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Genomic Medicine

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Reference in the text of the Report as follows:

(Q) refers to a question in oral evidence

(p) refers to a page of written evidence

(paragraph) refers to a paragraph in the report

SUMMARY

Modern, effective healthcare rests upon centuries of scientific advances and innovation that have been shown in clinical trials and other studies to prevent, cure or alleviate human disease. Every so often, a scientific advance offers new opportunities for making real advances in medical care. From the evidence given to this inquiry, we believe that the sequencing of the human genome, and the knowledge and technological advances that accompanied this landmark achievement, represent such an advance.

The 2003 White Paper, *Our inheritance our future*, recognised the potential impact of genetics and the genome project on our lives and our healthcare, and the importance of preparing the National Health Service (NHS) to be able to respond to this new knowledge. The investment that resulted from the White Paper enabled development of new genetics knowledge, skills and provision of services within the NHS. It targeted the diagnosis and treatment of rare single-gene disorders under the care of clinical geneticists based in Regional Genetics Centres and significantly advanced the capabilities and knowledge for managing these disorders. But the White Paper could hardly have anticipated the remarkable advances since 2003, including the charting of the genetic causes of a wide range of common diseases such as diabetes, coronary heart disease and several cancers. These scientific advances are with us now, and the use of genomic diagnostics to provide more rational and increasingly personalised management of common diseases has already started to permeate clinical practice in mainstream specialties across the NHS.

The new knowledge of these genomic studies is still very fresh. It will be several years, for example, before prediction of common diseases will lead to the realistic possibility of disease prevention. But the use of many types of genomic tests is increasing rapidly, both in the NHS and in tests sold directly to consumers, and the availability of these tests will, in time, have a dramatic impact on disease diagnosis and management. This is already placing strain on the expertise of doctors, nurses and healthcare scientists who at present are poorly equipped to use genomic tests effectively and to interpret them accurately, indicating the urgent need for much wider education of healthcare professionals and the public in “genomic medicine”. Advances in genomic science will present challenges for delivering genomic tests across the mainstream specialties, suggesting the need for greater co-ordination and consolidation in “molecular pathology”, with new models for service delivery.

Genomic advances also present opportunities for industry, with commercial opportunities in biotechnology as the power of genome sequencing methods continues to increase, and challenges and opportunities to the pharmaceutical industry who are increasingly using genetic testing in the drug development pipeline to develop more effective and safer drugs for which genetic tests are part of the prescribing process.

Scientific advances also present social, legal and ethical challenges, with increasing amounts of personal genetic information being generated for both research and healthcare, raising concerns about personal privacy, data security and the potential for discrimination. These challenges must be faced if an appropriate balance is to be found between legitimate use of genetic information in research and protection of individual choice and privacy.

In our inquiry, we have investigated these many aspects of genomic medicine, and make recommendations to ensure that the challenges afforded by advances in genomic science are met and the opportunities exploited. If our recommendations are taken forward, we believe that the UK will benefit in terms both of wealth generation and of improved health of the population.

Genomic Medicine

CHAPTER 1: INTRODUCTION

Background

- 1.1. Scientists in the UK have contributed significantly to the rich history of achievement in genetics and genomics during the last six decades: from the discovery of the structure of DNA in 1953 to the development of DNA sequencing in 1975, and as principal partners in completing the human genome sequence in 2000—hailed by President Bill Clinton and Prime Minister Tony Blair as “the most wondrous map ever produced by humankind”.
- 1.2. Until recently, geneticists have focused on identifying the genes that underlie “single-gene disorders”—rare diseases, caused by defects in single genes, such as Huntington’s disease, cystic fibrosis and sickle cell anaemia. This work has provided important benefits. It has enabled the accurate diagnosis of single-gene disorders and led, for example, to the development of screening programmes for cystic fibrosis and sickle cell anaemia in newborns.
- 1.3. But single-gene disorders account for a small proportion of the national burden of disease. Commoner diseases, which have a far more significant impact on public health, frequently have a complex genetic basis. As a result, these “genetically complex diseases” have not been susceptible to traditional genetic techniques. The completion of the human genome sequence, however, has opened up a new era in genetic investigation, and technological advances, such as a 1,000-fold increase in capacity to read a DNA sequence and a 10,000-fold reduction in the cost of DNA sequencing, have enabled geneticists to begin to chart the genetic basis of a wide range of common diseases.
- 1.4. These recent advances have led to identification of susceptibility genes for genetically complex diseases such as diabetes, coronary heart disease and several types of cancer, leading to the possibility of early prediction and possible prevention in some cases. Other advances have already entered clinical practice and include more precise, molecular diagnosis of established disease, for example in breast cancer and chronic myeloid leukaemia, allowing more targeted, personalised treatments to be prescribed. Other gene discoveries enable drug sensitivity and side effects to be predicted, for example in the use of warfarin and anti-HIV therapies.

The inquiry

- 1.5. Whilst acknowledging the benefits to individuals of these new discoveries, we need to ask how, in the context of competing priorities within the healthcare services, they might contribute most effectively to improvements in our public health and quality of life. In considering this question, other questions arise: are our health services in a position to take advantage of these new scientific advances? Can—indeed should—their translation into clinical practice be afforded? Does the appropriate ethical and regulatory framework exist so as both to protect the interests of individuals and also to encourage

further advances? Will such advances bring with them new economic opportunities and, if so, is the Government doing enough to ensure that those opportunities are exploited? The purpose of our inquiry was to investigate these issues.

Structure of the Report

- 1.6. Genomic medicine is a highly technical subject. In Chapter 2, therefore, we begin by describing the concepts used in genomic science and genomic medicine; we set out recent developments in the field and consider developments which are likely to occur in the future. In Chapter 3 we analyse how developments, such as genomic tests and targeted medicines, are being translated into clinical practice; we also consider the current barriers to further translation, how they can be overcome and how to encourage innovation.
- 1.7. In Chapter 4 we consider how advances in genomic medicine might impact on healthcare services and whether the National Health Service is in a position to meet the challenges they present. In Chapter 5 we examine aspects of the information technology that will be required for the development of genomic medicine and, in particular, the gap that exists between use of genomic datasets in a scientific context and the availability of similar datasets for delivering healthcare.
- 1.8. Chapter 6 explores some of the ethical, social and legal issues arising from the development of genomic medicine, such as data security, confidentiality and consent, the use of genetic information for research purposes, the provision of genetic test results direct to the consumer and the potential use of genomic information by the insurance industry and employers. Finally, Chapter 7 addresses issues relating to the provision of training and education and the need for workforce planning to meet the needs of genomic medicine.

