvious that we could find any gene. The markers were just becoming so easy to handle that mapping things was going to be even easier.

Ron Zimmern

Hilary is absolutely right. You asked the question, 'When did the ethics come in?' – I think she's absolutely right in saying that it was the Human Genome Project, because they set aside, I think 3-5% of the total budget for ethics. The first director was a guy called was Eric Juengst.[61] When Eric stepped down, it was taken over by Eric Meslin. Both were trained ethicists and philosophers.

[61] Professor Eric Juengst was Chief of the Ethical, Legal and Social Implications Branch of the National Center for Human Genome Research at the U.S. National Institutes of Health from 1990 to 1994.

Frances Flinter

And John Sulston, who was a huge figure in that [Human Genome Project], was on the Human Genetics Commission, and he was – although his background was very much science – he was very aware of all the ethical issues, so there were a number of reports at that time.

John Burn

By the time the Human Genetics Commission arrived we had all converged, because that was 1999/2000, and I think we all realised it was now big business…the battles over the BRCA gene and all the rest of it. I think, by that stage there was a convergence, a realisation that this was changing everything.

John Burn

What was the committee before the Human Genetics Commission?

Mark Bale

It was the Human Genetics Advisory Commission.

Rosalind Skinner

And there was the Advisory Committee of Genetic Testing. There were ethicists on that, because I remember being asked to find someone in Scotland, and the Bishop of Edinburgh agreed.

Mark Bale

Just to finish up this point before we move on – I think, from my perspective, possibly slightly different to Naomi's [Brecker] perspective, in the Department [of Health], the rhetoric around the Human Genome Project and all of the interest that it raised, both in the ethical, legal and social implications, but also something we haven't mentioned, and was particular relevant in cancer, is the interest around industry, about what the benefits were for drug discovery and also what the landscape was around patenting. Ros [Skinner] reminded me about debates around BRCA patenting and so on. So, all of that started to attract interest. What was most interesting – if you're looking at this in a very micro-lens way – the Human Genetics Advisory Commission was run by DTI [Department of Trade and Industry], which was something that was deeply disappointing, to say the least, to my colleagues in the Department of Health. In fact, most of the joint departmental meetings we had were about keeping an eye on each other. And then once the HGC was put into the Department [of Health], DTI kept a beady eye on it. So, it's quite an interesting tussle between the industrial perspective and the health.

John Burn

I think the industrial point is an important one because the pharmaceutical industry started to realise in the mid-1990s that there was a big story here. There's a whole new direction of travel. From a personal point of view, I got drawn in by Glaxo Wellcome, as was then…basically, they were headhunting. We were giving them lectures and stuff, but I realised afterwards they were basically looking for somebody to run genetics, and I didn't want to do it because I thought it was too soon. They were like a decade ahead of the curve. Allen Roses eventually took that job.[62] He was a geneticist. Then Peter Goodfellow. They were looking for geneticists and genomicists to bring in and try and hunt for genes. They could see there was a story here. Unlike medicine in our world, the big companies are always way upstream. They're looking ten, twenty years ahead – that's how they keep going. So, I think that was a very important influence in this whole story.

Naomi Brecker

It also provides a segue into your next question about policymakers, because it was the Human Genome Project that grabbed the attention of Ministers and Secretaries of State. I think that's why Alan Milburn wanted to make a speech, which then led to the White Paper, because it was getting big…it was the patents, it was BRCA, it was drugs…

John Burn

Alan was very receptive.

Naomi Brecker

I think it was also driven by the people who were holding the Director of R&D [Research and Development] posts in the Department of Health. So, it was John Pattison then Sally Davies.[63] Of course, with Sally Davies' background…then she became CMO [Chief Medical Officer], and you had someone nested right in the heart of things who actually understand the language from their own perspective.

John Burn

Sally was a haematologist, a Registrar, when I was at Great Ormond Street.

Ron Zimmern

Michael Peckham was the first Director of R&D that I first saw…[64]

[62] Dr Allen Roses (1943-2016) was Senior Vice President of Research and Development at Glaxo Wellcome from 1997 to 2007. Professor Peter Goodfellow (b.1951) was Senior Vice President of Discovery Research at GlaxoSmithKline from 2001 to 2006.
[63] Sir John Pattison (1942-2020) was Director of R&D at the Department of Health from 1999 to 2004. Dame Sally Davies was Director General of R&D at the Department of Health from 2004 to 2011.
[64] Sir Michael Peckham (1935-2021) was Director of R&D at the Department of Health from 1991 to 1995.

John Burn

The big speech that Alan gave when he announced the Genetic Knowledge Parks was in Newcastle, primarily because of two brothers from Sunderland who started the foot-and-mouth outbreak. So, he was about to give the lecture at Guy's, and all the ministers were pulled in at the last minute for the crisis meeting on the foot-and-mouth outbreak, so I contacted Alan and said, 'Why don't you do it in Newcastle?' and so he moved the lecture to Newcastle, so all the London journalists would have to travel to Newcastle, which he thought was amusing.

Phil Begley

I wondered if I could invite Ron – you mentioned Michael Peckham – could you say something about those two reports produced by Martin Bobrow and John Bell in 1995.[65]

Ron Zimmern

No, except that that was when I first started the PHGU. These were the first two official reports, together with a third one, which was a little A5 booklet on clinical genetics services, plus these two glossy reports. I didn't know the characters at the time, but clearly, now knowing them, it was very clear that was one written by John Bell and the other by Martin Bobrow. One was very measured. They all said exactly the same thing, but they were completely at odds about the timescales.

Frances Flinter

The one written by Martin – I was the scientific secretary.

Ron Zimmern

Yes, one written by Martin, who was very measured, and one by John Bell, which was the usual – 'Medicine will be revolutionised in the next 10 years'.

John Burn

That's been a recurring theme.

[65] *Report of the Genetics Research Advisory Group: A First Report to the NHS Central Research and Development Committee on the New Genetics* (London: Department of Health, 1995). The Genetics of Common Diseases: A Second Report to the NHS Central Research and Development Committee on the New Genetics. Martin Bobrow (b.1942) was Profess or Medical Genetics at the University of Cambridge from 1995 to 2005. Sir John Bell (b.1952) has been Regius Professor of Medicine at the University of Oxford since 2002.

Ron Zimmern

It has. It was also very interesting that, when we did the Nuffield Trust report – which all of you participated in, I think – everybody said much the same thing.[66] But again, the one area where we could not get any consensus amongst all the experts – and we pretty well saw through that process all the experts – was timescales. They all knew the endpoint. Nobody disagreed about the endpoint. But they were all over the place about timescales.

John Burn

I think it's fair to say that when the 2003 White Paper came out, the geneticists were very much in the ascendency and that was very much what made the document – what we could do and would do. Whereas the 2012 report *Building on our Inheritance,* which John Bell chaired, which I chaired the technology part of, that was very much more John Bell's moment of, 'Let's aim for the sky and hope we get there'.[67]

Sally Sheard

We're jumping ahead here. It's always a challenge keeping these things on track.

Ron Zimmern

Keep us in order.

Mark Bale

Can I just say – one of the things that I picked up when I joined the Department [of Health] in 1999 that touches on something we've said already and Frances in particular pointed out, was the interest around the 1990 Human Fertilisation and Embryology Act and what meant for eugenics, if you like – what that meant for areas like the ability to apply genetics to embryos. That was a debate that was going on. Another one was to do with the Gene Therapy Advisory Committee – which I think you served on initially, John – which wasn't just about what you could do to use gene therapy to treat disease, but the impacts on germline, and all those debates that we're still having now. Those were the two areas that I picked up when I was outside the Department, in which they were very interested in what was happening in genetics and we haven't touched on yet.

John Burn

Tied into that was also the HFEA [Human Fertilisation and Embryology Authority] and control of in vitro fertilisation and pre-implantation diagnosis. We were very heavily into that, and the 'three-parent babies' subsequently. The Human Genetics Commission was picking up the

[66] *Genetics and Health: Policy Issues for Genetics Science and Their Implications for Health and Health Service* (Nuffield Trust, 2000).
[67] *Building on our Inheritance: Genomic Technology in Healthcare* (Department of Health, 2012).

regulatory areas, like the moratorium with the insurance companies, which was perhaps its biggest achievement…and the Gene Therapy Advisory Committee, which I'd completely forgot that I was on.

Frances Flinter

I think the other really important thing that the Human Genetics Commission achieved was the change in the law that made it illegal to test somebody else's DNA without their consent.

John Burn

Yes…we're recording this meeting. That was…

Peter Farndon

Interesting.

John Burn

That was an interesting battle.

Phil Begley

If I may, I'd just like to prompt Mark to make the point about the 1995 Science and Technology Committee report that you alluded to earlier, because that was influential in terms of forcing the department, along with some political pressure, to get these kind of committees off the ground, to acknowledge that genetics was an issue.[68]

Mark Bale

I think there was an interesting thread there. I think the 1995 report was interesting because there were two of them. One was very detailed, like some of the other reports we've had recently, and the government response was deemed to be somewhat lacklustre, so they actually had a second inquiry, which is something you don't really want as a civil servant, and then a second response, which was much more accepting of the big principle, which was the Human Genetics Advisory Commission.[69] I think it also led to the Advisory Committee on Genetic Testing [ACGT]. Early carrier testing was one of the things they looked at. The other one was quality of laboratories and whether laboratories had what they needed. The ACGT was one that I picked the tail-end of, but they all came from that 1995 report and I think it generally helped to raise the awareness of some of this.

[68] House of Commons. Science and Technology Committee. *Human Genetics: The Science and its Consequences* (London: HMSO, 1995).
[69] *Human Genetics: The Science and its Consequences*, Cmnd. 3061 (London: HMSO, 1996). *Human Genetics: The Government's Response*, Cmnd. 3306 (London: HMSO, 1996).

John Burn

Since we've raised the point about control on DNA testing – Matt Ridley made a lovely point when he said that Angelina Jolie was the third most important person in making DNA public knowledge, the other two being Monica Lewinsky and O.J. Simpson.[70]

[Laughter]

And it's so true, because those three episodes transformed public understanding of the importance and power of DNA technology. The Human Genetics Commission was not really on the topic of control of who could test your DNA, but it was the American experience that led people to start realising, and Government, that this was a weapon that could be used in all sorts of settings of relevance to us too, so they wanted something to control it. We were very concerned – in fact, Mark [Bale] and I, probably our deepest conversations were about how we protected all the genetic DNA banks at all our regional genetics centres, because there was this threat that everything would just get thrown away if we didn't have specific consent to hold it, which, of course, you retrospectively didn't have.

Frances Flinter

There was a period of time when people started throwing away Guthrie cards wasn't there, and there was panic…

John Burn

I think Mark and his team found that beautiful way through it, whereby, if you had the DNA, that was OK, but it was illegal to take a sample in order to obtain the DNA, so it put the law on the obtaining of the sample, not on the holding of it, which got us out of a hole. We were really naive in the 1980s and 1990s. We just trusted that…Guthrie cards, we had hundreds of thousands of them in stacks, and no one thought that that was something that could be used against you.

Frances Flinter

And sometimes they were stored in their greaseproof-paper sleeve, which stopped one contaminating the next, and then some centres were so short of space that they were removing the greaseproof-paper sleeves, so that the cards were touching each other…

Rosalind Skinner

They were in cardboard shoeboxes at one stage in Scotland, the whole collection. Then at some point in time, we started discussions about the fact they weren't consented samples. Once the

[70] Matt Ridley (Viscount Ridley) (b.1958) is a journalist and popular science author.

Human Genome Project reports came out, the John Sulston sub-committee of the HGC was looking at, 'Should we use Guthrie cards to sequence the DNA of new-borns?' The whole debate started – well, certainly it was started in Scotland – 'Can we use this collection for research if they're not consented samples, and what should be the access arrangements that we would insist on?' I think it was the MRC that did some studies – population-wide studies – to judge people's attitudes to the use of Guthrie cards.

Ron Zimmern

But from the legal perspective, I think a few things happened. First of all, in the 1960s or 1970s, when we were medical students, the law of confidentiality was very simple, and you could summarise it in three pages in a GMC [General Medical Council] document what confidentiality was. Well, European law then brought in article whatever it is on privacy…then another thing that came on top of that, which was, again, different to the common law, different to the European law, was the 1984 Data Protection Act, and the European data protection principles, which added another layer of complexity. This stuff would have been easy if it had still been in the 1970s with just a simple common law of confidentiality.

Sally Sheard

Peter.

Peter Farndon

There's one sentence in the 1995 House of Commons Science and Technology Committee response from the government which I think is really interesting, compared with how things are now. It says, 'The Government believes the emphasis and direction that have been given to the provision of genetic services…are sufficient to ensure their orderly development without additional central oversight', which I thought was fascinating.[71] It wasn't envisaged that there would be anything top-down at that stage in 1995. Isn't that interesting?

Sally Sheard

Can I now take us on to some of those key individuals?

Peter Farndon

Sorry, can I just mention something else before?

Sally Sheard

Yes, please.

[71] *Human Genetics: The Science and its Consequences*, Cmnd. 3061 (London: HMSO, 1996).

Peter Farndon

The work of the consultant advisor to the Chief Medical Officer, I think resulted, in 1984, in getting special medical development funding – which is where Cardiff, Manchester and London got special grants from the Department of Health to set up and evaluate the DNA technology for certain single-gene disorders. That's really important, because that was the start of the regional genetics centres saying, 'Yes, we can develop a DNA service.'

Sally Sheard

Would somebody like to introduce us to Ian Lister Cheese and his enablement of some of these initiatives?[72] Is he a significant individual?

Rosalind Skinner

I think he was, because the first time I came across anyone talking about genetics in the Department of Health was when Ian invited me to a meeting – I think it was Peter Harper who had been lobbying Ian – and I remember it was somewhere in Regent's Park, with clinical geneticists talking about guidelines on how the service should work and setting up the first structures organising clinical genetic services.[73] It was something like that. I can't remember exactly, but he was certainly the person, I think, a lot of geneticists of our era went to speak to in the Department of Health. I know Ron [Zimmern], you spoke to him, and I know Peter Harper spoke to him a lot. So, I think he was influential.

Peter Farndon

I think he was in the Department of Health when Rodney Harris was the consultant advisor. When I worked in Manchester, I know that Rodney spent a lot of time talking to Ian Lister Cheese and he used to come up to Manchester to look round.

Rosalind Skinner

That's right…we were drawing up quality standards because it was soon after I joined the Scottish Health Department in 1988, and I was the first person that had set foot in that Department who actually had a background in genetics and knew something about it, so I got detailed straight off to go down to this meeting and find out what it was all about, and then we did a review in Scotland following that. So, I think Ian was very central to some of the early elements. He was a paediatrician by background.

[72] Dr Ian Lister Cheese (1936-2020) was a senior civil servant in the Department of Health from 1984.
[73] Sir Peter Harper (1939-2021) was Professor of Medical Genetics at Cardiff University from 1981 to 2004.

John Burn

I have a very fond memory of Ian, but I'm just trying to…he was one of those people, rather like Mark [Bale], who just facilitates so beautifully, I almost didn't notice that he'd done it.

Rosalind Skinner

Yes – a gentleman to his fingertips.

John Burn

He was a real gentleman. He was a very tall, elegant gentleman, but very much plugged into genetics. He got it – think that's the bottom line. I can't give you a specific example, but it wasn't his job to lead it. It was his job to make sure it happened, and it's quite difficult to pin down.

Mark Bale

I don't know if you remember Naomi…I didn't know him or work for him, but we had separate, parallel structures, with medical advisors and with policy advisors, and Ian was the medical advisor, and it was Tony Taylor who was...

Ron Zimmern

We've been trying to find Tony Taylor…nobody can find him…

Mark Bale

No – he's retired…

Naomi Brecker

I think what you're highlighting is that in those days the Department of Health was very fragmented. I came in working in Sheila Adam's empire… it was the Health Services Directorate or whatever it was called in those days.[74] I think she may have reported to CMO.

Ron Zimmern

She was deputy CMO.

[74] Dr Sheila Adam (b.1949) was Director of Health Services in the Department of Health from 1999 to 2001 and Deputy Chief Medical Officer from 1999 to 2002.

Naomi Brecker

She was deputy CMO at one point, wasn't she? And she had within her bit the people around the confidential inquiry into stillbirths and maternal deaths, which had a genetic flavour, so they wanted someone else to do a bit more genetics, which is why I started picking up some project work, and then it morphed into a post, and then it morphed into a unit and a grant, and then all these other bits started coming together.

Ron Zimmern

So, this is what I want to find out, because I started all this by inviting Sheila to come up to see me in Cambridge at the end of 1996 or the beginning of 1997, and that was when I was thinking about genetics and health. I knew Sheila from my public health days, and so she very kindly came up and I said, 'Look, the Department must start getting interested in all this.' And some months later, I got an invitation to speak to the NHS Departmental Board, which was, at that time, chaired by Sir Christopher Kelly.[75] But I have no idea what happened when Sheila went back to the Department.

Then the other thing, mentioning Rodney Harris – I'm just wondering the extent to which you will need to know something about genetics and primary care, because Hilary Harris is a key figure in that, but it never really took off until recently.[76] I think there's been more happening these last few years.

John Burn

Again, slightly ahead of its time.

Frances Flinter

In 2003 – out of the White Paper – they created GPSIs, didn't they – GPs with a Special Interest (in Genetics), around ten of them…

Rosalind Skinner

Prior to that, the Harris' in Manchester got involved because it was round about the time when Nick Wald was setting up cystic fibrosis couple screening, and David Brock was doing the same in Edinburgh, and I remember that MRC had a meeting and we were all there – Nick and David and so on – and they wanted to set up a series of pilot projects to see if carrier testing would work, and Hilary [Harris] got the money from that to do carrier testing in Manchester, in her primary care practice there. She was one of the first.

[75] Sir Christopher Kelly (b.1946) was Permanent Secretary at the Department of Health from 1997 to 2000.
[76] Dr Hilary Harris (b.1943) was a leading General Practitioner in Manchester.

Frances Flinter

And Hilary [Harris] was on the Human Genetics Commission.

Rosalind Skinner

Yes, I suggested her to the Department of Health…because she was the only primary care physician I knew who was involved in genetics at all at that time.