Acknowledgements

- 1.9. The membership and interests of the sub-committee are set out in Appendix 1 and those who submitted written and oral evidence are listed in Appendix 2. The call for evidence with which we launched our inquiry is reprinted in Appendix 3. On 19 March 2008 we held a seminar to which academics, representatives from Government departments and a variety of other organisations contributed. A note of the seminar is set out in Appendix 4. In June 2008 we visited the National Human Genome Research Institute in Washington DC in the United States and talked to a wide range of experts who were able to inform us about many aspects of genomic medicine. A note of the visit is set out in Appendix 5. We would like to thank all those who assisted us in our work.
- 1.10. Finally, we are very grateful to our Specialist Adviser, Professor Tim Aitman, Professor of Clinical and Molecular Genetics, MRC Clinical Sciences Centre and Imperial College London, for his expertise and guidance throughout our inquiry. We stress, however, that the conclusions we draw and the recommendations we make are ours alone.

CHAPTER 2: GENOMIC SCIENCE AND GENOMIC MEDICINE

Introduction

- 2.1. Using traditional genetic techniques, almost 2,000 genes for single-gene disorders had been identified by the year 2000. More recent advances in genomic science (most notably the completion of the human genome sequence) and genome technologies have allowed identification of hundreds of genes that contribute to inherited susceptibility to commoner, genetically complex diseases.
- 2.2. Because of the important role of genomic science in this report, we explain in Boxes 1 and 2 below some of the key concepts in genomic science and genomic medicine. A glossary and list of acronyms is set out in Appendix 6

BOX 1

Key concepts in genomic science

Genetic code

Genetic information is encoded within an individual's DNA (deoxyribonucleic acid), long, spiral-shaped molecules formed into the famous double-helix structure. The strands of DNA are made up of hundreds of millions of units or 'letters' called nucleotides. Joined together, these letters contain the chemical code of instructions that directs the development and function of cells in the body, controlling biological processes such as the production of proteins.

Proteins are essential building blocks of cells and tissues and also control the biochemical reactions that are vital to life. Variations in DNA sequence can alter protein sequence and function, as well as the amount of protein that is produced. DNA sequence variations are therefore key to inter-individual differences in body form and function and therefore health and disease.

What is a genome?

An individual's entire DNA sequence is known as its "genome". The word "genome" is a synthesis of the words "gene" and "chromosome". About two per cent of the human genome is made up of genes, the functional units of DNA that contain the instructions to produce proteins. The rest of the genome may regulate where, when and in what quantity proteins are made (known as gene expression, to control when a gene is "switched on" to produce a protein, for example).

An individual's genome is encoded within structures known as chromosomes. Humans have 23 pairs of chromosomes which reside in the nucleus of almost every cell of the body. One of each pair of chromosomes is inherited from each parent and, in this way, variations in DNA sequence are passed from generation to generation.

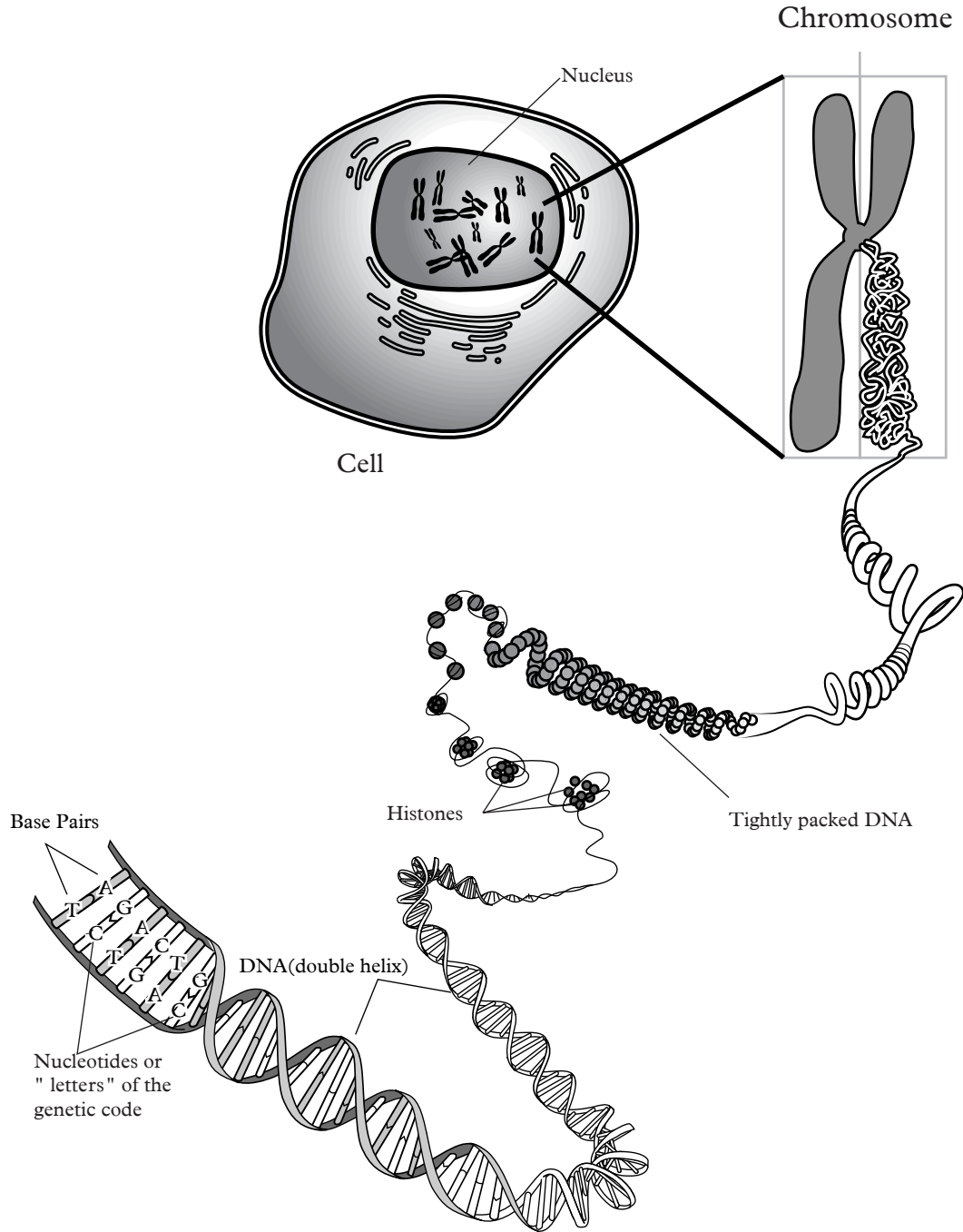
Genomic science

Modern "genomic science" may be considered as the study and use of genomic information and technologies, coupled with other biological approaches and computational analyses, to advance our understanding and knowledge of genes and genome function.

Identification of the genes and DNA sequence variants that underlie inherited susceptibility to rare and common human diseases has been a major preoccupation of geneticists for the last 50 years and has led to fundamental advances in understanding of the molecular and cellular basis of these diseases.

FIGURE 1

Illustration of DNA and chromosomes within the cell nucleus



Courtesy of the National Human Genome Research Institute

BOX 2**Key concepts in genomic medicine***Genomic Medicine*

“Genomic medicine” can be defined as the use of genomic information and technologies to determine disease risk and predisposition, diagnosis and prognosis, and the selection and prioritisation of therapeutic options.

Pharmacogenetics and pharmacogenomics

“Pharmacogenetics” is the study of the way in which a particular gene or small number of genes affects drug metabolism or responsiveness. “Pharmacogenomics” is the study of the way in which genetic variation across the genome affects drug metabolism and responsiveness.

Stratified or personalised use of medicines

The stratified or personalised use of medicines employs laboratory tests, including pharmacogenetic or pharmacogenomic tests, to stratify a patient group according to their predicted responsiveness to a particular treatment. Stratified use of medicines helps to improve the effectiveness of treatments by targeting individuals who will respond well to particular treatment based, for example, on genetic tests, or by excluding individuals who are predicted to have an adverse reaction to treatments.

Advances in genome technologies*Costs of sequencing*

2.3. Development of highly automated methods of DNA sequencing in the 1990s, compared with the labour intensive methods used previously, greatly increased the capacity for scientists to undertake DNA sequencing and paved the way for determining the first complete sequence of the human genome. Since then, costs have fallen significantly, capacity has continued to rise, and several further human genomes have been sequenced. Oxford Nanopore Technologies gave an indication of the extent of the cost reduction: “The first [genome], mapped by the Human Genome project, cost approximately \$3 billion, the second \$100 million and the third, that of the DNA pioneer James Watson, \$1.5million ... It is estimated that the current cost of completing a human genome is [now] in the range of several hundreds of thousands of dollars” (pp 322–23). According to Applied Biosystems, getting the price of sequencing a human genome “down to \$1,000” was “probably only one—maybe two, three—years away” (Q 662).

DNA microarray technologies

2.4. DNA microarray technologies also became available in the 1990s, enabling simultaneous measurements of hundreds of thousands of DNA molecules (and of the related RNA (ribonucleic acid) molecules). Microarrays allow gene function to be characterised on a genome scale, as opposed to earlier methods that made measurements on an individual, gene-by-gene basis. They also permit measurement of the extent to which every gene in the genome is switched on or off in a microscopic tissue sample, allowing construction of a “gene expression signature” or “expression profile”; and they can be used to determine an individual’s DNA sequence at thousands or millions of specified locations in the genome (thereby creating a “genome profile”). Microarrays provide powerful ways to investigate the role of single or multiple genes and DNA sequence variants in disease processes, both in individuals and in populations.

2.5. Advances in genome technology have permitted and driven extraordinary advances in genomic science. As will be seen in this report, these advances are now permeating the healthcare arena. This creates a significant new market for

genome technology companies, some of which are based in the UK, in diagnostics, drug development and continuing scientific discovery. Because of the leading role played by UK scientists in genomic science, because of continuing charitable and Government funding of genomic science, and because of the potential for genome-related clinical trials and research in the National Health Service (NHS), the UK is well placed to capitalise on this market.

Genetics of rare and common diseases

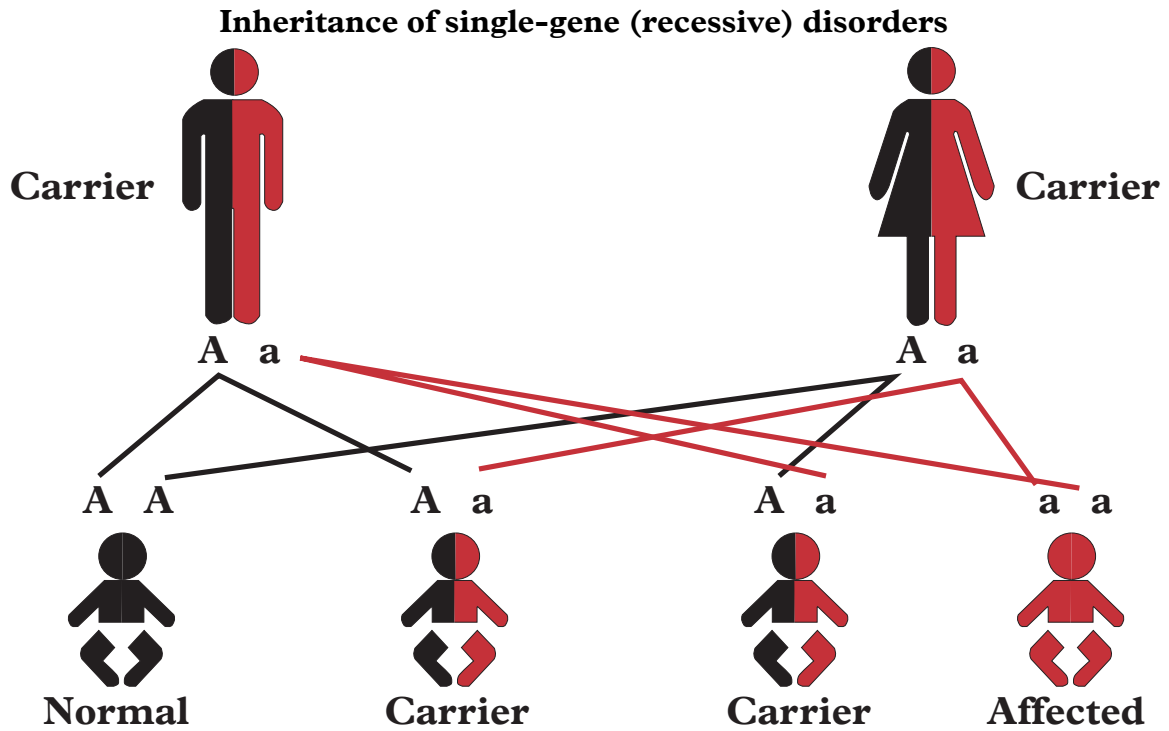
- 2.6. There are several thousand human genetic disorders each of which is caused by an important DNA sequence variation—a mutation—in a single gene. Examples are Huntington’s disease and cystic fibrosis. These disorders differ in major ways from the much commoner, genetically complex diseases that develop under the influence of multiple genes and the environment such as diabetes, coronary heart disease and several types of cancer.
- 2.7. In Table 1 below we describe some of the key differences between single-gene disorders and genetically complex diseases. These differences are illustrated diagrammatically in Figures 2 and 3.