Frances Flinter

Being married to a geneticist did help.

Rosalind Skinner

It helped.

John Burn

That pilot programme in Edinburgh ran for a long time but never quite got generalised, rather like the new-born screening for Duchenne [muscular dystrophy] in Wales. It's one of those things that flowered in one location but didn't spread.

Rosalind Skinner

That was because, for those kind of programmes to blossom, as it were, and become population-wide programmes, they had to go to the National Screening Committee and fulfil the criteria…I'll say no more.

Sally Sheard

Is there anything we need to note at this point on the role of the Royal Colleges or the Clinical Genetics Society? Tell us how British policymakers begin to get interested in genetics.

John Burn

The Clinical Genetics Society and the British Society for Human Genetics have always been influential right through as being the source of wisdom, I think it's fair to say.

Frances Flinter

In the early days, the Royal Colleges had much less of a role, other than overseeing the training and accreditation if you were training to become a clinical geneticist. It wasn't like the Joint Committee on Medical Genetics, which really does bring in all the different Colleges. The Clinical Genetics Society was basically a networking group, and people met once or twice a year and talked to each other, and they knew what was going on in the other centres and they knew which centre was offering a particular test and they knew how those centres were resourced and what funding issues they had and when they had posts coming up. It was very important. And they started to set up working groups to look at things like what should a clinical geneticist's role be, what should their workload be, what sort of training should they have...

Rosalind Skinner

The same for testing and all these things. They did a lot of influential work and I think they were the main lobbying group for genetics to the Department of Health. You [Peter Farndon] have got all the old papers.

Peter Farndon

I have.

I think we do have to consider the – what was it called – the Clinical Genetics Committee of the Royal College of Physicians, which ran alongside the Clinical Genetics Society. We're being recorded aren't we…In my various roles as chairman of committees, including being the chair of that very committee, and subsequently the Joint Committee on Medical Genetics, the Royal College of Physicians in the past sometimes had an interesting way of working and an interesting networking pattern, which allowed ideas to be tried out and things to happen, just like that. And so, I think there was a lot of information shared between my predecessors as the chairs of the Royal College of Physicians' Clinical Genetics Committee and the rest of the community, and particularly the Department of Health, because through the Royal College you could have access directly to the Minister.

France Flinter

I wonder what the subtext behind that is.

Sally Sheard

He was being very careful.

John Burn

I think the Royal College of Physicians in particular was very supportive, but we were a fairly minor item. The clinical geneticists were welcomed in…

Peter Farndon

But it was the Clinical Genetics Committee under Rodney Harris and Peter Harper who were able to do the seminal set of documents which were really important. So, the Clinical Genetics Society had done the original documents about population screening and amniocentesis and what should a clinical geneticist do, but then the committee at the Royal College looked at it from a population point of view, and Sarah Bundey wrote a lot of the documents which are still around about, 'What does the population need?' She tried to work out the incidence and prevalence of various disease, what staffing would you need, what would you expect, and there were five or six documents, and they all came from the Royal College.[77]

Frances Flinter

They were very important.

Naomi Brecker

What date was that?

Peter Farndon

Late 1980s, early 1990s.

Naomi Brecker

They're not represented around this table, but the Association of Genetic Nurses and Counsellors was very active in the late 1990s, early 2000s, in forming their professional identity and their accreditation, and that also was a big driver, because, of course, that increased the workforce and was very relevant to the kind of rollout into populations.

John Burn

Again, that's a very country specific development. In America, genetic counsellors have huge traction because the physicians haven't got time to do the job, whereas it's much harder to get them here, and in Germany I'm not sure they've even got them yet. So, at the European Society [of Human Genetics], we got a subcommittee on genetic counsellors specifically, because they were an endangered species at European level. Sorry, we're digressing…

[77]See for example, J.S. Fitzsimmons, M. Baraitser, B. C. C. Davison, M. A. Ferguson-Smith, N. C. Navin, and M. E. Pembrey. *The Provision of Regional Genetic Services in the United Kingdom. Report of the Clinical Genetics Society Working Party on Regional Genetic Services, Supplements to the Bulletin of the Eugenic Society*, 4, 1982. *Prenatal Diagnosis and Genetic Screening: Community and Service Implications* (Royal College of Physicians, 1989).

Sally Sheard

We are. I'm going to not let us go into the international realm because we've got so much more to talk about from the UK perspective. Can I just ask, before we move on to the break, Naomi, would you like to talk a bit about the Department of Health Genetics Unit?

Naomi Brecker

I was afraid you were going to say that.

[Laughter]

This is going right back. I think what I said before is fair. It morphed and it happened, and there was this increasing…I suspect it was driven by people like Sheila Adam, who really wanted the Department to take much more of an interest. She had people talking to her like Ron [Zimmern] and others, and I think she wanted to get more of a focus. So, what started off as a single post being project-funded, morphed into a few more people and civil servants who knew how to do civil servant stuff, and support for Ministers to get questions answered, tabled, to use the opportunities.

And then, from my memory, it somehow then morphed into getting more ministerial interest and the speech, which Alan Milburn gave in 2001. Before that, it was very much in Sheila Adam's part of the Department, because it was about specialised services commissioning and trying to get the commissioning and advisory groups interested in coordinating and bringing together and, as people were saying earlier, not having it regionalised and replicated, and trying to get some efficiency into the system. So, I think that's how the Genetics Unit really came together. You get traction and you get staff when you get resources when you have to do things like start with a Green Paper, which became sexier and sexier, probably because of the Human Genome Project and other drivers, they suddenly thought, 'Gosh, it's not Green anymore – we're going for a White Paper.' And then you get you Head of Branch who takes it all over and then you write a chapter, and then you go off to another job…

Ron Zimmern

When did you [Mark Bale] join?

Mark Bale

I'm glad you answered it that way, Naomi, because I think the fragmentation bit is something I was afraid I couldn't answer. I joined because the Unit expanded, or a unit expanded. I'm never quite sure whether it was Sheila Adam's unit, but…it reported to Marcia Fry, who also had the HFEA, as well as, I think, eventually, she had the Retained Organs Commission and all of the things that became the Human Tissue Authority.[78] We had a Secretary who used to

[7878] Marcia Fry was an Under Secretary in the Department of Health between 1989 and 2003.

answer the phone and say, ‘Genetics Secretariat’, and then somebody pointed out that sounds a bit like ‘Eugenics Commissariat’.

[Laughter]

We basically ran committees – we ran GTAC, we ran the ACGT – and then, as the Green Paper/White Paper speech work developed, it got into a full Branch.

Naomi Brecker

I think I just got morphed across, to be honest.

Mark Bale

I think that’s the way began working with you…

Naomi Brecker

I think it just happened. A bit like you’re describing with service developments, I think people realised that something needed to be done. They spotted opportunities, they seeded stuff, and then someone thought, ‘Well, things need to build and come together.’

Ron Zimmern

I didn’t know much about this history, but one thing I do remember is that I worked with Tony Taylor, and he was very helpful and very nice, but somehow the post-Tony Taylor period had a different feel. It seemed more professional, rather than just a *One Man and His Dog* sort of feel…

John Burn

I think an interesting point around Alan Milburn’s speech was – because he was a North-East MP and we’d just had huge publicity with the Centre for Life, I think he could see that it was good for the North-East as well. There was something around that. I think that probably helped. But I remember we had one meeting, where we all sat in a room about this size, and Alan came in with a whole bunch of civil servants – I can’t remember who was with him – and we all gave him a talk on genetics, just to get him on the right page, and he clearly just ran with it. I don’t know if the northern bit was important, but he certainly ran with it.

Sally Sheard

I think the northern links were important.

Mark Bale

The other Minister that was involved and I think gave us a very hard time was Yvette Cooper.[79] She was Public Health Minister at the time. She was helpful but she was really focused on delivery, and I think Alan gave big speeches and Yvette was the one who…

Naomi Brecker

But John Reid took over, didn't he.[80] I remember we briefed him to the hilt on something and he went, and he gave all the wrong answers…

[Laughter]

Rosalind Skinner

He was a very different person. Yvette Cooper was heavily lobbied, for instance, by the Cystic Fibrosis Trust, and she pushed cystic fibrosis screening. John Reid came from the west of Scotland and the minute he was appointed I knew things were going to change and be difficult on the genetics front.

John Burn

We had a meeting at Number 10 when John Reid had just been made Secretary of State for Health, and I sat next to him. He was just like a kid who'd got a toy for Christmas. He said 'It's great. I keep getting these jobs. I have no idea what I'm doing'.

[Laughter]

He basically was just very enthusiastic, but he admitted he had no knowledge of the space. He just got moved into the seat.

Peter Farndon

That was the launch of the White Paper.

John Burn

That's right.

Mark Bale

[79] Yvette Cooper (b.1969) has been Labour MP for Pontefract and Castleford since 1997 and was Parliamentary Under-Secretary of State for Public Health from 1999 to 2002.
[80] John Reid (Baron Reid of Cardowan) (b.1947) was Secretary of State for Health from 2003 to 2005.

He arrived not long before the White Paper was finalised, I think. I remember one thing that he did do, which I've quoted several times, is he personally wrote an extra couple of lines in the ministerial foreword [to the White Paper] about, 'You don't need to worry about genetic testing because we have the NHS. We're not like those overseas people with health insurance schemes'. That came from him. The other thing was that everyone used to remark that when you went into his office it was full of pictures of him climbing out of tanks and climbing into jet fighters, nothing about hospitals...I don't think he wanted the job…

[Laughter]

Sally Sheard

On that point, it's probably a good time to have a break…

[Break]

Sally Sheard

So, if we could resume by looking at some of the key policy developments – I think we've touched on some of these already – from the 1990s. Ron, I don't know if you wish to say anything more about those 1995 reports to the NHS Central Research and Development Committee or by the House of Commons Science & Technology Committee?

Ron Zimmern

Not specifically. I think I just want to say one thing about our Nuffield Trust genetics scenario report – which I think most of you participated in – which was published in 2000.[81] Looking back, I'm very proud of the fact that we identified pretty well all the issues in that report, that there was nothing we had missed. I am really very grateful to the Department and to all the actors in this – the publication of the White Paper etc. – as everything that we wanted to happen has happened. The surprise to me was that it took twenty-five years rather than just five to ten, but it is a great tribute to our policymaking colleagues that we have got to where we've got to. I think, Peter, you would agree.

Peter Farndon

I would.

[81] *Genetics and Health: Policy Issues for Genetics Science and Their Implications for Health and Health Service* (Nuffield Trust, 2000).

Sally Sheard

Thank you. Peter, would you like to say anything on the British Society for Human Genetics [BSHG] from 1996? Do you think that was something that had an impact on this trajectory?

Peter Farndon

Yes. Up to that point, there were four professional organisations – the Clinical Genetics Society, the Association of Clinical Cytogeneticists, the Clinical Molecular Genetics Society, and the Genetic Nurses and Social Workers Association – and it had become apparent for a number of years that we needed a unified voice, to give responses to questions which the professional societies were asked. So, it could be envisaged that, if one – for instance policymakers – didn't want to do anything, you asked the same questions to four similar groups, who gave slightly different answers, and then you could say from on high, 'Well, the four of you can't agree, so therefore we won't do anything'. We saw that happen for a number of developments that we hoped were going to happen, so it became more and more obvious to the four groups that the best thing to do would be to all come together.

So, there would have been one British Society for Human Genetics, but the cytogeneticists felt they couldn't join with the other three in a unified organisation, because they were a friendly society, and they felt that precluded them. So, the other three societies, with Andrew Read, Martin Bobrow and myself's encouragement, formed the British Society for Human Genetics in 1996 and said to the cytogeneticists, 'Please come along'.[82] If you read the minutes, they came along for the first year to see how it went, and then decided that it was a good thing and joined as part of the umbrella organisation. So, it then meant that the British Society had one voice on various national committees, and that we could ask the individual societies what their individual responses were and put them all together to give a unified voice. So, in some of the interesting pronouncements from on high about how the health service would be commissioned, particularly when the funding was put down to individual GP practices, the fact that the Society could make a very large noise about that was really quite important.

Sally Sheard

Thank you. Would anybody else like to comment on the role of the Societies?

Frances Flinter

I think the other thing they did was help with training very much, because instead of clinical geneticists just listening to presentations from clinical geneticists and molecular biologists just from molecular biologists, the fact that we had a joint conference meant that people were exposed to emerging things from the other areas of specialty. I think it made the laboratory scientists much more aware of the clinical impact of what they were doing, and it certainly helped me as a clinical geneticist have a better understanding of what was going on in the

[82] Andrew Read (b.1939) was Professor of Human Genetics at the University of Manchester from 1995 to 2004.

laboratories, and I think we were much more on top of how quickly the technology was developing.

Ron Zimmern

The other thing is links with Europe. I think the linkage between BSHG and the European Society was important…because I've noticed with ESHG that a lot of the documents were drafted by UK folk. There were one or two exceptions like Martina Cornel and people like that, but they were primarily UK folk, and I don't know, post-Brexit, what the relationship now is.[83]

Frances Flinter

It's continuing.

Ron Zimmern

It's continuing – good.

Alison Hall

Can I just mention one other aspect of that, which is the Genethics Forum, which was founded in 2001 by Mike Parker, Anneke Lucassen, and Tara Clancy.[84] That was a critical move in trying to have an interdisciplinary conversation about ethics in genetics and created a forum for doing that. That's kept going for over twenty years now. Although it's now predominantly attended by genetic counsellors and a few clinical geneticists, I think, in the early days there were lab scientists there as well, so there was that sense of trying to bring the communities together to discuss ethical issues.

Sally Sheard

Thank you, Alison. That's good to know.

Could we spend a few moments, please, just focusing on the creation in 1997 of the Public Health Genetics Unit? Ron, I think I'll go to you.

Ron Zimmern

Well, I've said, really, all there is to say. It's really difficult to know why I thought it had to be started, but I did. I met Muin [Khoury] who had those same thoughts. Interestingly enough,

[83] Martina Cornel (b.1959) is Professor of Community Genetics and Public Health Genomics at the Amsterdam University Medical Center.

[84] Michael Parker is Professor of Bioethics at the University of Oxford. Anneke Lucassen is Professor of Genomic Medicine at the University of Oxford. Dr Tara Clancy is a Consultant Genetic Counsellor and Honorary Senior Lecturer at the Manchester Centre for Genomic Medicine.

Muin was a first-rate genetic epidemiologist – he came from that background, a scientific rather than a clinical background – and we worked quite closely together over the years.

Sally Sheard

Hilary, is there anything you would like to add?

Hilary Burton

I think, with the Public Health Genetics Unit, we were very clear about the need to integrate knowledge, weren't we? There were only four of us to start off with. Alison Stewart, who's not here, was very soon on board as – although she hated being called it – Chief Knowledge Officer and a very good scientist. I think that what we had to bring, was not only our public health skills but also being clinicians, and then being very clear that we had to have a very good understanding of the science, of the ethics, so that we could have credible conversations with people. I think it was an uphill struggle to start off with, because I think the geneticists were saying, 'What on earth are these people doing, talking about genetics? They don't know anything about it.' And they were right to start off with, but we had to be able to have those conversations, didn't we, with lots of different experts, including the geneticists and the lab people over the years to be able to be credible and bring it all together, and that's what we aimed to do.

Ron Zimmern

Yes, and at Bellagio we did bring it together formally, with a definition and with the Bellagio diagram, which I can say a bit about later.[85] It was absolutely crucial to our thinking, but I think the seeds of this were already there when we first started. We were very fortunate to have Hilary come along and Alison, and who was the fourth? Carol Lyon, who was the administrator.

Hilary Burton

Alison was a very good scientist.

Ron Zimmern

She was a good scientist but a beautiful writer – a very good writer.

[85] *Genome-Based Research and Population Health*, Report of an expert workshop held at the Rockefeller Foundation Study and Conference Centre, Bellagio, Italy, 14–20 April 2005.

Hilary Burton

She was a very good writer. She'd been an Editor in genetics journalism. She was very good at that, and I think that was an important baseline skill.

Sally Sheard

A supplementary question to that for the geneticists in the room – when did you become aware that the Unit had been created?

[Laughter]

Rosalind Skinner

Gosh, I can't remember. I think I met Ron at GENCAG [Genetics Commissioning Advisory Group]. I certainly met Mark [Kroese] there.

Ron Zimmern

It could have been there or somewhere else. There were the odd meetings on genetics and health policy that we may both have attended…

Frances Flinter

I think it was the meetings.

Ron Zimmern

…where I remember meeting people like Allen Roses, who always turned up, and also Peter Goodfellow I think. Sally Davies came along to some of those. That was when we were all learning our stuff. People like Sally and I didn't know much about genetics. We just learned by coming along to these meetings.

Hilary Burton

I think because we knew we wanted to influence policy we had to work very hard at trying to get ourselves onto either some of the committees or invited to some of the committees, didn't we?

Frances Flinter

When did the ACCE framework [analytical validity, clinical validity, clinical utility, and ethical, legal and social implications] first emerge?[86]

Hilary Burton

I was actually looking at that, because…

Frances Flinter

I think that was pivotal…

Hilary Burton

Yes.

Ron Zimmern

That was early on.

France Flinter

I think that was pivotal to getting the geneticists involved, because if they could work their way through that in a systematic way they could then present new tests to the commissioners and say, 'Please will you fund this?'

Rosalind Skinner

That's where I met you [Ron Zimmern] – it was GENCAG and we were looking at setting up UKGTN [UK Genetic Testing Network].

[86] J. Haddow and G. Palomaki G, 'ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests' in M. Khoury, J. Little and W. Burke (eds.), *Human Genome Epidemiology* (Oxford University Press, 2004). W. Burke and R. Zimmern, *Moving Beyond ACCE: An Expanded Framework for Genetic Test Evaluation* (PHG Foundation, 2007).

Ron Zimmern

That's right.

Hilary Burton

We did work on the evaluation of genetic tests in about 2004.

Ron Zimmern

We did a lot of these. I did personally a lot of the early stuff on the UKGTN, setting up the evaluating documents and what they should look like, and that was based on the ACCE framework, which we got because of my working with Muin [Khoury] because it came out of the United States.