TABLE 1

Genetic differences between single-gene and genetically complex diseases

	Single-gene	Genetically complex
Frequency in the population	Generally less than 1 person in 1,000.	Up to 1 person in 3.
Underlying cause	Disease caused by DNA mutation in single gene, though disease severity and age-of-onset varies according to the individual mutation and may be affected by the presence of other modifier genes.	Disease susceptibility influenced by DNA sequence variation in multiple genes acting in concert with environmental factors (see Figure 3). Individual DNA sequence variations each contribute a small proportion of the overall risk of disease.
Familial inheritance	Simple dominant, recessive, or sex-linked inheritance (see Figure 2).	No simple mode of inheritance.
Familial risk	Possession of the disease gene confers a high and quantifiable risk to other family members.	Possession of “low penetrance” susceptibility genes confers a small increase in risk to other family members.
Success with gene identification before 2005	Over 2,000 disease genes identified. Most disease genes not identified to date are exceptionally rare.	Fewer than 20 disease genes identified.
Success with gene identification since 2005	Similar rate of gene identification prior to and since 2005.	500 new disease genes localised and, in many instances, identified.
Ante-natal diagnosis	Carried out in Clinical Genetics departments in conjunction with genetic counselling.	Not applicable in genetically complex diseases, in which individual disease genes have a small effect on disease risk.
Examples	Cystic fibrosis, Huntington’s disease, haemophilia, sickle cell disease.	Coronary heart disease, rheumatoid arthritis, common forms of diabetes and obesity.

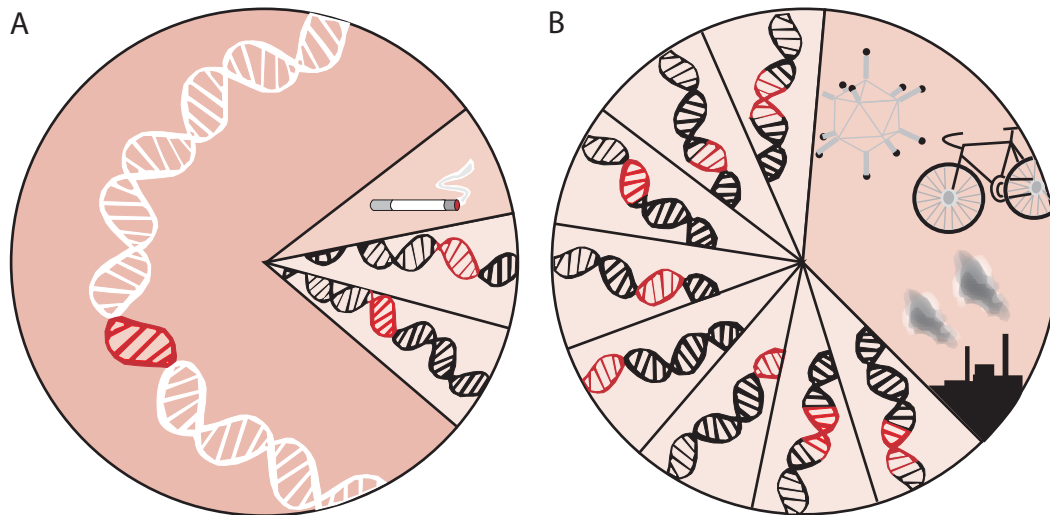
FIGURE 2



Courtesy of Kesson Magid, University College London

FIGURE 3

Genetic and environmental contributions to single-gene and complex disorders



[A] Single-gene disorders: a variant in a single gene is the primary determinant of this type of disease, is responsible for most of the disease risk, with possible minor contributions from modifier genes or environment.

[B] Complex disease: many variants of small effect contribute to disease risk, along with many environmental factors.

Reproduced with permission from the American Society for Clinical Investigation, Manolio, T et al, 2008, A HapMap harvest of insights into the genetics of common diseases, J Clin Invest 118:1590

Risk of disease

- 2.8. The likelihood of developing a single-gene disorder or a genetically complex disease can be expressed in terms of “absolute risk” or “relative risk”. The differences between absolute and relative risk with respect to single-gene disorders and genetically complex diseases are described in Box 3.

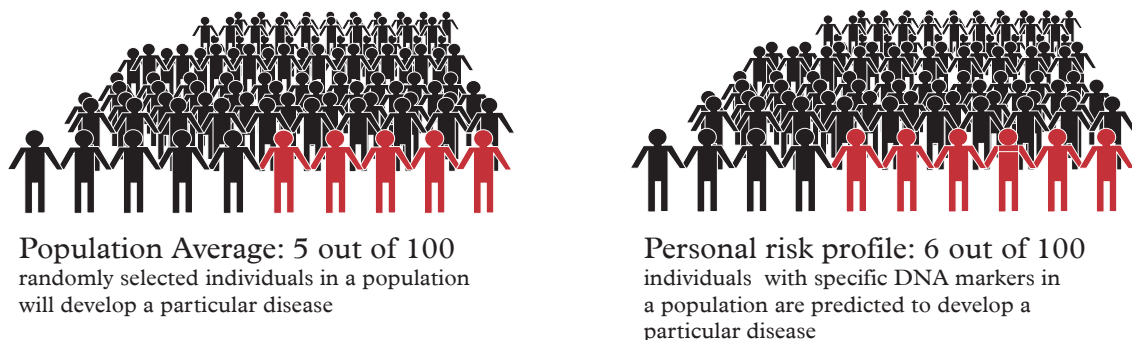
BOX 3**Understanding risks for single-gene disorders and genetically complex diseases**

“Absolute risk” is defined as the chance an individual has of developing a disease over a time-period. For example, a 65-year-old man has a one in 10 risk of developing dementia in the remainder of his lifetime.¹ This can be represented as 10 per cent absolute risk.

In single-gene disorders, absolute risk for family members can be accurately predicted. For example, in the dominantly inherited Huntington’s disease, the siblings and offspring of an affected individual have a 50 per cent absolute risk of developing the disease themselves.

In genetically complex diseases the effect of inheriting a particular susceptibility gene is often expressed as “relative risk”, which is used to compare the risk in two different groups of people (see Figure 4).

For example, the absolute lifetime risk of developing a disease may be five in 100 in the general population, and the relative risk of the disease may be increased by 20 per cent in people who carry a particular genetic variant. The “relative risk” ascribed to this genetic variant is defined as 1.2, because the risk has risen from 1.0 (“normal” population risk) to 1.20 (increased risk for people carrying the genetic variant). In this population, this 20 per cent increase in relative risk represents an increase in absolute risk from five in 100 to six in 100. While a (relative) risk increase of 20 per cent sounds high, the absolute risk increase of one in 100 extra cases provides a more practical indication of risk to a member of that population.

FIGURE 4**Multiple Genes and Risks****Genetic predisposition to developing a complex disease such as type 2 diabetes.**

Genetic research associates DNA markers with the risk of developing a complex disease. Testing for a number of markers builds an estimate of individual risk. This risk is expressed relative to an average individual of the same ethnicity and age.

Courtesy of Kesson Magid, University College London

¹ Seshadri et al, *Neurology*, 1997, 49:1498–504.

- 2.9. “Penetrance” is the proportion of individuals who carry a particular genetic variant who will go on to develop the disease. The breast cancer genes *BRCA1* and *BRCA2* are examples of genes with “high penetrance” because over 80 per cent of individuals who carry a mutation in one of these genes will develop breast or ovarian cancer, or both, in their lifetime. Genetic variants associated with common diseases are mostly of “low penetrance”, because the increased risk of developing the disease that is conferred by carrying the gene is relatively low.

Identification of susceptibility genes for common diseases

- 2.10. The completion of the human genome sequence, increasing knowledge of DNA sequence differences between individuals and rapidly advancing technology for reading DNA sequences have led to significant progress in identifying genes underlying common, genetically complex diseases (“susceptibility genes”). By January 2009, more than 500 new susceptibility genes for these diseases had been systematically mapped to the genome and, in many cases, the underlying genes were identified. Professor Sir John Bell, Chairman of the Office for Strategic Coordination of Health Research (OSCHR), described the coming together of these developments as “one of those inflection points that you get in medicine every so often” which give rise to “very significant opportunities to apply [a] methodology in a patient setting” (Q 422).

The genome-wide association study (GWAS)

- 2.11. The method that has led to the discovery of hundreds of new susceptibility genes for common diseases is known as the genome-wide association study (GWAS). It allows the entire genome to be scanned effectively for the genetic variants that influence the development of disease. It is described more fully in Box 4.

BOX 4

Discovery of susceptibility genes for common diseases—the GWAS method

Genome-wide association studies (GWASs) compare populations that have a particular disease with control groups without the disease in order to identify genetic differences between the two groups. If particular genetic variants are found to be more frequent in people with a particular disease than the controls, these variants are said to be “associated” with the disease.

Most of the letters of the genome, around 99.9 per cent, do not differ between individuals. However the small fraction that do differ—known as DNA sequence variants or polymorphisms—not only explain inter-individual differences in body form and function, but serve as the molecular signposts in GWASs that indicate association between genes and the development of different diseases.

Throughout the late 1990s and early 2000s, catalogues of millions of variations in genome sequence between individuals were generated and maps of their distribution in the genome assembled. In the mid 2000s, technologies (such as microarrays) were developed to read hundreds of thousands to millions of changes in single letters of the genetic code—Single Nucleotide Polymorphisms (SNPs)—from an individual’s genome in a single experiment, permitting the “genomic profiles” of large numbers of individuals to be constructed and analysed.

In 2006, the first GWASs were carried out. These expensive experiments required scanning of the entire genome and generation of genomic profiles in thousands of individuals. Statistical analysis of individual SNP frequencies in patients with different diseases and in controls was carried out to demonstrate an association between the possession of particular SNPs and susceptibility to particular diseases.

For example, the GWAS of the Wellcome Trust Case Control Consortium, published in June 2007, reported the localisation of 24 new susceptibility genes across a range of six common diseases: bipolar disorder, coronary heart disease, Crohn's disease, rheumatoid arthritis, and type 1 and type 2 diabetes.²

Medical applications of genomic science

- 2.12. The National Institute for Health and Clinical Excellence (NICE) gave us an indication of the current use and potential value of genetic tests and other genomic technologies:

“Genetic tests for more than 1,200 diseases have been developed, with more than 1,000 currently available for clinical testing. Most are used for diagnosis of rare genetic disorders, but a growing number have population-based applications, including carrier identification, predictive testing for inherited risk of common diseases, and pharmacogenetic testing for variation in drug response. These tests and other anticipated applications of genomic technologies for screening and prevention have the potential for broad public health impact” (p 394).

Predictive diagnosis and single-gene disorders

- 2.13. Identification of the disease gene in single-gene disorders has had a number of beneficial consequences: it has increased knowledge about disease development; it has enabled precise molecular diagnosis; and, in a small number of cases, given rise to new targeted therapies. Reliable prenatal diagnosis is possible in single-gene disorders and is used to inform reproductive decisions in the ante-natal clinic in families with a high risk of severe genetic disorders. Predictive diagnosis in post-natal life can be used to make lifestyle choices and to allow early disease treatment at a pre-clinical stage.

Predictive diagnosis and genetically complex diseases

- 2.14. Genetic susceptibility is only one of several factors that can be used to predict common diseases. Other factors include family history, environmental exposures (such as cigarette smoking) and non-genetic tests such as blood cholesterol.
- 2.15. Data from GWASs have enabled the identification of a large number of disease genes underlying common diseases. But, whilst the new data are scientifically promising, their clinical utility has yet to be demonstrated. Professor Sir John Bell commented that “the suggestion that the data that come out of the whole genome association data, with relatively small but robust odds ratios, can be used to stratify patients in breast cancer screening is an interesting idea but we will need to see the data” (Q 432). The Wellcome Trust Sanger Institute also sounded a note of caution: “for most common human diseases only a small proportion of disease susceptibility has been explained in terms of identified disease-causing [gene] variants” (p 329). Consequently, identification of such variants is unlikely to lead to a precise, individually-tailored diagnosis or measurement of disease risk save in exceptional circumstances involving only a small fraction of the population.