Rosalind Skinner

Yes. And then Hilary, the first time I came across you was when you started some of your work on education.

Hilary Burton

Yes. We were asked by the Wellcome Trust, actually, to do a piece on education in genetics for health professionals, not just medics. We did that with you [Peter Farndon]. That was 2003.[87]

Mark Bale

Didn't you use to run a training course for commissioners?

Ron Zimmern

That's right. So, in those early days we ran four such courses and people came and spoke at them. They were five days at Hinxton, and they weren't open to anybody, you had to be fairly senior. So we got people like deputy chief medical officers and things, and they were great fun to do but gosh, were they hard work, because everyone went away with two…you couldn't do this now…we could give them all the knowledge in two folders.

[87] *Addressing Genetics, Delivering Health : A Strategy for Advancing Dissemination and Application of Genetics Knowledge Throughout our Health Professions* (PHG Foundation, 2003).

Rosalind Skinner

Big green binders, Ron.

Ron Zimmern

Big green binders full of stuff. We had all the top people come and talk, but after four rounds we decided we couldn't keep it up.

Frances Flinter

It's amazing that commissioners found the time to go and attend a course that long, because they wouldn't do that nowadays.

Ron Zimmern

They wouldn't do that now…

Rosalind Skinner

We stayed in Clare College, I remember.

Ron Zimmern

And then on commissioning…not so much from the PHGU point of view but wearing my Director of Public Health hat…I did do a lot of work locally in East Anglia about disentangling contract prices, or trying to. It never got disentangled, because basically it was so embedded into the block contracts from the various specialities that nobody had any appetite for getting it out because there was no new money coming in. For genetics, you had to take it out of various block contracts from the different specialties.

Rosalind Skinner

It persisted, that problem.

Sally Sheard

We've essentially gone through the first half of the agenda, but are there any other key developments that you'd like us to record?

Peter Farndon

Could I bring up the Joint Committee on Medical Genetics [JCMG]? I think that was a major step forward.

So, first meeting of the Joint Committee on Medical Genetics was in 1999 – which was a tripartite committee, jointly run by the Royal College of Physicians, the Royal College of Pathologists, and the British Society for Human Genetics, with representation from other Royal Colleges, from the PHGU. And the marvellous thing about it was that there was a representative from the Department of Health Genetics Unit on it – Naomi [Brecker] – who I used to give a hard time to by asking lots of difficult questions to take back…and I've apologised.

That, again, was so that there could be a unified voice, but the great thing about the Committee was if the Committee decided something with everybody, all the different parties, agreeing, we had the mechanism to make it work. If it was education we could feed it through the Royal Colleges. If it was a service issue we could feed it through the BSHG into the genetics service. If it was policy issues we could ask the Department of Health what they thought about them. I think that the JCMG was the right thing at the right time. We did reports on services and education and consent and confidentiality, because there was a big problem around that time with one genetics unit saying, 'I can't give you the result of this DNA test, this mutation, to use in your patient, because that information belongs to this patient', and we had to say, 'It's family information so you are allowed'. We went to see the people at the Human Genetics Commission, the Patent Office and all kinds of people, the lawyers, to actually solve that.

Ron Zimmern

Were you the first Chairman, Peter?

Peter Farndon

I was, yes.

Sally Sheard

And where did the inspiration for that Joint Committee come from? Was it from you, or was it from one of the Colleges?

Peter Farndon

I think it just was obvious.

Ron Zimmern

It just happened, I think. We did a lot of talking together with everybody…

Frances Flinter

And it's still running.

Peter Farndon

Peter Harper was the Chair of the Clinical Genetics Committee of the Royal College of Physicians, so he was instrumental in actually convincing the Royal College that it was the right thing to do.

Sally Sheard

Thank you. Are there any other key developments that we've not touched on in sufficient detail?

Ron Zimmern

The other group were pathologists. At one time we did quite a lot of work about the evaluation of genetic testing. This was done in conjunction with Peter Furness, who was President of the Royal College of Pathologists.[88] We ran a couple of meetings and produced a number of reports, and that was important for us as the PHGU because it had the rubber stamp of the Royal College of Pathologists on those reports as well.[89] Peter Furness was extremely helpful, and he was extremely interested even though he was – was he a biochemical pathologist? Yes, I think he was.

Alison Hall

The context for that also, thinking about pathology, was the Alder Hey scandal, the Bristol inquiry, the sense of having all these researchers and clinicians having lots of samples in their cupboards and drawers, and a push for more transparency, more accountability. So when I joined the Public Health Genetics Unit I gravitated towards thinking about the governance of samples and got swept up in all that discussion about the Human Tissue Bill, and then subsequently the 2004 Act, and then thinking about how the Act impacted on clinical genetics practice, which is sort of taking us a little bit ahead, but I think there was this other driver around the public, and families, and patients being more involved in their care and holding the professionals to account in some way.[90]

[88] Professor Peter Furness (b.1955) was President of the Royal College of Pathologists from 2008 to 2011.
[89] *The Evaluation of Diagnostic Laboratory Tests and Complex Biomarkers* (PHG Foundation, 2008).
[90] K. Liddell and A. Hall, 'Beyond Bristol and Alder Hey: The Future Regulation of Human Tissue', *Medical Law Review*, Vol. 13, No. 2, 2005

Sally Sheard

Thank you.

Ron, do you want to say a bit more about the Genetics Scenario Project?

Ron Zimmern

The Genetics Scenario Project…well we were new to the game, we didn't know what the hell to do, so we thought the best way to start is to get all the experts in the field together. We designed a process and we had six or seven meetings, and the way we designed it was that we had the same set of people in each meeting. We had one for the clinical geneticists, one for other physicians who were not clinical geneticists, one for the pharmaceutical and diagnostic industry, one for ethicists and lawyers, and so on and so forth. We squeezed as much information out of them as possible, and then we had a two-day synthesis meeting where we put all this stuff together and put it in a report.[91] We have to be extremely grateful to the Nuffield Trust, to John Wyn Owen in particular for funding it.[92] Not just for that, but he provided splendid dinners and splendid wine. It worked, because people rolled up, because they knew they were going to get a jolly good dinner after working all afternoon. Peter, did you come to one of those?

Peter Farndon

Yes, though I'm not sure that's why I came.

[Laughter]

Ron Zimmern

Anyway, it's been our guide really. The participants were very good. They didn't miss a trick. They set out all the issues. We didn't solve any of them, but we just had them on the table. I don't think it got much external visibility, but as an internal thing it was very useful to us.

Sally Sheard

Thank you.

Ron Zimmern

Hilary, do you want to say anything about that?

[91] *Genetics and Health: Policy Issues for Genetics Science and Their Implications for Health and Health Service* (Nuffield Trust, 2000).
[92] Professor John Wyn Owen (1942-2020) was Secretary of the Nuffield Trust from 1997 to 2005.

Hilary Burton

No, I think that's it. With all of them we had a process by which we started with very open questions. It was a sort of facilitation thing, wasn't it, really, and then a grouping and a sorting and an analysis process that therefore had its value because people all had their say.

Sally Sheard

Have we said enough on the Human Genetics Commission [HGC] yet? Rosalind, Frances, do you wish to add anything?

Frances Flinter

I think all the reports that the Human Genetics Commission produced were very carefully written, with synthesis of a lot of information collected from all sorts of people that it would be appropriate to consult. In terms of which ones had the most influence, I think there was one published about ten years ago on neonatal genomic screening, which was one of the ones that John Sulston chaired, and he said, 'I don't think we're going to be looking at this for at least another ten years,' and here we are ten years later facing the prospect of whole genome sequencing in neonates.[93]

Rosalind Skinner

Absolutely. There was one on prenatal diagnosis, I'm fairly sure, back in the early days that Martin Richards chaired.[94]

Frances Flinter

Making Babies was another very important one.[95]

Rosalind Skinner

That's right, yes. There was one where they coined the phrase, 'genetic altruism'. What was that about?

Mark Bale

That was the first report on data.[96]

[93] *Profiling The Newborn: A Prospective Gene Technology?* (Human Genetics Commission, 2005).
[94] Martin Richards (b.1940) was Professor of Family Research at the University of Cambridge from 1997 to 2005. *Choosing the Future: Genetics and Reproductive Decision Making* (Human Genetics Commission, 2004).
[95] *Making Babies: Reproductive Decisions and Genetic Technologies* (Human Genetics Commission, 2006).
[96] *Inside Information: Balancing Interests in the use of Personal Genetic Data* (Human Genetics Commission, 2002).

Frances Flinter

I think pretty much the final report, which was about a framework for principles for the regulation of over-the-counter genetic testing, was very interesting, because actually it didn't just consult experts in this country.[97] It was the result of an international working group that included people from the companies that were marketing these services, as well as all sorts of people like the MHRA [Medicines and Healthcare Products Regulatory Agency], the Advertising Standards Authority, and clinicians and so on. That ended up with a lot of recommendations, and then almost immediately after that Human Genetics Commission was dissolved in the bonfire of the quangos.

It's very interesting, having been involved very recently in the Science and Technology Committee's report on commercial genetic testing – I was scientific advisor for that – and Mark and I were just discussing this beforehand – funnily enough, it's come out with very similar recommendations, something like ten or twelve years later, which makes you realise that sometimes you write these reports that at the time feel quite important, and you're aware how much work's gone into them, but it doesn't necessarily mean anything will happen.[98]

Mark Bale

Could I just add to that, because I was the Secretary [of the Human Genetics Commission] for quite a long time and it was under my wing after that. Something I just wanted to pick up, because it was hinted at by what Ron and Hilary said, is that the process was quite interesting. Certainly, as a civil servant everyone looked at me aghast in that it met in public, and it toured around all four capitals and elsewhere.

Rosalind Skinner

Absolutely. We were in Edinburgh twice.

Mark Bale

We came to Edinburgh, we went to Northern Ireland. I think it set its stall out…sometimes a bit too much grandstanding…to be engaging with the public, to actually reach out beyond the Commission and talk to a wider audience. It wasn't cheap to do that, and it wasn't universally popular. We never really got our fingers burned. Everyone assumed that we would immediately get shot down or be on the front page of the *Daily Mail*, but we didn't, largely down to the Commission, but also Baroness Kennedy's own confidence.[99] But it was very expensive to run, and one of the big things that happened with the bonfire of the quangos is we don't work like that anymore. We just don't do committee meetings in public.

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[97] *A Common Framework of Principles for Direct-to-Consumer Genetic Testing Services* (Human Genetics Commission, 2010).
[98] House of Commons. Science and Technology Committee. *Direct-to Consumer Genomic Testing*, 2021.
[99] Helena Kennedy (Baroness Kennedy of The Shaws) (b.1950) was Chair of the Human Genetics Commission from 2000 to 2007.

Frances Flinter

They had a consultative panel of people affected with genetic conditions, and that was really very interesting, very rich in terms of what they delivered, but also quite challenging sometimes for the Commission in terms of what they were being confronted with. It really forced people to think very, very carefully.

Mark Bale

I'm glad you mentioned that, because actually that's been replicated a bit in the 100,000 Genomes Project for Genomics England, and actually they are equally as challenging and they keep everyone on their toes, both in terms of being clear about the language, but also actually addressing real concerns, not just assuming that they're not a problem because they don't apply to professionals. As much as the content, the process was novel at the time. There's lots you can talk about in terms of office politics, but we were very conscious of the Commission being different to previous committees, and maybe the National Screening Committee and so on.

It was very interesting when we started the 100,000 Genomes Project to reflect with Sir Malcolm Grant, who was the chair of the Agriculture and Environmental Biotechnology Commission, which was the sister committee of the HGC.[100] He reflected on the way that that process had been open and transparent, and wanted to do the same for the 100,000 Genomes Project when NHS England looked like they were leading it. So, there's some carry-through there that – I don't know if you've touched on that, but public dialogue, public engagement, public involvement is a theme that blows hot and cold.

Rosalind Skinner

Absolutely.

Frances Flinter

The other thing that I was always struck by is that as a clinical geneticist I was very much in the minority on the Commission. I think there was one clinical geneticist, there was one laboratory scientist, but other than that the Commission was made up of philosophers, lawyers, religious people, all sorts of different backgrounds. That meant the challenges were much wider. I frequently was asked questions during those meetings that I had never even thought about before. They seemed to come completely from left-field – people like John Harris would challenge me on something and I would suddenly think, 'Well, I suppose I've always just thought that was how something was'. It was very stimulating.

[100] Sir Malcolm Grant (b.1947) was Chair of the Agriculture and Environment Biotechnology Commission from 2000 to 2005.

Mark Bale

And just to pick up on that point because I forgot that – we had a patient representative, but we also had someone from a disability rights perspective who had a genetic disease. They were always excellent…I forget her name, but she was…

Frances Flinter

Alice Maynard.[101]

Mark Bale

Yes…really interesting perspectives and very, very important.

Ron Zimmern

So, something that needs to be sorted out in this narrative is the Nuffield Council on Bioethics, and to explain why we have a Nuffield Council on Bioethics – not a statutory body, as well as a Human Genetics Commission. Now, there would have been reasons why we went down that road, because in most countries it would all be…

Mark Bale

I think it's going slightly off-piste, but I think we were lobbied heavily to have the equivalent of a national bioethics committee, frequently, and the standard response – quite rightly, I think – is that we have things like the Nuffield Council on Bioethics we have the Royal Colleges that do a lot of the ethical work, the General Medical Council. We have the Select Committees, and we have the House of Lords and so on. If we had a National Bioethics Committee we would endlessly be arguing about how many vicars you would have on it, how many Catholic priests and so on, and it would end up becoming highly politicised.

Ron Zimmern

Absolutely.

Mark Bale

So, we'd rather have a mixed model and have lots of them. This is my standard government line.

[101] Dr Alice Maynard (b.1957) was a lay member of the Human Genetics Commission from 2006 to 2012.

Ron Zimmern

I'm not suggesting we should, but I think it should be reflected in the narrative as to why we've got to this point in this country.

Frances Flinter

But when the Nuffield Council on Bioethics – of which I am a member – interacts with equivalent bodies elsewhere, the other Bioethics Councils are government funded and government supported, but they are otherwise regarded as complete equivalents. We have trilateral meetings, for example, with the bioethics committees in France and Germany each year, and they're actually very productive.

Diana Walford

Can I ask about the ESRC [Economic and Social Research Council], because the ESRC had a Genomics Network that we haven't mentioned, and they were looking at the social sciences side of genomics. Actually, it carried on for a number of years and then unfortunately was disbanded. I was on the Advisory Board of their Genomics Forum, and there was a lot of very interesting stuff there across the board in relation to population views of genomics in all its aspects. I think there were annual reports – it would be good to perhaps disinter them from somewhere, because I think they had a lot of good stuff in them.

Rosalind Skinner

Absolutely. There were two of those units set up in Edinburgh. There was one looking at economics and one looking at policy issues and holding a forum, as it were. When we did the review in Scotland I actually engaged a lot with that unit, the policy unit in Scotland, and asked them to set up public engagement work on behalf of the Scottish Health Department in genetics.

Mark Bale

There was one in Exeter as well, wasn't there?

Rosalind Skinner

Yes, there was Exeter and there was Lancaster.

Sally Sheard

That's really helpful. Thank you, Diana.

Ron Zimmern

On that, our links nowadays are mainly with the lawyers and philosophers, but right at the beginning the biggest influence on this ELSI front was Martin Richards, who wrote a seminal book.[102] Martin was really right there in the very earliest days.

Rosalind Skinner

He was there from the beginning on the HGC…

Ron Zimmern

Martin Richards is an important character.

Sally Sheard

Thank you.

Can we move onto the Genetics Knowledge Parks because we've not really given them any attention so far?

Peter Farndon

They were a good idea, but they were too soon, and when they were set up nobody worked out that there weren't actually enough qualified people in the country to fulfil the posts in all of them.

Mark Bale

I guess this is something that could be worked out – but they were a bit of an afterthought. They didn't fit neatly within the Departments. I think they were funded through DTI [Department of Trade and Industry], and I think initially everyone assumed they'd be a bit like a business park, with lots of little car parks and incubators and stuff like that, and they didn't know what they were. We had the name first and then we tried to work out what the hell to do with it.

Peter Farndon

They were a really good idea – they just couldn't do what they wanted to do because the technology and everything else that they were supposed to do hadn't come on stream by then. This is about the time when the Department of Health started talking about UK PLC.

[102] T. Marteau and M. Richards (eds.), *The Troubled Helix: Social and Psychological Implications of the New Human Genetics* (Cambridge University Press, 1996).

Mark Bale

Yes, that's where the money came from, in other words. They went their various different ways, but Cardiff continued.

Peter Farndon

It did.

Mark Bale

So…don't quote me on this – 'It wasn't my fault', sort of thing…but if the money had continued would they have found a better purpose?

Ron Zimmern

Of course, the distinction was Cambridge. I was the Director there and didn't have a day job. All the other Directors had day jobs. John [Burn] was Director [of the Northern Genetics Knowledge Park] and John had a day job, so when they folded up they went back to the day job. That was precisely why we set up the PHG Foundation because we either went out of business or we had to turn ourselves into something else.

But I think, Peter, you're absolutely right. Each of them had a lecturer – law lecturer, social sciences lecturer, philosophy lecturer – and there were not enough of these people to go around. I think also, given that the Directors at most of the Knowledge Parks were jobbing clinicians it was actually quite difficult for them to really try to create what was needed. I had a little bit to do with it because I was working with Richard Himsworth, who was our East Anglia Regional Director of R&D, and Richard and I had been toying around with some of these ideas, but certainly not with a Knowledge Park like Milburn came out with, so when this came out Richard and I were both flabbergasted, because it wasn't what we'd tried to feed into the system, it was what came out of the system.[103]

Peter Farndon

And the remit for each one was more or less the same, if I remember rightly, therefore there was a problem then trying to decide what each one would actually try and do. But the other thing about the White Paper which really was important were the National Genetics Reference Laboratories in Manchester and Salisbury.

Sally Sheard

Can you say a little bit more about why?

[103] Professor Richard Himsworth (1937-2020) was Director of Research and Development in the Eastern Region of the NHS Executive from 1998 to 2002.

Peter Farndon

Golly…didn't the Salisbury one do quality control and the Manchester looked at DNA analysis?

Ron Zimmern

Salisbury…did they do cytogenetics because of patterns, J-curves, and all that?

Peter Farndon

No, cytogenetics had long gone by then, I think.

Rosalind Skinner

They went into things like exome sequencing.

Peter Farndon

It was. It was exome sequencing.

Rosalind Skinner

Salisbury did exome sequencing, because they were going to set up a big project around about the time the DDD [Deciphering Developmental Disorders] project was set up.

Peter Farndon

Manchester did all the bioinformatics.

Mark Bale

Manchester did the bioinformatics and some of the tools, and they also did…

Rosalind Skinner

I'm sure they did quality control, because…

Mark Bale

Yes, they did.

Peter Farndon

In UKGTN we relied on a lot of that information.

Sally Sheard

We've already talked about the 2003 White Paper. Do we want to pursue anything on that line? We've talked a little bit about the impetus, Alan Milburn...

Frances Flinter

That was such an exciting time. It suddenly felt that genetics was recognised, it was on the map, and we were going to be given proper sums of money to really establish ourselves. It was brilliant.

Hilary Burton

Wasn't the NHS Genetics Education Centre set up in parallel at the same time as the Knowledge Parks?

Peter Farndon

Yes, as part of that White Paper.

Naomi Brecker

And there was quite a lot of money for kit, wasn't there.

Peter Farndon

There was.

Naomi Brecker

And I can remember – I think it was you [Peter Farndon] – saying that it was a pity that you'd bought kit outright rather than leased it…

[Laughter]

…because down the line all the labs were saddled with aging equipment, and you'd need another cash injection.

Mark Bale

Yes. Then, fast-forwarding, John Bell [in *Building on our Inheritance*] heavily criticised the age of the kit in laboratories, and it was just because we'd put that cash injection into them in 2005.

Frances Flinter

But I don't think we were allowed to rent it. You had to buy it.

Rosalind Skinner

Was it through your unit, Peter, or was it an independent initiative that there was enhanced training for genetic counsellors, because there were only the two courses, weren't there?

Frances Flinter

Manchester and Cardiff.

Rosalind Skinner

Yes.

Peter Farndon

No, we supported training, but we didn't do a special course.

Rosalind Skinner

Right, because I'm sure they got extra money because we started increasing the number of training places and so on in Scotland. The need to boost the genetic counsellor workforce was recognised.

Frances Flinter

There was, and that's also I think when they began their battle to try and become a state-registered profession. If I remember correctly, the feeling from the Department [of Health] was

that they were really too small to become state-registered in their own right. There's a lot of history behind that.

Peter Farndon

And that they should join the HPC [Health Professions Council].

Mark Bale

From my perspective the only thing I would add is that it [the 2003 White Paper] got Number 10 and Tony Blair directly involved. Tony Blair had already been involved with Bill Clinton and the Human Genome Project, but Number 10 was very active then. I think John Burn mentioned the breakfast they hosted to launch it, so that gives you quite a lot of impetus. It gives you a lot of pain as well, because you constantly have to report on progress – and then it happened again in 2012 with David Cameron and the 100,000 Genomes project. Getting Prime Ministerial interest suddenly is both the best thing and the worst thing that can happen, sometimes.

[Laughter]

Rosalind Skinner

You get more money but more work.

Ron Zimmern

When did a number of us roll up to Number 10 on one occasion and sit round a table for Tony Blair to turn up for about five to ten minutes?

Mark Bale

That might have been it.

Peter Farndon

That was the White Paper breakfast…and you'd all been told to say particular things in answers to questions.

[Laughter]

Ron Zimmern

It's a very vague memory.

Peter Farndon

John Reid was there.

Sally Sheard

That probably then moves us on to 2006 and UK Biobank. Is there anybody who would like to comment on that?

Ron Zimmern

I was involved in some of the very early stuff, as was Mark, but only the first year or two – well, whilst it was being set up – and I remember one of the most argued about topics when it was setting up was the question of whether you should return results back to participants. At that time, it was an absolute no-no. Participants could be given a monthly newsletter or whatever it was, stating the general things, but individual results, at least genomic results, were not to be returned. That's my main recollection of the early days.

Mark Bale

I agree with that. I think the planning was being discussed and debated for three, four, or five years before 2006 because it was of direct relevance to the Human Genetics Commission when they were doing their work on privacy and so on. I think what I reflect on so much now is that a lot of people were really, really critical of it because they thought it would suck in funding from other research funds, and it's so fantastically interesting now to look at how many people say it's the jewel in the crown of the UK life sciences. It's just interesting that they had to go through that pain.

I don't really think that genetics or genomics was up at the front of their mind when they were developing this, because they didn't really have all of the consents thought through. They didn't even think they could do any of the sequencing, it was all done with genotyping, but money was dripped in to it to allow high quality DNA to be stored, and then it was genotyped, and now it's the basis of lots of other things. I guess it was kind of in parallel, but it never felt like it was a genetic thing. It was a biobank.

Frances Flinter

We knew it was going on, but we weren't involved.

Mark Bale

Yes, it wasn't really a direct link.

Ron Zimmern

It was never clear then, and probably isn't clear now with the 100,000 Genomes Project…the distinction between money for a research project and money for a resource. That ambiguity still sits around today.

Frances Flinter

It still sits around the proposed whole genome sequencing on the NHS as well. That really important distinction still hasn't been made, and I think it's because some people don't think it's important.

Ron Zimmern

No, it's a really important distinction.

Alison Hall

And a resource for who? Just thinking back to your point, Mark, about commercial interests in that resource, that's something that's been heavily debated and still isn't resolved.

Ron Zimmern

Yes. This idea of economics…in Public Health 101 there's this picture which has two blobs on it. One says wealth and one says health, and there's an arrow going from both of those. So, I think the UK PLC has picked this up. I mean, everything in biology has a wealth component attached to it as well as a health component.

Mark Bale

Yes, I think the commercial angle is really important. I still think there's a discussion still to have around how you monetise, for want of a better word, some of these assets, and whether that's something you see a direct responsibility of Biobank or Genetics England or someone, or whether you're actually seeing this in the same way that you did initially in the 100,000 Genomes Project, saying it's a bit like building a library or a railway. You build it as part of the infrastructure, and that grows the economy indirectly. I think we've gone for the latter in both of those cases.

What hasn't happened, though – I'm not a health economist, but we haven't necessarily got the meta-economics. We haven't got the meta-analysis of what's really happened to the economy on the back of that. I think the commercial agenda, the ownership and IP [Intellectual Property]

have…well, they're not much further developed than they were in the HGC days and Bill Cornish's report I'm afraid, because it's just too difficult to do.[104]

Ron Zimmern

Even without the detailed IP law stuff, if we just reflect on Covid in the last three years – we would have never got to where we are now had it not been for that infrastructure of UK Biobank, of genomic sequencing. That was absolutely essential. Without that Britain could not have developed those vaccines and I think that it's well worth saying that.

Mark Bale

It's being noticed more, I think, now.

Sally Sheard

It's an important point. I'm glad we've got that on record. We're transitioning from that focus on genetics to genomics. It's coming automatically, really, as we move through the history. The next key thing on my list is the 2009 House of Lords Science and Technology Committee report.[105] Can I ask for some initial thoughts on the impact of that?

Ron Zimmern

I thought that was a seminal report. When that report came out I picked up the Nuffield Trust Scenario Project and said, 'We're there. They're doing everything that we said they should do'. There was a White Paper to come a few years later, but that was a seminal report, I thought, absolutely.

Frances Flinter

I remember going along with John Sulston to give evidence to it on behalf of the Human Genetics Commission, and certainly there were people like Robert Winston and others on the Committee who clearly really had thought long and hard and had learned a lot about what was going on in genetics. The sorts of questions they were asking us and the way they were probing, you realised the people they'd been speaking to beforehand…they clearly had been given a lot of useful information. It was a very interesting experience.

[104] William Cornish (1937-2020) was Herchel Smith Professor of Intellectual Property Law at the University of Cambridge from 1995 to 2004 and Chaired the Intellectual Property Working Party of the National Academies Policy Action Group.
[105] Science and Technology Committee, House of Lords, *Genomic Medicine: Volume 1: Report* (London: The Stationery Office, 2009).

Mark Bale

From my perspective it was, as Ron said, a seminal report. I can't remember who the committee expert was now…

Rosalind Skinner

Tim Aitman.[106]

Mark Bale

Yes, of course. I thought that was a very interesting report. I can't remember a Minister giving evidence to it, but I know that the CMO did, and it was a very insightful set of questioning. We felt we had a lot to point to around the White Paper, which wasn't that old, and a few other things, but I still think – if I'm honest with you – it gave us two bonuses. One is it actually looked at the topic in the light of new technology, if you like, and effectively where we stood now with the technology and what could be delivered.

It made a rather interesting recommendation for another White Paper, just at the time everyone could see that the Labour government was not necessarily going to be the winner of the next election. As a result of that we decided that it was pointless trying to commit to a White Paper, so we said we'd have a strategy, and – I think it's been commented on previously – but the person who seemed to be quoted most in the report was John Bell, so we asked him to chair the group. That was the work that we did to follow up the report, so that was another big piece of work.

Whether you like it or not, it was still quite a useful exercise to get a lot of people from the NHS, a lot of people from the professions and a lot of people from research to actually sit down and write a strategy. I think it's a pretty good report, I have to say.[107] I think it's actually like your [Ron Zimmern] scenario thing, because it predicted a lot of things that are now, for better or for worse, being delivered through things like the laboratory hubs and the clinical alliances and so on, to actually put this on a firmer footing in the NHS. That was all driven by Sue Hill who led that chapter.[108] I think you had a hand in some of that, Hilary…

Hilary Burton

The HGSG [Human Genomics Strategy Group]?

Mark Bale

Yes, in 2012.

[106] Tim Aitman (b.1958) is Professor of Molecular Pathology and Genetics at the University of Edinburgh.
[107] *Building on our Inheritance: Genomic Technology in Healthcare* (Department of Health, 2012).
[108] Professor Dame Sue Hill (b.1955) has been Chief Scientific Officer for England since 2002.

Hilary Burton

I think there was a slight divergence in the HGSG between John Bell's group that were just absolutely determined that the whole genome sequencing thing, the equivalent of the 100,000 Genomes Project, would happen, and that genome sequencing was it, and the group of clinicians, to some extent, that said, 'We're not really ready with it, with the health services, so let's try and get those right first. If we have that much money to spend let's try and get the genetic services in mainstream medicine right'. I think in many ways John Bell won the day, but there were – I've looked back at it just in the last few days – there was some quite good bits still in there about the developments of the NHS, so it probably ended up being very useful – but it was uncomfortable at the time.

Mark Bale

It was separate to the 100,000 Genomes Project. That happened behind the scenes, type of thing.

Hilary Burton

It was, but John Bell was very, very keen that this personalised medicine was going to happen, and stratification and all of that, which…hasn't really.

Mark Bale

True.

Hilary Burton

So, it was slightly uncomfortable, but I think it's politically probably very effective.

Frances Flinter

I think the feeling amongst the clinical genetics community – several of us worked on the HGSG – is that they didn't really understand – and I'm not sure that some people still fully understand – the role of the clinical geneticist. We were not being protectionist and saying, 'We are the only people who can discuss genetic testing or who can interpret the results,' and so on, but there is a role for the clinical geneticists, working together with colleagues in all these other specialties. I'm not sure that that's fully appreciated.

Hilary Burton

I think that came out in the later work that we did on genomics and mainstream medicine, where in fact what we were saying was, 'This is actually very complex, and it's actually got to

be properly done. We accept that more people are going to have to do it, and it's a wider thing,' but the geneticists had to really lead it because they could understand the complexities.

Frances Flinter

But I think some people felt that the technology was so clever that the clinicians would be redundant. And they aren't, and they won't be. You need both.

Hilary Burton

I think that was slightly uncomfortable in the HGSG, because there was a feeling that…sorry, I know this is being recorded…the John Bell group would consider the geneticists group as being dinosaurs and protectionist and sticks in the mud, who don't want to be dragged forward.

Peter Farndon

It was indeed difficult, wasn't it, to put forward reasoned arguments that were listened to.

Naomi Brecker

It's interesting hearing this, having not been a part of it for a while, that actually similar themes kept coming up, so the thing about getting services right, I heard you [Hilary Burton] say, was something that's been a theme all around…

Hilary Burton

And getting enough of them.

Naomi Brecker

And getting enough of them. Also, the whole thing about when would personalised medicine come out of that, had also been talked about at different times. I'm sensing from this that at different points in time different things rest and bite, and the rest of it stays. As you were saying Ron, you got it in your report, then they've got it in the report, and it seems as though each time it's something else that bites that you can run with that makes a step change difference. But it's not all of it, it's only some of it.

Sally Sheard

So, is it the technology that changes or is it the individuals who are driving things?

Ron Zimmern

I would say that individuals are very important, because exactly what Hilary was saying was reflected back in those two original reports written by Martin Bobrow and John Bell, and their tone. That's exactly what Hilary was describing. If you go back to those two reports you've got this, 'Yes, it's all going to happen. Everything will be great'.

Naomi Brecker

But the technology becomes easier, and the technology becomes less centralised and more diverse, and more people understand it, and more people understand the applications. I wonder if policy has always lagged behind the technology.

Peter Farndon

Well, in this instance people could see that it was blatantly obvious that the technology was there. You could do it. You could get a result. What is the problem? The problem that was tried to be explained was that there is actually a person who needs to have the result explained, and the problem is that for the majority of the results which were likely to come out of the techniques which were being proposed, there wasn't actually a 100% answer. Some people on the HGSG tried very hard to get this concept over. It's exactly what Ron has been saying year after year about the difference between actually doing the assay and interpreting the result. It was played out in the HGCG yet again, and I think that comes out in the report.

Frances Flinter

I think those who were so impressed by the technology felt that it was much more deterministic than actually it really is.

Ron Zimmern

Yes.

Frances Flinter

It's not just the result of the test that predicts everything that's going to happen in the future, but that concept is quite hard to understand.

Peter Farndon

The other thing that was very difficult – and I understand it's still being played out in the clinical services at the moment – is the idea that consent is not just 'This is okay, isn't it?' – as a comment when taking blood for a genetic test, for instance – when you're dealing with

something that may not give you a 100% answer. There were huge discussions, I remember, about consent and who's going to do it. It's the same old story.

Naomi Brecker

Also, consent is only valid at a point in time, but the information you're dealing with has ramifications for others and ongoing in time, and that's why it's so difficult.

Rosalind Skinner

Very much so.

Ron Zimmern

This week's *Nature* editorial written by Ewan Birney and Mark McCarthy makes the point that if you want to predict disease, genomic information is only half of it.[109] The other half is the rest.

Hilary Burton

I think, in a way, the holy grail of this personalised medicine, and things that are held out in things like the HGSG report, have inspired people, if you like, to set up things like the 100,000 Genomes Project and put money into it, but it hasn't really yet turned up the goods in terms of what they hoped it might achieve, and actually there is very little in the HGSG report about public health or population health. I did look back at that chapter, and there's almost lip service paid to it. What might happen in a pandemic – I think there's a line.

Sally Sheard

Hilary, you say there's very little about public health in the Human Genomics Strategy Group report. Do you think that reflects the balance of the committee? Were there vocal public health people?

Hilary Burton

There weren't vocal public health people. I think probably I was the 'public health person' there. There have never been proper, card-carrying, or mainstream public health people at any of these committees, and that's been one of the problems.

[109] M. McCarthy and E. Birney, 'Personalized Profiles for Disease Risk Must Capture all Facets of Health', *Nature*, 6 September 2021.

Sally Sheard

That is a significant issue.

Hilary Burton

In any of those committees, they would ring up people like us [PHG Foundation] to say, 'Oh, we have to send a representative. Will you go?' and in a way we wanted proper, card-carrying, almost doubting public health people to go along to it, rather than people like us that were pretty steeped in the genomics and the genetics in the first place.

Sally Sheard

So, that for me is something that we need to explore further. Phil [Begley] and I have not yet dug deep enough into that, but what does that say about the state of the public health profession at that point in the mid-to late-2000s?

Ron Zimmern

I think to put it bluntly, even without talking about genetics, the state of the public health profession in the UK is not as I would wish it to be.

Sally Sheard

Let's keep it historical.

Rosalind Skinner

I don't think it's changed.

Naomi Brecker

Well, it's all the reorganisations, isn't it? In public health, where every two years they've had to reapply for their own jobs, they work for different masters, they work for different organisations. I know you're in the mid-2000s, but at some point they went into local authorities, and they lost their clout and their influence. They've tried to valiantly hold onto some of their big-ticket things that make a difference, and they're finding it a bit of a struggle to do that.

Ron Zimmern

And then one of the big issues in public health is the extent to which public health is just a profession, a field that looks only at the wider determinants of health – at inequalities, at

poverty, at smoking – or whether it needs to take and understand the biological determinants of health with it. Now, at one time Britain was really good at not only dealing with health promotion and health protection but how health services should be organised...

Hilary Burton

But that was taken away…

Ron Zimmern

Yes, that was taken away. So, we've got now public health people not sitting in Health Authorities, but sitting in Local Authorities, who deal with these wide determinants of health, and in relation to clinical issues they say 'Well, nothing to do with me, mate. This is biology. We don't get involved'.

Naomi Brecker

Ron, I think they are a hard-working, minimised, overwhelmed profession trying to influence political masters who are not interested, where their budgets are being robbed…

Ron Zimmern

Oh yes, absolutely.

Naomi Brecker

So, I think there is a massive problem for public health.

Hilary Burton

I think in respect to what they thought about genetics, and at the time they were right – genetics is mainly about rare diseases, and rare diseases are quite rare. I think where it came into screening, public health did start to get interested, because there were some principles about screening – you're taking a test that someone that hasn't sought, hasn't asked a clinical question. But I think we've never been able to persuade public health of what genetics and genomics can really do on a big scale for disease prevention and health promotion.

As Naomi says, they are overwhelmed with poverty, poor housing, and all of the other determinants of health, and poor lifestyles and so on. That's where they see they have to place their emphasis, and we haven't yet persuaded them to do anything differently, partly because the evidence is not there.