² Wellcome Trust Case Control Consortium, “Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls”, *Nature*, vol. 447, 7 June 2007, pp 661–78.

Furthermore, gathering data through the GWASs is still at an early stage and therefore, according to the Academy of Medical Sciences (AMS), “the ability to interpret genomic data accurately, and to use this information to develop interventions to prevent or treat disease, still requires a great deal of research effort” (p 464).

- 2.16. Potential benefits are, however, beginning to emerge. For example, Professor Rory Collins, Director of UK Biobank, told us:

“We may well find genetic variants that produce only very small effects on risk, but what that could mean is that we have identified a new pathway for disease. That pathway could then open up the discovery of treatments that would act on that pathway which could be of substantial benefit” (Q 499).

- 2.17. Furthermore, identification of a SNP or set of SNPs (defined in Box 4 above), whilst not enabling individually-tailored diagnosis, could contribute to the information needed to stratify disease risk within the population, thereby enabling more accurate targeting of treatments. This has important implications at the population level as screening programmes will be able to identify individuals at high risk of disease. For example, seven SNPs associated with breast cancer, when taken together, “can identify women who have quadruple the average risk in society of developing breast cancer ... These seven markers ... can reliably identify five per cent of women in our society that have more than a 20 per cent absolute risk of breast cancer,” thus justifying screening (Q 531). Similarly, “if you take eight sequence variants ... discovered recently in eight places in the genome, it allows us to identify the one per cent of males in our society who have triple the risk of prostate cancer” (Q 531). The Joint Committee on Medical Genetics (JCMG) provided a further example in relation to colorectal cancer (p 552).

Diagnosing genetic subtypes of common diseases

- 2.18. In a small proportion of cases—and in a minority of families with multiple cases of the same disease—a disease develops not because of the predisposing effects of multiple genes (combined with environmental factors) but because of a mutation in a single gene (“single-gene subtypes”). Single-gene subtypes occur in a wide range of conditions including diabetes, Alzheimer’s disease, Parkinson’s disease, some cases of blindness and several types of cancer. The proportion of single-gene subtype cases varies markedly from disease to disease (less than five per cent in Alzheimer’s disease but as high as 50 per cent in children diagnosed with diabetes under the age of six months). Distinguishing between single-gene subtypes of common diseases and their genetically complex form is important. The two categories of the same disease may progress at different rates and may therefore require different treatments. In addition, the risk to relatives in single-gene forms of a disease is extremely high—up to 50 per cent of siblings or offspring of an affected family member may develop the disease—so if a precise molecular diagnosis is made in one family member, reliable prediction of disease risk and appropriate treatment can be offered to other family members.
- 2.19. Identifying this distinction within common diseases is having a profound effect on patient care. According to Professor Steve O’Rahilly, Professor of Clinical Biochemistry and Medicine at Cambridge, “what genetics is doing increasingly is actually helping us to subdivide [common diseases] into separate entities, some of which may end up having specific therapies”. He

gave the example of diabetes: “a very large number of people who had diabetes in the first few months of life had a particular mutation. All of those individuals, even after 30 years, could be taken off insulin and put onto a tablet and they became insulin-free, having been a slave to this injectable drug for many, many years. It caused dramatic changes in their health benefits” (Q 182). The range of diseases in which single-gene subtypes are now recognised is such that genetic diagnosis is increasingly used within the NHS for these conditions.

Predictive genetic tests sold direct to the consumer

- 2.20. Although the clinical utility of the disease association data from GWASs remains to be demonstrated, an increasing number of private companies in different parts of the world, including the UK, offer individual genetic tests or entire genomic profiles for sale directly to consumers. These tests, known as “direct to consumer tests” (DCTs), are mainly marketed and sold over the Internet. We return to this issue in more detail in Chapter 6.

Genomic tools for managing common disease

- 2.21. Whereas it may take some years to ascertain the utility of DNA sequence variation in predictive testing for common diseases, genomic tools are already being used in established diseases to make more precise molecular diagnoses. This is leading to new disease classifications and opportunities for more “personalised” treatment.
- 2.22. Cancer genetics is generally seen as leading the field. For example, Professor Sir John Bell told us that DNA microarray measurements of gene expression in tumour tissue are already generating data that can “separate women with breast cancer into high and low risks groups in a way that you cannot do with other technologies. It may allow some women who would have been exposed to chemotherapy to be able to avoid chemotherapy, and other women with bad prognosis disease who would not have been treated aggressively to be treated aggressively” (Q 432). Professor Sir Bruce Ponder, Director of Cancer Research UK Cambridge Research Institute, told us of trials which, it was hoped, would identify “with sufficient precision” those with “bad tumours who need the extra therapy” and those who have not. If a trial currently being conducted in Europe was positive, “it will be in routine practice within the next two or three years” (Q 534).
- 2.23. In the same field, the level of expression of the HER2 protein in the tumour is recommended by NICE as a guide to treatment with the drug Herceptin.³ In the diagnosis and treatment of leukaemia, according to the Royal College of Pathologists,

“... it is already a requirement that information about genomic changes in the tumour must be available before the drug can be given. Data from one haematopathology laboratory⁴ indicate close to a threefold increase in the use of these techniques in the last two years. It is inevitable genomic analysis will soon be a standard requirement for many much more common tumours” (p 107).

³ <http://www.nice.org.uk/Guidance/TA107>

⁴ Professor Finbarr Cotter, Barts and the London School of Medicine.

- 2.24. Some of these tests are carried out by simple techniques, others require more sophisticated sequence-based or microarray-based techniques. In screening for cervical cancer, present tests with Pap smears produce data whose “sensitivity is about 50 per cent so you identify the problem about 50 per cent of the time. By using genetic tools to look for papilloma virus ... you might be able to eliminate the Pap smear altogether, which would be a significant benefit, but you also get up to a sensitivity which is nearer 90 per cent” (Q 432).
- 2.25. The use of genomic tools is not limited to cancer management. In the treatment of HIV, viral sequencing can guide the way medications are applied; in tracking the spread of infectious diseases, viral sequencing can precisely categorise strains of virus, such as swine flu virus. Genetic testing is used to screen patients for likely hypersensitivity reactions to the drug Abacavir, used in the treatment of HIV infection. A commercial test for predicting foetal abnormalities such as Down’s syndrome, based on sequencing foetal DNA found in very small quantities in the maternal bloodstream, is now being launched in the United States, thereby avoiding the need for the traditional amniocentesis test which carries a small risk of foetal mortality.
- 2.26. The potential for such genomic tests is increasing. For example, cancer-causing changes in DNA sequence have been detected in tumour cells, and microarray studies have found structural changes in the tumour cell genome (such as gene duplication and deletion), some of which correlate with drug responsiveness. These advances are likely to lead to new tests for classification of tumours which will, in turn, guide treatment.
- 2.27. Professor Sir John Bell thought that applications of genomic technology which can be applied in the clinical setting “are likely to happen in a very short timeframe, particularly as the incentive to do it is enormous”. He suggested that “certainly within five years” there was going to be a lot of activity with regard to the application of genomic technologies to common disease (Q 424).