Naomi Brecker

I was going to say, the evidence isn't there, but has genomics actually delivered that ticket? It hasn't yet.

I was going to throw in something that came to mind in a slightly earlier part of the conversation when we were talking about personalised health. Of course, a lot of personalised health in public perception and the media is almost snake oil. It's about getting information about yourself, but you're actually being peddled things that actually won't probably make a big difference in the long run and almost certainly isn't very much to do with your genetics, and a whole range of pseudo-tests that are giving you data to understand yourself better that doesn't actually really make a difference. I think that's muddying the water as to what the pure genomics can actually deliver and what maybe the population understands about personalised medicine.

Ron Zimmern

I think it's all to do with timescales. I think Martin Bobrow is absolutely right – this stuff will deliver, but it's probably twenty, thirty, forty years from now.

Naomi Brecker

But we were saying that twenty years ago.

Ron Zimmern

Well, we've gone a long way in these twenty years, as we've heard today, in terms of what's been achieved for health. I think for genomics to bite on the big public health problems will take another twenty to thirty years, not, 'It will revolutionise medicine in ten years,' as John Bell would like to say, but from today, another thirty, forty years.

Hilary Burton

I think that there are little bits that will really bite, like getting FH [Familial Hypercholesterolaemia] right, but I think in terms of common, chronic diseases it might bite a little bit, but…

Frances Flinter

The traction is in things like treatment of haematological malignancies and so on, isn't it? There are certain specific areas – and we share it – where we have good proof that it can work, but it's not nearly as generalised.

Ron Zimmern

So, in the next fifty years more of this space will be filled. It is that sort of timescale – thirty, forty, fifty years.

Sally Sheard

Can we talk about Genomics England? We have already mentioned the 100,000 Genomes Project, and Mark, I think you raised the point that one of the key influences behind that was John Bell, in parallel to the Human Genomics Strategy Group. Can we say a little bit about both the 100,000 Genomes Project and about Genomics England as a concept, and where that came from?

Mark Bale

I can give my perspective, but it'll be really interesting to hear how it appears to others. I think – coming back to my point about the Tony Blair interest – one of the things I think is in the public domain, broadly speaking, is that when David Cameron was Prime Minister, I think it was John Beddington who was the Chief Scientific Adviser, they initiated a number of science seminars for the Prime Minister, and one of the early ones was genetics.[110] I'm reliably informed that David Cameron sat down and looked around the table and said, 'I'm probably one of the only people in this room who's had genetic counselling, and I want to improve it,' because he had it for his son Ivan. So, he literally set us a bit of a challenge there around how this looks for patients, how it appeared to him as the father of a child with an undiagnosed, rare disease.

I'm interested in perspectives on this, but that was probably one of the areas where John Bell was then able to say, 'One more big heave and we will solve this missing question of inheritability, what does 97% of the DNA do, by doing a big, whole genome sequencing project, centred around the NHS but allowing the best of research and commercial brains to look at the data'. That was his pitch, and that's what led to the 100,000 Genomes Project. I think it's interesting to note that the 100,000 Genomes Project was first announced as a report for the Life Sciences strategy, so it's definitely coming back to the UK PLC point that somebody raised. It's definitely a UK PLC first agenda.

Genomics England, it's a little bit…it wasn't in our mindset for a brand-new arms-length body. We'd have been crucified if we tried to set up a new quango, but this was something the NHS were asked to deliver with very little chance for reflection. When the NHS Commissioning Board was being established, they were asked, and they said, 'Yes, we'll do it,' so all the early meetings were NHS-focused in Malcom Grant's office at UCL [University College London]. I think it was only in about the April [of 2013] after the project was launched in December that we got a real rocket from Number 10, saying, 'What's the progress on this? It's in the plan for government. There has to be progress,' and so as an attempt to move it faster – recognising it wasn't a proper NHS service, really, it was a hybrid – Genomics England was established as a company, literally overnight, and announced as part of the NHS anniversary in July. So, it was

[110] Professor Sir John Beddington (b.1945) was UK Chief Scientific Adviser from 2008 to 2013.

very rapid, and without very much policy consideration about what Genomics England did, other than deliver the 100,000 Genomes Project.

I think ever since then, and as part of Sally Davies's report in 2016 and also now as part of the Genome UK strategy, there's been trying to clarify the role of Genomics England, the relationship with the NHS services and what it does that's new.[111] So that's my perspective, and I've been quite close to that, probably too close to that to have an objective view yet.

Sally Sheard

Thank you, Mark.

Alison Hall

That hybrid activity was new, wasn't it? We're still grappling with the governance of and the approach to that boundary between research and clinical care, which previously had been rather implicit, that if clinicians had had a particular interest in a condition then they might put their patients into a research project, but this was formalised through the 100,000 Genomes Project into this hybrid project. To an extent the Deciphering Developmental Delay [DDD] project had done that, in that that was also a hybrid project and it had used the NHS to recruit participants and face some of the ethical challenges, the same sort of ethical challenges about, 'What do you do with findings that you don't expect, additional findings, the incidental findings. What's your approach to that? How do you maintain communication with patients? How do you deal with all those patients who don't get the results that they have been promised and expect, and how do you manage your clinicians, and keep them engaged?' In a sense, that was a precursor to the 100,000 Genomes Project.

Frances Flinter

There was quite a difference between the DDD and the 100,000 Genomes Project. The 100,000 Genomes Project came at us pretty much left-field, and it was an enormous shock to the system. I remember at the time I was chair of the Clinical Reference Group, which was the group that was liaising with NHS England in terms of the commissioning of clinical genetics. I remember Mark Caulfield came along to one of our meetings, and he said, 'Right, this is the project that's going to happen. You're all going to be involved in delivering it'. For the first time ever suddenly the regional genetics centres were competing with each other, because we each had to submit our own applications to be a centre that would be involved in this. We were competing with each other for a very generous pot of money. Nobody was going to say, 'No thank you,' to £100 million to do a whole lot of genetic testing on patients, when up until now resources had been somewhat constrained.

But DDD was looking at exomes, and it was very clearly badged as a research project. It was delivering what we needed, so there was initially considerable uncertainty as to whether really doing whole genome sequences was the right thing to be doing from a technological point of

[111] *Annual Report of the Chief Medical Officer 2016: Generation Genome* (Department of Health, 2017). *Genome UK: The Future of Healthcare* (HM Government, 2020).

view. It felt like leapfrogging over a technology (exome sequencing) that we were beginning to understand much better, and which was proven to be very useful. We really didn't have any choice as to whether or not we did it, and this issue of the sort of conflation of research and service was really uncomfortable, sitting with patients in the clinic. They'd say, 'Well, is this research? What are you trying to do?' It was very oversold in terms of what it could deliver and how quickly it could deliver it. At the beginning patients were told, 'Well, you'll get a result in six months,' and then it was modified a bit, 'It might be 12 months or 18 months', and then, there we were three, four years down the line, with a lot of our patients still waiting for their results.

It was extraordinarily hard to manage on the ground, because we suddenly had all these new staff in the department – very welcome – to help us with consenting the patients and so on, but they all needed to be managed, they needed to be helped, all the patients needed to be bled. The people who were trained to consent the patients were not phlebotomists. It was a very, very tough call. The fallout on the laboratories afterwards, having to validate all the results, to do Sanger sequencing to confirm whether what had been found was genuine, created a lot of extra work. We also had to set up multidisciplinary team meetings to look at all the results and decide which ones were likely to be significant, and because a lot of the follow-up work actually wasn't resourced this created tremendous pressure on the NHS services.

Ron Zimmern

I think this is absolutely right. I've sat on the Ethics Advisory Group [of Genomics England] since its inception, and the one thing that I couldn't get an answer on is, 'Define it. Is it a research project or is it a clinical project?' I think now, looking back, the obfuscation was deliberate.

Frances Flinter

It was a fudge.

Ron Zimmern

The fudging was deliberate. But this then raises the point – again, as with John Bell, Martin Bobrow…go steadily, as a scientist would – to what extent, is it legitimate for politicians to hype things up in order to get things going? I don't know the answer to that one, but you could argue that is what the whole John Bell approach is about, deliberately hyping things up. Now, I don't know whether he genuinely believes it or not, but is it legitimate to do so just in order to get the resources in and to get the politicians engaged, to get the public engaged? To what extent…

Naomi Brecker

That's not unique to genetics.

Ron Zimmern

It's not unique to genetics.

Naomi Brecker

Ministers want to make announcements.

Mark Bale

They want something eye catching.

Hilary Burton

It depends on what the opportunity cost is.

Ron Zimmern

Yes, I think that's right as well. We're in that area, I think, at the moment.

Sally Sheard

That's a really interesting question Ron, thank you. I'm keen that we recognise the individuals and their personalities as factors here. So, we've talked about John Bell, both overt and behind the scenes. Can we talk a little bit about Sue Hill, please?

Mark Bale

Well, I can talk about Sue Hill's role in this. Sue, as the Chief Scientific Officer, has been involved in a lot of the background discussions around genetics and genomics laboratories. She certainly had a very strong hand in the HGSG report in terms of how recommendations that came from the 2009 [House of Lords Science and Technology Committee] report were built into something that looked more NHS friendly. There was talk in the 2009 report about an Institute of Biomedical Data or something, something that sounded very academic-led. We wanted to make that much more hard-wired into NHS services. I think her blueprint was either the right blueprint, or it has just been lifted and copied and pasted, is now what the Genetics Laboratory Hubs and the genetics and medicines clinical alliances look like in the way that the NHS has been re-coordinated.

I have to say, given her own personal circumstances, she's been an absolute tireless champion of delivering the 100,000 Genomes Project and keeping it on track, and probably giving, unfortunately, people like Frances a hard time, but I think it was supremely confidence-inspiring for me in the Department [of Health] being hassled about delivery, that Sue, Mark Caulfield, and people like that were so focused on delivery, and hopefully not to the exclusion

of everything else. So, I think she's had a hugely powerful role here, and that was recognised in her award [of a Damehood]. That's my perspective, and I'm sure there'll be other ways of looking at this.

Sally Sheard

Would anybody else like to offer any comments?

Rosalind Skinner

She's a focused lady who is highly organised and pursues her goals, often successfully. I'll leave it there.

Diana Walford

It sounds like an annual appraisal.

[Laughter]

Sally Sheard

Thank you. I appreciate everybody here has personal interests in this, but it is part of the history, and we will find an appropriate way in which to convey these issues.

Thank you all very much for coming today. It's been an enormously useful session. It's generated discussion. It's generated points that we wouldn't have got from you through individual interviews…

Frances Flinter

It's our failing memories.

[Laughter]

Sally Sheard

Thank you very much. Have good journeys home, and we will be in touch.

The Development and Influence of Public Health Genomics

Part 2: The International Enterprise

The Transcript of a Witness Seminar held online on 15 November 2021

Contributors

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Professor Wylie Burke: Professor of Bioethics and Humanities, University of Washington, USA.

Dr Hilary Burton: Director, PHG Foundation, 2010-2017.

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Dr Eric Meslin: President and CEO of the Council of Canadian Academies.

Dr Ron Zimmern: Chair of Board of Trustees, PHG Foundation.

Transcript

Sally Sheard

Welcome to you all and thank you so much for finding the time to do this. It's wonderful to have this opportunity. It's also particularly useful to bring a slightly wider set of individuals into this conversation. A witness seminar is an invited event where we bring together a group of people who have participated or been closely involved with the development of a significant policy or scientific development. And in the case of this witness seminar, we are focused on the development and influence of public health genomics and of course, that applies very much to all of your careers. I will begin with a really broad question, and it's to get your personal perspectives on the background and the experience of those individuals who have been associated with the development of public health genetics. Perhaps I could ask you to begin, Muin.

Muin Khoury

Well good morning, or good afternoon, everyone. This is Muin Khoury from the Centers for Disease Control and Prevention [CDC] in the US – at what is now the Office of Genomics and Precision Public Health. We've changed our name a few times over the last 25 years, just to meet the challenges of the moment and the occasion. So, I've been at CDC for a very long time. As a matter of fact, I'm a paediatrician with training in medical genetics and then genetic epidemiology at Johns Hopkins [University]. I joined CDC in the epidemic intelligence service many years ago, decades ago, and at the time I was interested in the field of birth defects and new-born screening. Having stayed at CDC for so long and watched the Human Genome Project get started in 1990 and having had the training in genetic epidemiology, I started making the case that this new technology of human genome sequencing, and other technologies, will have or could have a broad impact on the mission of CDC and what public health does in general. So, to cut a long story short – much of what I'm talking about has been written up in papers and on our website, so I don't want to be too redundant – but the idea was to try to start a movement that goes beyond the traditional scope of genetics and public health, which at the time was only limited to a few areas like new-born screening or birth defects. We didn't call it public health genomics at the time or anything we just talked about genetics in public health.

At the time the Director of the Centers for Disease Control was David Satcher, who happens to be a human geneticist.[112] So, I got receptive ears from the leadership of CDC, and they said 'OK, tell us what we need to do'. So, we had a taskforce and discussions with stakeholders and brought people together and back in 1997 we formed the Office – at the time called Genetics in Public Health. Then we had a first meeting in 1998 in Atlanta on genetics in public health and I think that's when I first met Ron Zimmern. At the time Ron had just created the Public Health Genetics Unit in the UK and we started a conversation that has now spanned over four decades. So, I'm going to stop here because I can talk for the whole two hours and let others speak, but I am sure we will come back and revisit some of these things.

[112] Dr David Satcher (b.1941) was Director of the Centers for Disease Control and Prevention from 1993 to 1998.

Sally Sheard

Could I ask Wylie or Eric perhaps to come in and pick up on that please.

Wylie Burke

Well, I can follow up to Muin and talk about how I got connected to Muin and Ron. My background is training in genetics – a PhD in genetics followed by medical school, followed by a focus on primary care, general internal medicine. The question that arose for me at that time was 'What are the implications of genetics, not for the rare and unusual diseases, but for the common diseases?' That was sort of a starting point. At that time a major funding initiative was being developed at what is now the National Human Genome Research Institute called the ELSI programme. That was funding in the ethical, legal, and social implications of genomics and they were, indeed, very interested in funding research that had to do with the bringing of genetics into clinical medicine.

My first formal participation in this arena had to do with research that looked in a general way at the different kinds of ethical issues that arise when you bring genetics into clinical medicine, and then drilled down into the ethics of the emerging breast cancer genetics and cancer genetics issues. As a part of that work, I became a member of what is now recognised as the ELSI community. The ELSI community held lots of meetings as issues arose and one of the meetings was at the CDC on hemochromatosis. The gene for hemochromatosis had been discovered, and represented a quintessential problem for bringing genetic information into routine clinical care – is there a screening opportunity, for example? I attended that meeting and met Muin and began a conversation that has continued. We did, I think, some interesting work about hemochromatosis. It's an interesting example of what seems at first glance a slam dunk – we should be going out and genetically testing everyone for hemochromatosis. Then when you start looking carefully, it's not so simple. So, we did some work together but mostly we got into conversation about this issue of population health and genetics and where do they meet. That led to my doing a sabbatical at the CDC, right at the time that the Office of Public Health Genomics was being initiated and sponsoring meetings dedicated to public health genomics. I was at the first sponsored meeting and that was my entre into a conversation that was led by Muin and Ron, and it was wonderful to be part of it.

Sally Sheard

Thank you Wylie. Eric do you have anything to add at this stage?

Eric Meslin

I sort of feel a bit like Muin. I could probably do an hour and a half as well as all of us. I'm smiling partly to see Wylie and Muin on the call because they are part of the antecedents of this. So, it's always fascinating to watch others talk about else was in the room. I come at this from a slightly different perspective. My training and background are in bioethics. I'm a Canadian by birth, who did his PhD at Georgetown University – I would say not so much

during its hay day, because Georgetown is still quite a leader, but at that time one of the few preeminent bioethics research organisations probably in the world. I was fortunate to have had some fantastic mentors who are themselves part of the history of this – LeRoy Walters was my PhD supervisor, Tom Beauchamp was on my [thesis] committee and Bernard Dickens was on my committee and Charles McCarthy, the legendary Director of OPRR [Office for Protection from Research Risks], with whom I worked, was also on that committee.[113] So, I was schooled in the, forgive the mixed metaphor, the Mecca of bioethics and public policy in the early 1980s.

I mention the biography because my non-linear career intersects at several places with some of the points that Muin and Wylie have raised. The field of bioethics in some ways got its start through a number of the technologies and moral problems that genetics and genomics presented, far before the genome project was a glint in anyone's eye. Bioethics focused quite a lot on ethical issues in genetics. The eugenics topic was probably among the most prominent of those worrisome trends and that is sort of where I was initially introduced, but then through a series of fortuitous, and to this day rather gratifying experiences, I intersected with several of the streams that Wylie and Muin have spoken about. So, having returned to Toronto for many years I was then invited to come back and apply to be one of the Directors of the ELSI programme that Wylie mentioned. So, my namesake and couple of years older, Eric Juengst who was the founding Branch Chief of the ELSI programme, called me in Toronto and said 'I'm going to be leaving would you like to come down and apply for the position?'

On another day – Wylie will appreciate this – I will describe some of the challenging issues that arose when I returned to the ELSI programme and found that they had changed the name of the Branch Chief position to being a Director. We'll keep this inside baseball for this conversation, but at that time I was working with some very distinguished colleagues. Obviously, Francis Collins was the Director of what was then the National Centre for Human Genome Research and it changed during my time to the Institute.[114] But running the bioethics portion of the ELSI programme also brought me to CDC and we're all on that haemochromatosis paper from way back in the day, which I think was an underappreciated antecedent academic contribution to this discussion, for reasons that we could go into at great length.[115] What was fascinating was what I thought was the initial knee-jerk reaction of the 'broad community' – 'Look we can do this. We should. We must. Why can't we? If you can, you should', followed by a momentary 'Well, wait a minute, should we?' I don't think enough attention has been given to how that paper was a kind of an initial test to how the public policy conversation would occur. I mean people like Allen Buchanan, a legendary philosopher, who himself had haemochromatosis, was one of the most powerful conversants on this topic, describing the form of discrimination that he received when he chose to have his blood drawn and was not allowed to donate it at that time and chose to take his blood back home with him to put it on his roses.[116] These are not issues that come out in the public conversation but when you think about antecedents – people like Allen Buchanan, who had a conversation about,

[113] LeRoy Walters (b.1940) is Professor Emeritus at the Kennedy Institute of Ethics and Department of Philosophy, Georgetown University, USA. Tom Beauchamp (b.1939) is Professor Emeritus of Philosophy at Georgetown University. Bernard Dickens (b.1937) is Professor Emeritus of Health Law and Policy at the University of Toronto, Canada.

[114] Dr Francis Collins (b.1950) was Director of the National Human Genome Research Institute from 1993 to 2008.

[115] W. Burke, E. Thomson, M.J. Khoury, S.M. McDonnell, N. Press, P.C. Adams, J.C. Barton, E. Beutler, G. Brittenham, A. Buchanan, E.W. Clayton, M.E. Cogswell, E.M. Meslin, A.G. Moltulsky, L.W. Powell, E. Sigal, B.S. Wilfond and F.S. Collins, 'Hereditary Hemochromatosis: Gene Discovery and Its Implications for Population-Based Screening', *Journal of the American Medical Association*, Vol. 280, No. 2, 1998.

[116] Allen Buchanan (b.1948) is Professor of Philosophy at the University of Arizona, USA.

hemochromatosis, or Wylie's involvement in BRCA1, and the many meetings of the bioethics community.

I will just mention one other intersecting stream – when I left the ELSI programme I moved over to the White House to run, what was called, the National Bioethics Advisory Commission [NBAC]. This was the national commission established by Bill Clinton. There have been seven such Commissions in the US, and of course the Nuffield Council [on Bioethics] is the closest analogy. I mention this, not because of the history of NBAC or many of the other bioethics commissions, but because the idea that there would be public advisory bodies…and not limited to a White House commission, there are, I would say hundreds, but there are certainly tens of dozens of committees in the US, in Canada, in Europe and indeed around the world that have focused on genetics issues. So, as we come later to your questions, that activity of how public advisory bodies influence or accelerate, or you know in the case of George W. Bush's Commission run by Leon Kass maybe decelerate the conversation in some way.[117] So, I will stop there. I haven't gotten to GRaPH-Int or Ron or our Australian colleagues, or others, but I'm sure that will come up.

Sally Sheard

Absolutely Eric, that will come up, but that's a really helpful trajectory to set us on and I think your point about the timings and the utility of commissions is a really critical one. Thank you for that. Is there anybody else who would like to come in before we move on?

Stefania Boccia

Yes, I think it's my turn?

Sally Sheard

Thank you Stefania.

Stefania Boccia

OK, I'm appointed as Professor of Hygiene, Preventive Medicine and Public Health at the Università Cattolica del Sacro Cuore in Rome, and as a background I have a five-year degree in Biology, so postgraduate school in Biology. Afterwards I had five years additional postgraduate school degree in Clinical Pathology. Then I was appointed in 2002 as a young researcher at the public health department of my university. In 2005 I entered also Master of Science in Epidemiology and Biostatistics and I decided that my main focus would have been cancer epidemiology, but then in 2006 I met Cornelia van Duijn.[118] She was Professor at the Erasmus Medical Centre and the leader of the Genetic Epidemiology Research Group, and so I decided to enter the PhD school in Genetic Epidemiology at the Erasmus Medical Centre in Rotterdam. I think it was exactly during that time that I met Ron and Hilary first, because of

[117] Professor Leon Kass (b.1939) was Chair of the President's Council on Bioethics from 2001 to 2005.
[118] Cornelia van Duijn (b.1962) is Professor of Epidemiology at the Nuffield Department of Population Health, University of Oxford.

the Public Health Genomics European Network (PHGEN). The next steps of my career were oriented towards research in cancer (genetic) epidemiology and prevention, and public health genomics in Italy and Europe. In fact, in the last decade an important part of my career was supporting the Italian Ministry of Health in the context of the 'Inter institutional committee of public health genomics'. That was the hardest part of my job – it was for free of course, in my extra time – but thanks to that I contributed substantially to support policymakers in developing two main institutional documents. One was the first national guidelines on genomics in public health published in 2013, and secondly the innovation plan of health systems based on 'omic' sciences in 2017, and thanks to this plan it was possible in 2016 to have dedicated paths at regional level. Thanks to this plan it was possible to have dedicated paths at regional level, and reimbursement across Italy for BRCA genetic testing for hereditary breast cancer. So, it was an achievement, but – as will probably come up during this witness seminar – it was very difficult in my experience, ten years' experience working at the interface with policymakers, to convince them about the importance of this topic. Because they are very well oriented in addressing the environmental determinants of health, and far less prone to evaluate the potential for relevance of the contribution of genetic/genomic beyond rare disease and cancer.

The PHGEN meeting in Rome in 2012 was definitely the first time I met also with Muin. The European Commission supported the Public Health Genomic European Network from 2005, asking for an inventory report on genetic determinants relevant to public health. Only later, the Personalised Medicine (PerMed) Initiative started, as a follow-up of the PHGEN initiative, with different leaders though.

Sally Sheard

Thank you so much Stefania, it's really good to have that European perspective coming in and we will pick it up as we go through. I am going to move us back to Question 2 which is 'When did the possibilities of genomic medicine become apparent and what influence do you think this had?' And again, I would like to get the international perspectives please, so Muin would you like to start us off again?

Muin Khoury

So, thanks again. Just listening to all of you speak here brought back all these memories from different touch points. There is Rome in 2012, there is Ickworth in 2010, there is Bellagio etc. So, the answer to your question is there is no sort of bright line. I think what Wylie started the conversation on when she talked about hemochromatosis was the idea that because you can do something, why not do it. The meeting happened I think in 1997, and we all published a paper together in 1998. But the possibilities for the people who do the sequencing, the enthusiasts, the technologists, the geneticists who have been entrenched in the world of genomics, were kind of immediate – 'We can do it, so why not do it?' The ultimate enthusiast was Francis Collins himself who in 1999 wrote his famous paper, which I quote all the time, which was his own vision of medicine in the year 2010.[119] He describes this hypothetical man named 'John' who is 23 years old and goes for a check-up or something, then he is offered his genome, and

[119] F.S. Collins, 'Medical and Societal Consequences of the Human Genome Project', *New England Journal of Medicine*, Vol. 341, No. 1, 1999.

then personalised prevention, treatment, early screening, regimens based on the genome. So, for people like Francis Collins the possibilities were there from Day 1.

For those of us who are more in the translation, population game…some of us come from the ethical perspective…I had a hard time convincing people within CDC. Remember our Office was formed in 1998 and I was an enthusiast, but at the same time I was embracing the concepts of equity and ethics and above all evidence-based genomic medicine. So, part of the discussions and the processes I initiated within the CDC was an evidence-based process that would take into account the evolving evidence on any particular topic or application. We even formed a working group called EGAPP – Evaluation of Genomic Applications and Practice and Prevention – similar to other taskforces or bodies within the US, that would explore the evidence around clinical preventive services. As a matter of fact, the Chair of EGAPP, which was formed in 2005, Alfred Berg from the University of Washington, was the Chair of the US Preventive Services Task Force for many years before. So that group kind of established an evidentiary framework for clinical validity, analytic validity – the ACCE [Analytical validity, Clinical validity, Clinical utility, and Ethical, legal, and social implications] framework that people have talked about.[120] Then we started doing the methodological hard work of reviewing evidence and then pointing to research gaps that need to be filled.

I think where we are in 2021…there are still early enthusiasts, every time you see something. Liquid biopsy – 'why can't we do it?' DNA based analysis in the stools – 'we can do it in terms of colorectal cancer screening'. So, at least in the US I think that the evidentiary framework for establishing when something can be used in practice, and for us in public health, in population screening…remember that the bar for population screening tends to be a bit higher. Screening everyone is different to using a genetic test in the context of diagnostic work up or treatments. I feel that the possibilities now are far more than before, but maybe not as far as the enthusiasts expected. I mean if you ask Frances Collins today about his vision…as a matter of fact you don't have to go too far. The National Human Genome Institute, last year in *Nature*, published their vision for the next ten years, and guess what, now they're predicting that the scenario that Francis Collins predicted for 2010 will happen now in 2030.[121] So we keep pushing the goalposts out. For me, we've been there for so long that you need to look at this field on a more holistic basis and fund the whole translational continuum, not just the discovery phase. That's one of the things that I've been advocating over the decades, that you need a robust public health sciences, ELSI work, clinical trials when they're needed etc.

I'm going to stop here. Maybe I didn't answer your questions but it kind of forced me to think about this, because it was a natural continuation of some of the things we did when we first founded the Office and continue to do to the present day. So, I will stop here and then maybe we will pick up more conversations along the way. Thank you.

Sally Sheard

Thank you so much Muin. Wylie.

[120] J. Haddow and G. Palomaki G, 'ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests' in M. Khoury, J. Little and W. Burke (eds.), *Human Genome Epidemiology* (Oxford University Press, 2004)
[121] E.D. Green et al., 'Strategic Vision for Improving Human Health at the Forefront of Genomics', *Nature*, Vol. 586, No. 7831, 2020.

Wylie Burke

Yes, thanks Muin. What Muin is describing is central to the story, but it also illustrates what public health genetics tried to do – I think to some extent succeeded in doing, certainly very important in the U.S – and that is to introduce an evidence-based framework, to introduce a rigor to looking at how genetics might be introduced. What's interesting here is that the rigor that EGAPP, for example, introduced wasn't relevant only to public health as we routinely think about it, it was relevant to use of genetics across a clinical spectrum. It's interesting that the first several reports of EGAPP were negative basically – 'No, we don't have the evidence to do this now', or 'There's insufficient evidence to go down this pathway', in some cases. I think that introducing that rigor into the conversation was extremely important. As Muin says, we still have the enthusiasts, we still have this notion that if you get your genome you're going to know what to do. I'll just add one more thought at this point and this is where I think we need to go in the future and where I think that rigor introduced by public health genetics tells us we must go, is to a much more robust acknowledgment of the fact that we are not genetically determined, that genetics plays a role but so does social environment – a powerful role, in health – and if we don't figure out how to think about genomics within that larger context we're just going to be creating expensive gene-based products that provide no health.

Sally Sheard

That's a brilliant contribution, thank you. I really appreciate that and it's a nice follow on from Muin's points. Eric do you want to contribute on this question?

Eric Meslin

I do, and I'm sure that Hilary will want to jump in since you're going to genomic medicine shortly. My smile is as much responding to Muin reflecting on all this and Wylie's stories, and just reminding all of us that this is about people and places and events and not just historical sign markers along the way. Had there not been a Ron Zimmern, or a whomever, bringing people together, these conversations just would not have occurred. So, I feel quite strongly. The kind of enthusiasm that Muin was referring to…gets muted a little bit when the evidence comes in. Without rehearsing my CV, I just was remembering a paper that Jim Evans and Theresa Marteu and Tim Caulfield and I wrote, many years ago, which was called 'Deflating the Genomics Bubble'.[122] We started off with a quote that Jim used which was just spectacular, and it relates to the Frances Collins comment that Muin had – 'Soccer is the sport of the future, and it always will be'. We were writing that during the World Cup, but it was an example of how the optimists say it's just about to happen, the pessimists say it will never happen, and the pragmatists sort of fall somewhere in the middle.

I wanted to highlight two quick things just in terms of background, in relation to the question 'When did the possibilities of genomic medicine begin to become apparent?' I think that the answer to the 'when' can be described from the medical and public health perspective which you have heard – the technology presented itself, so that meant that we were able to have a conversation. I vividly remember Mark Skolnick from Myriad Genetics coming to a meeting

[122] J.P. Evans, E.M. Meslin, T.M. Marteau and T. Caulfield, 'Deflating the Genomics Bubble', *Science*, Vol. 331, No. 6019, 2011.

of what was then called the Society for Health and Human Values in the US, a bioethics meeting, where he presented a slide deck, with the beautiful Wasatch Mountains behind him, of the Myriad facility and described, at that time, the status of BRCA1 testing. It was very new, the data were uneven to say the least, and he said to this group – it's an example of not knowing your audience – 'You know, we've got this fantastic test', and pointed into the audience…I don't know if Muin or Wylie were at this meeting but I remember it vividly…and said 'To all you women out there who are mothers and daughters and grandmothers, how could you live with yourself if you didn't go out and get this test today?' A test that had not been validated. A test that, as I say, was early days. Now, why do I mention that in answer to this question? I think some of it is about the public's uptake in willingness to respond to this fascinating science fiction/science reality…it's not underappreciated because many people write and think about this today…but at the time we didn't have social media, we didn't have the 24 hour news cycle…the idea that the public's willingness to listen, to get excited, either over excited or frightened was – and this is sort of early-1990s, mid-1990s by that time – was a phenomenal, not so much antecedent, but time connector to the technology.

The other point is whether or not the regulatory environment was either sophisticated enough or prepared for this, because…Muin and Wylie know this far better than I would…public health regulation, just like medical research regulation, was not designed for genomics. It was not designed for genetic testing. It was designed for the police power of the state. It was designed for vaccinations and quarantine. It wasn't designed for haemochromatosis testing or colorectal screening, in the same way. I'm talking about the 1990s. I'm not limiting this to the US – this is largely the developed West and the global North – but the timing of how the technology, the regulatory environment and the public's willingness to take this on, I think all double or triple Helix themselves, if you don't mind the analogy, into the answer to your second question, in my view.

Sally Sheard

Thank you, Eric. Hilary, Eric suggested you may wish to come in on this.

Hilary Burton

Yes. I think these first two questions run together in many ways, because we were talking about antecedents and I think that one of the distinctions that is important to make is that in the UK the public health profession had a responsibility for health services, so we could see straight away the potential power of genetic – at that stage – science within health services. Wylie did mention that, not only healthcare but also screening. At that time, it was actually very much about genetic testing and single gene disorders, and the potential of genomic medicine didn't really start to become clear until much later. To my mind it was more like about 2010 or 2011 when the potential for whole genome sequencing at anything like a sensible scale came in and you could start to see how whole genome sequencing could not only be used to fast track some of the genetic testing and do multiple testing all at once, but then potentially could help you to look at all of a person's genome at once and think about what the preventive aspects of that might be. I think that was actually much later than what we've been implying, and that to me was the shift from public health genetics, when we were thinking about clinical services and single gene disorders and chromosomal disorders, to then what is the potential for the whole

of the genome for preventive health. I was quite surprised at how late that was when I started to look at our papers again.

Wylie Burke

Hilary you are absolutely right about the timing, and I think it's really important to acknowledge that, to say that there was a certain conversation that started much later that had to do with the genome. Muin already mentioned Frances Collins' 1999 paper, the one where he projected what we were going to be doing in 2010, and what I want to suggest is that in that paper he included some thinking that laid the foundation, that made it very easy for people then to start talking about a genome. If I'm recalling, he had some case examples where he's plucking different kinds of genetic information. He's proposing that individuals come in for routine care and they'll find out that they're at increased risk for complications of smoking and this will supposedly incentivise them to not smoke. Even though we weren't thinking in terms of doing a genome then, it didn't even seem credible that we could, we could only do that in 2010, there was already this idea, I think, of a comprehensive evaluation of a range of genetic risks, such that when the genome then becomes feasible at a cost level it's kind of like the enthusiasts are already primed, I guess, to think in those terms.

Sally Sheard

Thank you. Ron, would you like to come in? Then Stefania.

Ron Zimmern

I will come in at this stage because the first thing I was going to say is that Stefania and Europe's importance in all this came a bit later, about 5-10 years later, than these very early days and I would really like to hear what Stefania has to say about how she and Walter Ricciardi and other European people came in at that time. But a few comments to those early days – I remember very well that first meeting in 1998 that Muin ran at a not very edifying hotel in Decatur in Atlanta. The thing that struck me was that I was the only person from this side of the Atlantic. All the other 119 delegates were from North America or Canada. So, we were behind, and I don't think we really got into this properly until probably 2000 when we did our work with the Nuffield Trust.[123]

The second point is that we have our Francis Collins as well – he's called John Bell – and every ten years he says that this genomics stuff will revolutionise medicine this genomics stuff in the next ten years. The third point I would like to make is the importance of the ACCE Framework, which was developed in the US, but it really had a huge impact on the development of the UK Genetic Testing Network, which I was very much involved in in the early days, and Mark Kroese took over. Having that as a framework for evaluating genetic tests was really very important. Finally, just as in the U.S., when we did the Nuffield Trust project it was very clear, every person involved in that came to the same conclusion about what the ultimate destination was. There was little dissent, but boy there was dissent about timescales. There were the

[123] *Genetics and Health: Policy Issues for Genetics Science and Their Implications for Health and Health Service* (Nuffield Trust, 2000).

optimists – 'It's all going to revolutionise in the next 10 or 15 years', and then there were the realists – 'This is going to take 50 years to get right'. So, those are my points to what has been said about those early days

Sally Sheard

Thank you Ron. Stefania, please.

Stefania Boccia

Thank you Sally. Well, in order to answer the question about when the genome-based application started influencing…my answer is in line with the one Muin and the others said. In terms of genetic testing, I always refer to breast cancer associated genes that in fact the Netherlands and Germany started reimbursement for in 2005. For drugs used in an oncology setting for metastatic lung cancer or for melanoma, drugs that are used based on the genetic makeup, we have to look a bit later – 2012 for melanoma, 2015 for lung cancer. But generally speaking, just reflecting on genomic medicine and the impact of population health, I want to refer to a European project that I started coordinating in 2014, about personalised prevention and population health because. The problem is that on the European side the personalised medicine initiative PerMed, that was a sort of follow up of the Public Health Genomics European Network, which is the largest umbrella European initiative of personalised medicine, was basically dealing with treatment. So, they were not dealing much with the potential of genomics to inform population health, or screening or even in a primary prevention perspective. One the same line, the European Commission probably did not publish, until recently, dedicated calls to fund translational research to dissect the potential the use for genomics in the primary and secondary preventive setting for chronic diseases. As such, in 2013 and I decided to apply to apply to get funds to work on the aforementioned issues in the context of some funding calls – that were not top down but bottom up. You can decide the topic and then they fund it. Thanks to that work, I was able to get funded to run the Personalized Prevention of Chronic Diseases (PRECeDI) project (2014-18), and we published a report, that Ron also reviewed, that released the first recommendation on how to integrate personalised prevention for chronic disease in public health.[124]

At the time I was the Vice President of the European Public Health Association, so it was easier for me to engage European public health professionals to have a look at this report about how to integrate personalised prevention in public health. We published the recommendation and also an accompanying book.[125] I just wanted to say that because now, luckily now, the Commission devoted a number of funding efforts to support translational research in genomics and public health. In fact, they just published a call to fund €6 million in the cancer pillar for genomics in public health (DG Health call from the Mission Cancer funding scheme).