The stratified use of medicines and pharmacogenomics

- 2.28. “Pharmacogenomics” is the study of the way in which genetic variation across the genome affects drug metabolism and responsiveness. It can be used to develop tests to classify or stratify patient groups according to their response to a treatment (see Box 2). Pharmacogenomic tests are therefore one of a number of tests that can be used to personalise a patient’s treatment.
- 2.29. Professor Munir Pirmohamed, the UK’s first Professor of Pharmacogenetics, commented that although the term “personalised medicines” was now commonly used, as a physician, he had always carried out some personalisation of medicines—“I will try to personalise it depending on what their background characteristics are, what other drugs they are on and so on” (Q 719). This “personalised prescribing” is indicative of a new range of genetic tests that can be used to identify better drug treatments for individual patients. Dr Annette Doherty of Pfizer said that “the effect of pharmacogenomics and targeted medicines is being felt in every aspect of research and development within the pharma industry” (Q 719).
- 2.30. Although the Wellcome Trust suggested that “the impact of genomics on drug development pipelines has not been as profound as many had

predicted” (p 75), the Human Genetics Commission (HGC) regarded pharmacogenetics as the area from which new developments were “most likely to come into clinical practice ... within the short term” (Q 288). The Royal College of Pathologists indicated that they would welcome this. They anticipated that DNA and RNA-based diagnostic approaches will “guide more appropriate treatment and avoid ineffective treatment, and will identify some patients who do not need treatment. [They] will be an absolute requirement before the administration of many new treatments, especially new anti-cancer drugs; [and] will increasingly allow the prior prediction of severe adverse [drug] reactions” (pp 107–8).

- 2.31. The Bioindustry Association referred to the increasing numbers of drugs for which genetic tests may guide treatment or prevent side effects (p 481). In the United States, pharmacogenomic information is contained in about 10 per cent of labels for drugs being currently approved by the Food and Drug Administration (FDA).⁵ The FDA had been “very proactive in encouraging the submission of [drug side effects] data under a voluntary scheme which takes account of the fact that much of the science is at the exploratory stage at present” (p 478). According to the pharmaceutical company AstraZeneca, the FDA’s activities had placed the United States “at the forefront in progressing [pharmacogenetic] research towards translation into medical practice” (p 478).

Bioinformatics and genomic medicine

- 2.32. “Bioinformatics” may be defined as a discipline which uses computers and computational expertise to analyse, visualise, catalogue and interpret biological information in the context of the genome sequences of humans and other species.
- 2.33. As we highlighted in our 2001 report on Human Genetic Databases,⁶ there has been a dramatic increase in our capacity to collect genetic and genomic data in recent years. Genomic tests in a clinical setting and genomic experiments for basic biology generate quantities of data for which manual analysis is unthinkable. Indeed, for many genomic experiments, even the most advanced computers may struggle to undertake necessary tasks.
- 2.34. According to the Wellcome Trust Sanger Institute, “our ability to understand basic human biology has been transformed via the high throughput data production platforms ... which have ... resulted in the rapid advancement of genomic research and in major breakthroughs in our understanding of the biology behind human health and diseases” (p 328).
- 2.35. Meeting the information technology (IT) requirements of genomic medicine is therefore critical. Professor Dame Janet Thornton, Director of the European Bioinformatics Institute, described its importance in this way: “genomic medicine is very exciting and does have enormous potential ... For us the informatics challenges that this poses are enormous. It is clear that it will be the biomedical informatics that will allow translation from knowledge and research into medical practice, delivered through the doctors ... in the clinics, in the hospitals and ultimately for the GPs” (Q 695).

⁵ http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

⁶ House of Lords Science and Technology Committee, 4th Report, Session 2000–01, *Human Genetic Databases: challenges and opportunities* (HL Paper 57).

- 2.36. Within the NHS, Dr Elles, Director of Molecular Genetics at the National Genetics Reference Laboratory, described the challenge of interpreting DNA-based clinical results, telling us that:

“[an] immediate need ... which faces us day in and day out, is increasingly that we find variants in the DNA sequence of patients and we are not always sure what that variant means so it is the task of the laboratory scientist to try and interpret that by comparing whether for example that variant has been seen in another laboratory in the UK. That search may need to go much further afield and ask where in the world has that variant been seen; is it associated with the condition; can we produce a sensible clinical report for that patient” (Q 264). We consider bioinformatics in more detail in Chapter 5.

The role of epigenetics in disease

- 2.37. “Epigenetics” refers to changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence. Epigenetics is a scientific discipline that has run in parallel with genetics, and the two have recently converged because of their shared use of genome technologies and the desire to link genetic and epigenetic changes to traits such as disease susceptibility. The molecular basis of epigenetic changes is a modification of DNA or a modification of the packaging proteins known collectively as chromatin. Since these changes are not encoded in the genome sequence (unlike mutations), they are not generally passed down from generation to generation.
- 2.38. A fundamental feature of the epigenetic characteristics of an individual is that they can be modified by environmental factors such as the intrauterine environment, nutrition, stresses, tobacco and alcohol. Professor Sir John Bell commented on how the new sequencing tools were providing a “fantastic window” on epigenetic modifications and that maps would soon appear of epigenetic modifications in the development of different types of common diseases (Q 440).
- 2.39. Although the science of epigenetics is progressing very rapidly, it appears that it will be several years before epigenetic science will impact significantly on healthcare in the NHS due to the lack of understanding about the cause and effect of epigenetic changes on disease prevalence, and lack of specific therapies that target epigenetic processes. For this reason, we do not consider epigenetics further in this report.