Sally Sheard

[124] S. Boccia et al., 'How to Integrate Personalized Medicine into Prevention? Recommendations from the Personalized Prevention of Chronic Diseases (PRECeDI) Consortium', *Public Health Genomics*, Vol. 22, No. 5-6, 2019.

[125] S. Boccia et al. (eds.), *Personalised Health Care: Fostering Precision Medicine Advancements for Gaining Population Health Impact* (Springer, 2021).

Thank you, Stefania. That's really helpful context and I'm sure we will come back. Are there any specific things that people would like to add about what led to the establishment of the Public Health Genetics Unit, the CDC Office for Genomics and Public Health and the Institute for Public Health Genetics?

Muin Khoury

You have heard the story of the formation of our Office and the Public Health Genetics Unit, but the evolution from genetics to genomics and then from genomics to precision medicine, then from precision medicine to precision public health, I think has a lot of underpinning in some of the issues that are being discussed. Let me just give you a couple of examples. So, Hilary talked about genetics and genetic testing and the fact that genomics came later. So, our Office tries to keep…I mean although EGAPP doesn't exist anymore, we developed a light touch EGAPP-like function by trying to classify the evidence around genetics and genomics by tier. So, Tier 1 are those applications for which there is the highest level of evidence for integration and to practice. Tier 3 is sort of – 'don't bother'. Tier 2 is more clinical validity, but we don't know about clinical utility. Most of the Tier 1, even today in 2021, are single gene disorders. We are still dealing with the implementation of BRCA, Lynch syndrome, familial hypocholesterolaemia, hypertrophic cardiomyopathies, hereditary hemochromatosis, on and on the list of 73 genes from ACMG [American College of Medical Genetics and Genomics]. They're all related to the practice of medical genetics at the population level. So, the implementation, the equity, the access, some of the rules and regulations, are still medical genetics based.

Now genomics, where the application of whole genome sequencing, let's say for the diagnosis of sick kids in the intensive care unit or around the new-born area, is coming along but it's lagging behind a bit, and will continue lagging behind because the evidence to collect around utility will continue to evolve in a slower way. But along the way other things came along, like the applications of pathogen genomes. We are in the midst of a pandemic. So, from a public health perspective…CDC right now is into pathogen genomics like you've never seen it before. As a matter of fact, human genomics has taken a back seat. There are millions of dollars spent on COVID sequencing and looking at variants and genomic surveillance etc, which is what it's supposed to be, because you use the tools that allow public health to make a difference at the population level. On the human side those tools are still evolving, and they're applied to smaller fractions of the population, especially when you are dealing with genetic diseases. When you're dealing with a genome, like polygenic risks scores etc, they're still lagging behind. They're mostly Tier 3 applications, although the enthusiasts…I recently listened to a talk about polygenic risk scores and they sell them like crazy, like they are the best thing since sliced bread. I would like to believe that because we all have polygenic risk scores for different things. I have a polygenic risk score for heart disease, colorectal cancer etc, and I'd love to use those numbers if I could, but we are lagging way behind. So, in the meantime, public health is using the tools of genomics to respond to public health needs, and I think that's where the conversation around the evolution of the field should go. As you follow the needs, you take the technology, you apply it in an evidenced based ethical way and then you deploy it, and that's where pathogen genomics is right now. As a matter of fact, CDC formed a parallel office to mine called the Office of Advanced Molecular Detection. I know that person very well. They do pathogen genomics in and out and most of the CDC labs and the labs in public health departments are being funded more and more.

Look at the human side – I'm still struggling to sell the enterprise at a public health level. Why? It's not for the lack of my personal selling skills – maybe I'm lesser than Frances Collins – but if I follow my own rules I shouldn't be selling certain things, and I don't. I remember, since we are talking history here, in the early days I interacted with the diabetes division at CDC, and I remember the Director of the division back in 2001 – he's now retired. He attended all our seminars and conferences. We had one on diabetes and he came up to me and said 'Muin, I love what you guys do, but when it comes to diabetes why don't you wake me up when we get there, because obviously we are not there'. That was in 2001. In 2021, maybe we are about to wake up, maybe not…Wylie is smiling here…so we will see if there is more movement around human genomics and type 2 diabetes – which, for the most part, is age related, BMI related, all these other factors. Yes family history is important, but its multifactorial, and I would say family history is even more important than having your polygenic risk score because it puts together, not just the genome, but the shared environmental, nutritional, social determinants of health. So, this is where I'm going to stop, because again as Eric said each one of us can go on for two hours, but I had to say those words, so thank you.

Sally Sheard

Thank you. We have a lot of background information on the establishment of the centres, but is there anything specific that people would like to bring up at this point? Ron.

Ron Zimmern

Can I just ask Stefania…what was very influential, for me personally at any rate, was the European programme called EuroGentest.[126] Were you ever involved in that and what dates was EuroGentest? It was in the mid-2000s. Hilary, can you remember?

Hilary Burton

No, sorry, I can't pinpoint it. I think it was after the work or towards the end of the work that we were doing on the UK Genetic Testing Network.

Ron Zimmern

That was interesting because it was mainly clinicians not public health people, and they were beginning to start thinking and using…again, the ACCE framework was very influential there. So, there was a group of genetic clinicians who were interested in really saying 'Well, what's the evidence base for using this genetic test clinically?'

Hilary Burton

[126] EuroGentest was a 5-year project from 2005 funded by the European Union which established a European Network of Excellence in genetic testing. P. Javaher et al., 'EuroGentest: DNA-Based Testing for Heritable Disorders in Europe', *Community Genetics*, Vol. 11, No. 2, 2008.

The same was true in the UK with UK Genetic Testing Network, apart from us being involved...

Ron Zimmern

Absolutely.

Stefania Boccia

EuroGentest was running at the same time as the Public Health Genomics European Network. The European Society of Human Genetics, soon after the EuroGentest finished, set up a taskforce, where Prof. Martina Cornel from VUMC in Amsterdam contributed a lot, and they were working and publishing some recommendations that were really at the interface with public health. So, there was a follow up around evidence-based genetic testing that was took over from the division of European Society of Human Genetics.

Sally Sheard

Thank you very much.

[Break]

Sally Sheard

Welcome back. We are going to resume by talking about the nature and impact of international collaborations, and in particular we would like your thoughts on the Bellagio Meeting, the GRaPH-Int network and the role of WHO [World Health Organization]. I think, Muin, it's probably logical again for you to start.

Muin Khoury

OK. So again, we can each take an hour on all three…but here's the high point. I think Bellagio was just a delightful experience in so many ways – not just the magical location of the place, but the fact that we were all sequestered together working on a common issue. I just emerged from that meeting much more refreshed and thinking that 'Here's a group of people from around the world that are struggling with the same issues I've been struggling with'. Of course, we come at it from all different perspectives – Wylie was there, Ron was there, Hilary was there, everybody was – but we came at it from an international perspective. I still use the definition of public health genomics that emerged from Bellagio. We defined the field together and then we defined the idea of networking. I remember us strolling across the lake and we conceived of GRaPH-Int. I think GRaPH-Int was imagined as a result of that initiative.

Then on to WHO – I think I give most of the credit to our friend Ron here in the convening function, and you are still doing it. Look at us today, we are still being convened. There is an important context for how movements can rise and evolve over time, and this is one of them.

As long as we're talking about predictions of the future and how technology shapes health and public health and healthcare, those conversations were very, very important. They shaped the dialogue going forward. Now were they completely successful…you know the frustrations with WHO. I know I'm being recorded now so I can't say too much, but it's a different type of organisation. Sometimes I'm frustrated with how the US system works, but WHO is more of an international conglomerate where they try to meet the needs of multiple nations, then as the pressures of different things come their way, things that are not as important, they fall behind. I think human genomics captured their attention for a while, but it didn't capture their attention as much as, let's say, pathogen genomics. Look at it now, in terms of the COVID pandemic. So, I don't see that as necessarily good or bad, but it's part of the interactions that needed to occur internationally in order to make progress in the field, in order to arrive at commonalities and visions. Then there was the Ickworth meeting, then the Rome meetings, and then we convened in Montreal a couple of times, so all of these events made some progress in their own way.

Sally Sheard

Yes, Stefania, please. Then, Hilary, I will come to you.

Stefania Boccia

The European Observatory on Health Systems and Policies depends on the WHO, and it is co-directed by Professor Martin McKee, who is a champion of public health.[127] The European Observatory have been asked many times to look at the advancement of genomics in the context of broader public health application. Only this year however, they published a report titled *Regulating the Unknown*.[128] The European Observatory also organised an event in October, to disseminate the fact that this report exists, and I spoke very briefly at the time.[129] The story of this report started a long time ago – in 2014, Italy, during the six months of the Presidency of the European Union, hosted an event in Rome with all the general directorate of prevention of the member states. The event was co-organized with the European Observatory, with the contribution of Martin McKee and Prof. Walter Riccardi, and Martin McKee asked, 'Why don't we write a policy brief about genomics, so that people might start understanding what this is about'. Unfortunately, although me and Ron were working on a preliminary version of that brief, at some point everything stopped. In 2018 there was the declaration towards one million genomes (1MG) that's been signed initially by six European member states and at that time the Finnish Minister of Health (during the Finnish presidency of the EU) took over the responsibility for drafting the policy brief. An important contribution came from Markus Perola in drafting the policy brief.[130]

[127] Martin McKee (b.1956) is Professor of European Public Health at London School of Hygiene and Tropical Medicine.

[128] G.A. Williams et al., *Regulating the Unknown: A Guide to Regulating Genomics for Health-Policymakers* (European Observatory on Health Systems and Policies, 2021).

[129] https://eurohealthobservatory.who.int/news-room/events/item/2021/10/19/default-calendar/what-do-policy-makers-need-to-understand-about-using-genomic-data-in-health-care

[130] Markus Perola (b. 1966) is Research Professor at the Finnish National Institute for Health and Welfare.

It is also worth mentioning the contribution of Prof. Natasha Azzopardi-Muscat.[131] Natasha is the former European Public Health Association President (EUPHA) and she's now Director of the regional office of the WHO in Copenhagen. She is very sensitive to this topic, luckily. In fact, I also invited Natasha to Amsterdam when the PRECeDI recommendations were first discussed, where she had a talk with the perspective of the EUPHA President at the time.

Sally Sheard

Thank you, Stefania. Hilary, please.

Hilary Burton

Yes, so just experience from WHO – we worked with them probably around 2010 and obviously they had to be very focused on the burden of disease, the international burdens of disease, and they are also pretty underfunded. Where we did find that we had some traction with them was the work that we did on birth defects. That was very interesting, because you had to bring together not only the genetics and the genomics for prevention, so things like sickle cell and thalassemia, but also things like neural tube defects, which are obviously diet related, alcohol and so on. I think that was fairly effective work really because it had a huge importance for developing and middle-income countries, where if they were coming out of the worst of poverty, if they weren't doing something fairly good to prevent and look after children with birth defects, they had a massive health service impact. So that was some work that I think was pretty effective, that actually showed how genomics genetics needed to be integrated for prevention in major public health areas.

Sally Sheard

Thank you, Hilary. Wylie can I bring you in here for some reflection both on Bellagio, the formation of GRaPH-Int, and maybe the role of WHO?

Wylie Burke

I can comment on some of those things. I can certainly echo Muin's comment about Bellagio. It was a magical meeting, it brought together a diverse set of perspectives, there was a wonderful series of conversations, and I think for everyone at that meeting it was an important moment, often an important starting point. I will also echo Muin's comment about Ron's crucial role as a convenor. Many things, really most of the things I think that we've been talking about, flowed from that. As far as GRaPH-Int is concerned, yes it evolved from that. It was a very good idea and I think, I can speak only from my personal experience, it was a project that started and achieved some important things, most significantly perhaps the journal *Public Health Genomics*. But I don't think it retained retain that convening function…or I wasn't part of the convening at a certain point.

[131] Dr Natasha Azzopardi-Muscat is Director of the Division of Country Health Policies and Systems at the WHO Regional Office for Europe.

On WHO, I can only say I have not been a part of those conversations. I can't comment on them specifically. What I can say, as a generalisation…and it speaks I think to the important comment that Hilary just made, but also to previous comments…is that what public health genomics has to do, I think, is it has to go where the need is. It has to be in dialogue in different arenas around public health challenges and then go where they respond to those challenges. So, in one case it might be thinking deeply about birth defects and how genetics and other things like diet are important, and in another place it might be growing infectious disease genomics because that's what needs to happen. I think that perspective has perhaps not always been as conscious as it should, but that perspective has driven, either subconsciously or unconsciously, a lot of public health genomics activity.

Sally Sheard

Thank you, Wylie. Eric would you like to comment please?

Eric Meslin

I will be brief because I may be one of the few people on the call who didn't attend the Bellagio meeting, and it's one of those items on my list of wishes. I've heard lovely things. As for the praise we're all heaping on our friend Ron – it's not intended to make him blush, I just don't think we could say too much about the value of convening power as well as the opportunistic advantage taking. It's one thing for people to be brought together, it's another thing for people to take that opportunity. So, in my case, I believe this is true, I think I first met Ron at a meeting in Freemantle, Western Australia. I was spending a mini sabbatical with Fiona Stanley at the University of Western Australia.[132] Fiona is a legendary figure, of course, in public health and health services research. It was Ron and the GRaPH-Int public health genetics world that was meeting simultaneously that lead to a delightful coffee. I remember it sort of like it was yesterday – Fiona said, 'I want you to meet Ron, and then Bartha [Knoppers]'. It was that meeting in Freemantle that led to, not just GRaPH-Int's evolution, but other follow-on networking and collaborations. There are many besides those that arose from Bellagio or GRaPH-Int or WHO. There were a number of Roche meetings in Geneva that arguably could be one or two steps removed from these seminal events. Since I am speaking to you from Ottawa, there was large collaborative work being done by Genome Canada and its sort of ELSI equivalent called the GE3LS programme, which is a long acronym that covers genomics, environment, economic and ethical, as well as legal or social. So, there is a common trunk or route system that I think gave rise to many collaborative activities. Indeed, we are now at the point of sort of an ELSI 2.0 community that has moved beyond the original ELSI discussion.

I did want to drop one little penny in the pond here that may come up in the next couple of questions, so I will make a deposit and you can withdraw it later if you wish. That is, where technology designed for non-specific purposes gave rise to specific use in public health. I'm thinking about the collaboration arising from the sequencing of the SARS coronavirus many years ago – a result of collaborations by Canadians, Americans, Brits, to suspend all of the usual grant and peer review and typical strategies and say, 'We are going to do this together'. Technology presents itself. SARS becomes a case study in how collaboration arises. It wasn't

[132] Fiona Stanley (b.1946) is Distinguished Research Professor at the School of Paediatrics and Child Health, University of Western Australia.

called public health genomics; it was called figuring out what this coronavirus is. Now we are seeing it again…shameless self-promotion for Genome Canada, but it's collaborating with many around the world now for the host virus and sequencing here in Canada as a result of COVID-19. So, that's a deposit in the bank of goodwill for later. It's not that all roads started with Ron, but he certainly paved many of them in Australia, the US, Canada, Hong Kong and much of, certainly, western Europe. In fact, I don't even know if we can identify all of the progeny of some of those early meetings, and maybe that's all for the good.

Sally Sheard

Thank you, Eric. I think it would make a fascinating graphic, to almost to do a family tree, to show what came out of Bellagio and GRaPH-Int. Ron.

Ron Zimmern

I've got a particular question that I'd like Eric and Wylie to sort of reflect on…Muin, we were at WHO at their invitation, and the thing that stuck in my mind was this big argument between very distinguished people. One was Charles Rotimi, who was saying that it is absolutely right that low-and middle-income countries should have new sequencing facilities, and they should be taught the science and they shouldn't just be the recipients of that from the US and Europe.[133] People like Victor Penchaszadeh, the South American geneticist, and Arnold Christianson from South Africa, said 'Money can't be used twice over. There is a thing called opportunity cost. If we use it on new sequencing facilities…we haven't even got the most basic clinical genetic services. We can't even look after Down's syndrome properly, and all these other common disorders'. This really had an effect on me. Eric and Wylie, from your perspectives, where has this gone? This was around 2009. I have no idea whether there is consensus about which way low-and middle-income countries should go.

Eric Meslin

Wylie, would you like to go first?

Wylie Burke

So, Ron, you're posing an issue that needs its own movement. My perspective for responding to your question comes from the things I have done over the past 10 years that are mostly sort of post-public health genomics, but certainly informed by it. That is, building and implementing a research network with Tribal communities in Alaska and Montana. Even getting that research programme off the ground was a process of deliberation that did touch, not on sequencing machines, but on the issue of where genomics fits in traditionally marginalised, traditionally underserved, underfunded communities. I do understand where Charles [Rotimi] is coming from, and in a sense we heard the same thing in our communities, although I think our communities, our partners are acutely aware of opportunity costs and

[133] Dr Charles Rotimi (b.1957) is Scientific Director and Distinguished Investigator at the US National Human Genome Research Institute.

acutely aware of the limitations of current genomic science for their community's wellbeing. The issue has to do with colonialism, basically. It has to do with traditionally disenfranchised communities not wanting experts from the US or Europe to be in charge of major enterprises for them. So, I would say maybe NIHR [National Institute for Health and Care Research] needs to supply the training and the machines and then let African intellectual centres move forward. What we hear from our communities is 'capacity development'. Capacity development is a huge concern – in the form of making sure that we're doing everything we can to train Indigenous science leaders, but also bringing genetics education to communities, creating research infrastructure in communities etc. I think that's the fundamental issue posed in your question in the starkest of terms. I agree it doesn't make sense for them to spend money on sequencing machines, but it does make sense for there to be a partnership that is focused on generating capacity in traditionally underserved communities.

Eric Meslin

I would echo Wylie's comment and maybe add a couple of nuances to it. In a way Ron, your leading question is almost best reframed as 'What is the problem that Charles' answer is intended to solve?' I think what Charles' answer is intended to solve is what Wylie was referring to when she spoke about colonial disenfranchisement, which we should be careful about. So, we have watched this for the last 20 years. We watched it probably most starkly in the early 1990s when the legendary ACTG 076 HIV trials – placebo-controlled trials – were all the rage and on the front page of the *New York Times* and *New England Journal of Medicine*, and the debate was 'Let's not do that'/'Yes we should'. What I can only describe as my favourite response to the question of whether you should do a placebo control in a country when there's already an existing proven treatment in a rich country was, 'Why don't you ask them what they think?' The legendary response was in an editorial by the Minister of Health from Kenya who said, 'Would you like to know what Kenyans think about a placebo-controlled trial in our country' before David Satcher and Harold Varmus and Marcia Angell all have an argument in the US literature.[134] The answer was 'Yes, we would be prepared to have it'.

Second, there is that history – you could even go back hundreds of years, not just 20 years – that Charles's point is again reflecting – 'Why should we be the recipients of someone else's benevolence, charity, or knowledge translation. We can do it ourselves. We should be PIs [Principal Investigators] on grants. We should be first authors on papers. Why should we be invited to participate in someone else's work? Let us do it here'. I think that is a bracketed argument which is contrasted with…if Victor Penchaszadeh was saying what I think you said he said, it's a pretty reasonable position to say, 'What's the best and most efficient use of scarce resource?' If a scarce resource is a million-dollar sequencing machine, there are probably A: better ways to use the million dollars, and B: why do they cost a million dollars anyway, but that's sort of a side point. I remember watching a PBS show here when I was growing up in Toronto that said there were more MRI machines in Seattle, Washington than there are in all of Canada. What's that's all about? So, you don't necessarily have to go to marginalised communities, or Kenya, or Alaska. In Canada we have the 'First Nations' issues where there are currently 36 'boil water advisories' on our nation's reserves. 36 in 2021. If you ask them what they need, they don't need sequencing machines to figure out what's going on with diabetes in the far north of Canada, they need clean water.

[134] Dr Harold Varmus (b.1939) was Director of the National Institutes of Health from 1993 to 1999. Dr Marcia Angell (b.1939) was Editor of the *New England Journal of Medicine* from 1988 to 2000.

Ron Zimmern

Thank you. The reason I asked was that I just wanted to make the point that the history of it…we've done some wonderful things, but there are huge problems that we haven't even touched.

Muin Khoury

I am glad Ron is probing us. I wanted to comment on WHO, because I remember that WHO meeting. I remember Victor [Penchaszadeh]. The highpoint of the discussion here ties with health around the world – social determinants of health and health equity, forget genomics for a while. It's about opportunities, it's about how to tackle the problems that are around the world with the best tools that we have. This is where maybe the tools of precision public health could offer something, because precision public health is about using the best available data to try to get better outcomes for everyone. The best available data comes from genomes of people, animals, pathogens, geographic locations, the health context, the policies, and if you can develop more precision in our measurements or these tools of the health status and the best way to tackle them, they can be generalisable to where you are. At the time we were talking about human genomics, and we are still talking human genomics. Part of me has kind of moved on. There is that question at the end that says have we reached our natural conclusion? No of course not, the field hasn't matured long enough. But coming back to the determinants of health, we have to be holistic – social determinants, environmental determinants, genetic determinants, they have to be all examined together and I think this is where we are going. CDC is talking about modernisation in the way we collect data, we are trying to integrate genomics into it, but we are beyond looking at one field by itself, we are in a more integrative fashion. I think GRaPH-Int and public health genomics was the kernel of integration, because we talked about 'omic' technologies, about genome-based technologies. Remember the definition of public health genomics – we went around, and it took us two days to define 'genome-based'. But then there are other technologies like big data, machine learning, electronic health records, artificial intelligence. All of these are tools and technologies and if you can put them together to solve the problems, the health needs of a particular community, that becomes to me precision public health. So, that chapter in the WHO discussion was important. We emerged with some frustrations, which we've explained away or tried to tackle. I'm glad to offer my points of view on this because I've had those discussions with Keiji Fukuda, who is my friend and was at WHO, multiple times since we had those meetings.[135] He did express the sort of prevailing notion of what WHO is, but also the fact that WHO has evolved over time. Right now, the WHO of 2021 is not the WHO of 2005. So, we have to keep that in mind.

Sally Sheard

That's helpful, thank you very much. The next question was on the role that public health genomics played in shaping genetics and genomics policy. I propose to move over that unless people can give some specific examples.

[135] Professor Keiji Fukuda (b.1955) was an Assistant Director-General at the WHO from 2009 to 2016

Muin Khoury

Yes, I think we've talked about some of these areas and how public health genomics has helped in shaping the policies, in shaping the need for evidence to be introduced into practice and public health programmes – an ethical framework, a multidisciplinary framework.

Sally Sheard

Thank you. The next question up, if we're happy to move on, is around what you think the most important achievements of public health genomics are to date – again, I think we have begun to discuss some of this. Are there any further reflections that we would like to record?

Muin Khoury

My only reflection at this point is the fact that public health genomics exists – it's a term, it's a discussion, it's a field – to me, that's the biggest achievement by itself. I don't think the goals of public health genomics have been met, but the fact that it brings together multiple scientific disciplines to try to tackle the genome, the human genome in this case, but other things, is its most important contribution. I think that's where I land on it. The approaches of public health genomics have been the precursors to precision public health. So, that evolution was born out of public health genomics.

Wylie Burke

Yes, I would echo that. I would like to add at least a couple of training programmes, and there may be additional training programmes. We have an Institute of Public Health Genetics at the University of Washington, that has an MPH and a PhD programme and for 20 years now we have been sending out MPH students and PhD students into to the world, and they've done a variety of different things. So, I think that's a corollary of a field coming into being. It then creates a way of training, that creates a body of professionals who wouldn't otherwise be there.

Hilary Burton

I think in the UK, the work that we did, particularly with the health services, brought the perspective that managed to persuade clinicians that the use of genetic medicine and genomic medicine was far too important and much bigger than could be dealt with just by specialist genetics alone. I think it was actually very hard for the specialist geneticists to let go of it, and I think it was public health looking at achieving health benefits on a population basis that helped to persuade them that they needed to let go of some of it.

Sally Sheard

That's really interesting Hilary, and I wonder to what extent our international colleagues have had that experience?

Stefania Boccia

Yes, if I can follow up in the line of Hilary and Wylie – in terms of training, I think that the public health genomics movement did a lot. It was clear soon after that clinical geneticists cannot do everything. So, it took a long time to start discussing how to integrate genetics into the curriculum of some health professional, to deal not only with patient care but also with population uses of genetic testing. Personally, I'm aware that some years ago there was as an initiative, under the Erasmus+ funding scheme, titled GenEquipe, that was coordinated by a colleague in UK. It was a very first initiative that attempted to deliver some webinars and some courses online of genomics and genetics directed to physicians. I think it was eight or nine years ago. More recently, the Innovative Partnership for Action Against Cancer (iPAAC), which is a large joint action funded by the European Commission to tackle cancer using a public health perspective. I was involved in a small task about human genetic testing for cancer and another about core competences in oncogenomics for physicians and nurses, and we did publish some reports and we did set up a web-based course for free.

Sally Sheard

Thank you Stefania, that's a really good example. Muin would you like to give any comments – perhaps about whether public health genomics as a term has the same visibility in each of your countries?

Muin Khoury

Well, in the US public health genomics is alive and well. I'm not sure about the rest of the world, but I think our efforts, some of the universities and others, have firmly established the field as a parallel to medical genomics or clinical genomics. The population perspective that we are talking about is very important and some of the public health disciplines, in terms of behavioural and social science, communication science, ethical discussions, are kind of sets of scientific disciplines that are important in the translation of genomics into population health benefit. So, I feel good about the idea that it's an established arena. Wylie just talked about the University of Washington programmes – there are others within the US

Sally Sheard

Thank you.

Ron Zimmern

In the UK – we've probably been partly to blame for this – but we've tried to play down the public health bit of public health genomics because the Faculty of Public Health Medicine has been so negative about all this. There has been, politically, a dismantling of what one might call healthcare public health. Public health has been put into the local authorities, so they don't have as much to do with clinical services and their organisation as they used to. So, rightly, or

wrongly, my steer has been to turn the PHG Foundation more towards policy and genetics and play down the public health aspect, even though behind the scenes we still aspire to the integration of all the different determinants of health together. This has become slightly political, the extent to which the public health community in the UK is very much focused on the standard determinants of health, ranging from poverty and unemployment to environmental things. So, it's a really interesting one. I don't quite know what to do, because the heart is still with the public health, but in the UK there has been a loss of integration between the biological models of disease and social models of disease. Clinicians practice biological models of disease, public health people in the UK tend to practice social models of disease and turn their nose up at biological models, and vice versa. That's putting it rather starkly, it's not quite as bad as that. I think Hilary might offer a slightly different perspective.

Hilary Burton

Yes – I suppose the question is to what extent it ever really was a sort of discipline or a subdiscipline within public health. I think maybe part of the difference is that we weren't trying to just be academics about it. The academic side of public health genomics is still there very much, but I don't think it's ever been integrated into the practical side of public health because of the changes that you've just described and also because of the priorities that, in many ways, they rightly have. I think where we've had some traction within public health has been within the screening programmes…

Ron Zimmern

Yes. The traction you have had when you looked closely at fields like cardiology and ophthalmology has been huge…but there is no one following behind you to do all this stuff…[136]

Hilary Burton

…and that hasn't involved public health at all.

Ron Zimmern

No, that's right.

Sally Sheard

Eric, would you like to reflect on the use of the term please from your perspective?

Eric Meslin

[136] T. Moore and H. Burton, *Genetic Ophthalmology in Focus: A Needs Assessment and Review of Specialist Services for Genetic Eye Disorders* (PHG Foundation, 2008). H. Burton, C. Alberg and A. Stewart, *Heart to Heart: Inherited Cardiovascular Conditions Services – A Needs Assessment and Service Review* (PHG Foundation, 2009).

Sure – the term has been used but I think its integration has largely been at the level of public health surveillance, and less so in clinical care. I'm a non-physician so my observations need to be tempered in that regard, but, for example, it took the SARS story to create a new agency called the Public Health Agency of Canada, which is a different organisation than Health Canada. It may be more the similar to the CDC than anything else. Our National Microbiology Laboratory, with its international reputation, is where the term public health genomics is used, I would say, more extensively. I did a back of the envelope review of the medical school curricular in Canada a year or so ago, and I would say that it has been unevenly integrated as a term of curricular development and training. That's not to say that our public health schools in Canada, much like Wylie was referring to, aren't producing people whose specialty interests are in that area, but of course the MPH and PhD programmes in the public health schools are different from what our medical schools are teaching. These are different schools in Canada, as they are in other places. So, I would say it's been a modest integration. There hasn't been the same debate yet. We sort of joke about the personalised medicine and precision medicine…that becomes kind of an interesting observation about what happens in the US. So, we are sort of typically following in some areas and leading quietly in others.

Sally Sheard

Thank you, Eric. Wylie, do you wish to reflect on the use of the term?

Wylie Burke

I don't think I have anything really to add to Muin's comments. It is a term that's alive and well. I think it's a field, I think there are people that acknowledge that they're members of the field. Maybe the one thing I'll say is a reflection on Ron's comment, and that is that public health genomics feels very specialised, and there are a lot of people who actually have interests that intersect with those of people doing public health genomics, but they don't realise it. So, it may be that we need to think very carefully about terminology and how we approach the creation of multi-specialty, cross-disciplinary collaboratives in ways that don't push people away because they say, 'I don't do public health', even though their work is related.

Muin Khoury

May I add a few things? Ron – thank you for pushing the envelope and I share a lot of your frustration in terms of the impact and acceptance of the field. Look at the progress in 25 years, and how far we could have gone. Where we are right now reflects…I remember Kathy Hudson at NIH [National Institutes of Health] – she was the policy person, and she came and gave a presentation one time in the public health genomics series that I used to facilitate.[137] She talked about genetics and policy and at the end I kind of joked with her and said, 'You've been doing public health genomics and you didn't realise it Kathy, is that right?' The idea is that intersection between technology and policy *is* public health genomics.

[137] Dr Kathy Hudson was Deputy Director for Science, Outreach, and Policy at NIH from 2010 to 2017.

Just reflecting on the famous 'schism' paper that a number of us wrote a few years ago, when we talked about the schism between medicine and public health – that schism is still alive and well.[138] Its latest manifestation is precision medicine. I wanted to hijack the discussion, so I pushed precision public health. Just like when genomic medicine was created, I pushed public health genomics. When precision medicine was created, I pushed precision public health, because both public health and medicine have to work hand in hand to solve the health needs of communities at the individual level and at the population level. So, it turns out precision public health is a much bigger umbrella than public health genomics because it ties in social determinants of health in a major way, and while some people in public health are upset with me now…Sandro Galea, the Dean of the School of Public Health at Boston University, still talks about precision public health as an oxymoron, because 'This is not about the health of individuals, it's about the health of populations'…so yes, Sandro, it is about the health of populations, and you need the best data and policies to deal with health of populations and programmes, and if they involve the human genome, so be it. They may not involve the human genome. So, you follow the technology, you use technology to solve population health problems with more precision

All the buzzwords – precision medicine, precision public health – are really just next generation medicine and next generation public health. That's what it is. We just play with words – whether they are personalised or precision or genomic or genome-based. I think it's all about the technology and its ethical and effective use to improve the health of populations. That's where the Bellagio definition comes in handy – replace the word genome-based with technology-based and you're in, you move from public health genomics to precision public health. We need another Bellagio meeting, by the way, for precision public health. Are you up for it ?

Ron Zimmern

We are. I think this is a very good idea. We are on the same page, because by calling ourselves the PHG Foundation…we don't define what PHG could be. It could be Precision Health Genomics, Population Health Genomics, Policy, Health, and Genetics – it could be anything.

Muin Khoury

Yes. You can even take off the G. We don't need the G anymore.

[Laughter]

Add Technology – call it PHT.

Sally Sheard

I am grateful to all of you. Thank you very much everybody. It's been a tremendously exciting and very interesting discussion.

[138] M.J. Khoury, M. Gwinn, W. Burke, S. Bowen, and R. Zimmern, 'Will Genomics Widen or Help Heal the Schism Between Medicine and Public Health?', *American Journal of Preventive Medicine*, Vol. 33, No. 4, 2007.

Muin Khoury

Thank you all.

Sally Sheard

Thank you everybody.

[Ends]

Appendix

Witness Statement by Professor Bartha Knoppers – Canada Research Chair in Law and Medicine, McGill University

While technical difficulties prevented me from participating in the witness seminars, I recently had the privilege of reading the complete report *The Development and Influence of Public Health Genomics*.

To date, most of my involvement in the development of public health genomics has centred on participating in the meetings and initiatives described in Part 2 on the 'International Enterprise'. As an ethico-legal policy comparatist, I was also well aware of the two decades of active UK contributions. It is worth mentioning that from 1994 to 2004, I chaired the international Ethics Committee of the nascent Human Genome Project (HGP) while also particularly active in the creation of both the *Public Health Genomics* journal and GRaPH-Int (with a secretariat in Canada). Today, I direct the Centre of Genomics and Policy at McGill University.

Let me note several commonalities between the British and international public health genomics initiatives as illustrated by this report, before providing some personal remarks.

A. Of Commonalities: Technologies and Individuals:

The contributions and roles of: industry, legislation, patents (e.g. Celera knowledge privatization in the HGP and BRCA patenting controversies), and more recently, data protection efforts, cross all seminar discussions. But, most striking are the references in both seminars to the remarkable leadership of individuals. Indeed, it was (and still is) the visionary leaps of faith and actual policy action by individuals (including researchers, clinicians, institutions, and civil servants) with regard to ethics in the science of genomics that was the most important catalyst for the emergence of public health genomics crossing fields hitherto so narrowly circumscribed.

Another common theme in the seminars is the ethos of data sharing – key to the success of the HGP (e.g. Bermuda principles, 1994). The HGP was followed by the creation of population biobanks around the world from 2000 onwards – an example of altruistic citizens contributing samples and data to the building of resources for infrastructure science. It should be noted however, that traditionally, data collection and sharing have always been the foundation of both public health and population screening efforts. In particular, since the 1960s new-born screening programmes (NBS) for immediately treatable genetic conditions still remain *the* international public health success story. Public participation and data sharing requires collaboration and trust and this across borders from the lab to the clinic and back again. Recent international response to the COVID pandemic has sorely tested and yet reaffirmed the centrality of this global public goods nature of public health genomics.

B: Of Public Health Genomics: Quo Vadis?

The discussion in the 'International Enterprise' seminar not only illustrates the gradual integration of genomics into public health (and vice versa) but also new challenges. The emergence of precision public health genomics brings a new 'stratified' understanding of the

important genomic contributions, susceptibilities, or resistance of diverse communities and sub-populations. Polygenic risk scores also illustrate this phenomenon. However, public, and even clinician understanding that risk scores are not diagnoses but levels, is still missing. Likewise, for the 'holding out' promises of the introduction of whole genome sequencing (WGS) into new-born screening programmes. As mentioned above, such programmes have sought out at-risk asymptomatic new-borns for immediate clinical intervention. While WGS has rightly entered the neonatal intensive care unit for diagnostic clarification purposes as a paediatric standard of care, this is distinct from the populational and public health mandate of NBS. Around the world NBS programmes ensure that every child is 'noted and counted' whether treatment is available or not. A WGS neonatal, futuristic report card may damage public trust and participation to say nothing of ensuring health department government funding and the rights of the child.

Knowing my colleagues as I do, I would say that while we were builders and collaborators in the last decades, we may not let such challenges go by – let the new genomic public health adventures begin!