The importance of biobanks and population cohorts for advancing genomic science

- 2.40. In recent years, two large national epidemiological cohort collections have been established in the UK: Generation Scotland and UK Biobank. These large cohort studies have the potential to contribute significantly to our understanding of the complex interplay of genetic and environmental factors that lead to the development of common diseases (p 11). Professor Andrew Morris, Chairman of the Generation Scotland Scientific Committee, suggested that the setting up of these collections demonstrated a recognition “that we need very, very large studies to be able to have the power and the certainty to tease out the modest clinical impact that many of these genetic

variants have ... We are looking at very small effects in large populations, hence the numbers are so important” (Q 485).

- 2.41. UK Biobank plans to recruit a sample group of 500,000 people by 2010. The project is collecting biological samples, and also lifestyle and environmental information, and will make samples available to researchers, subject to certain conditions, to conduct genetic studies. Generation Scotland differs from UK Biobank in being family-based rather than population-based. Generation Scotland will recruit 50,000 subjects from families. The family structure is believed to give additional information over a population cohort of equivalent size due to the ability to trace disease prevalence through families, therefore strengthening the genetic associations with disease.
- 2.42. A further cohort project, launched in January 2008, is the 1,000 Genomes Project. This project, in which the Wellcome Trust Sanger Institute is a major partner, will use new sequencing technology to sequence the entire genomes of 1,000 individuals to identify very rare variants, found at frequencies of less than one per cent. This will allow a much more detailed view of human genetic variation than was previously available. Dr Francis Collins, former Director of the National Human Genome Research Institute, said that the 1,000 Genomes Project was expected “to increase the sensitivity of disease discovery efforts across the genome five-fold and within gene regions at least 10-fold ... This will change the way we carry out studies of genetic disease”.⁷
- 2.43. It is expected that diverse databases, such as the 1,000 Genomes Project, will ultimately be combined with the UK Biobank lifestyle and environment data. At present, UK Biobank is not linked to death records or hospital episode statistics in the UK.

Conclusion

- 2.44. Genomic science has built rapidly on the achievements of the human genome project, bringing new-found understanding of the genetic basis of common diseases, and other advances that have already started to be used in healthcare. The use of genetic and genomic tests has become established in the management of diseases such as leukaemia and HIV, in predicting individual responsiveness and side effects to certain drugs, and in diagnosing genetic subtypes of common diseases such as diabetes, sudden cardiac death and blindness. These developments have enormous further potential in improving and rationalising management of a broad range of diseases, and in advancing strategies for disease prevention and public health. In the chapters that follow, we consider how such developments in genomic medicine can be brought more widely into clinical practice.
- 2.45. We are also aware of developments in related areas, such as gene therapy and stem cell therapies, and other technologies such as proteomics and metabolomics that have the potential to impact on clinical practice, either now or in the future. However, these areas are beyond the scope of this inquiry.

⁷ http://www.1000genomes.org/bcms/1000_genomes/Documents/1000Genomes-NewsRelease.pdf

CHAPTER 3: TRANSLATING HUMAN GENOMIC RESEARCH INTO CLINICAL PRACTICE

The framework for translational research in the UK

- 3.1. “Translational research” is the research which bridges the gap between basic or clinical research and the application of innovations in a healthcare setting. It is vital to realising the potential of genomic medicine. Examples include developing diagnostic tests to a marketable product and research to assess their clinical utility (that is, their benefit to patients).

The Cooksey Review

- 3.2. In a White Paper published in 2003, *Our inheritance, our future: realising the potential of genetics in the NHS* (Cm 5791) (“the 2003 Genetics White Paper”), the Government outlined their vision for the NHS in the context of genetic science. It was:

“... to lead the world in taking maximum advantage of the safe, effective and ethical application of the new genetic knowledge and technologies as soon as they become available”.

- 3.3. But Sir David Cooksey, in his 2006 *Review of UK Health Research Funding* (“the Cooksey Review”), identified translational research as an area of weakness and warned that the UK was at risk of failing to reap the full economic, health and social benefits that public investment in health research should generate. Two key gaps were identified: first, the translation of ideas from basic or clinical research into development of new products and new approaches to treatment of disease and illness; and, second, the use of those new products and approaches in clinical practice. In this chapter we focus on the first of these gaps.
- 3.4. The Cooksey Review identified a range of cultural, institutional and financial barriers to the translation of publicly-funded research into clinical practice and made a number of recommendations to overcome them. They included:
- better co-ordination of health research and coherent funding arrangements to support translation through the establishment of an Office for the Strategic Co-ordination of Health Research (OSCHR) to co-ordinate research between the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) and to monitor progress; and
 - the inclusion of additional funding streams in ring-fenced funding for Department of Health (DoH) research, and additional funding in key areas including Health Technology Assessments (HTAs) to support the uptake of new ideas and technologies.

In 2007, the Government set up OSCHR in accordance with the review recommendation.

- 3.5. Since its creation, OSCHR has been responsible for the co-ordination of public sector health research in the UK, estimated to be worth £1.7 billion a year by 2010–11. Its partners, the NIHR and MRC, have jointly developed a new approach to translational research, including a more coherent funding arrangement which involves each organisation taking the lead on funding for

core activities (the MRC for early development of new opportunities from discovery research and development to early-stage clinical trials and the NIHR for large-scale clinical trials). The recent injection of funding through OSCHR for translational research has, according to Professor Peter Donnelly, Director of the Wellcome Trust Centre for Human Genetics at the University of Oxford, “had an extremely positive impact” on translational research (p 79). **We commend this strategic and co-ordinated approach to translational research and the work of OSCHR in achieving this co-ordination.**

- 3.6. None the less, OSCHR’s first progress report, published in November 2008, indicated that significant challenges remain; and the recent report by the Bioscience Innovation and Growth Team, *The Review and Refresh of Bioscience 2015*, published in January 2009, confirmed this: “despite all of the activity [to improve the translation of health research into clinical applications] ..., the adoption of new therapies, drugs and procedures in the NHS remains painfully slow ... and the translation of these improvements into patient benefit has not yet materialised”.⁸ As for genomic medicine in particular, the Foundation for Genomics and Population Health (“the PHG Foundation”) told us that although genomic science was in a “robust state”, “progress is dramatically slower in evaluating the clinical and public health relevance of these scientific advances and in developing systems for effective translation of validated tests and interventions into clinical practice” (p 134). Oxford Nanopore expressed a similar view (p 325).

Funding and translational research in genomic medicine

- 3.7. In the 2003 Genetics White Paper, the Government made a commitment to provide £50 million to help the NHS make better use of advances in genetic science. This included investing £18 million capital on upgrading NHS genetics laboratory facilities, £2 million “start-up” funding over three years for initiatives to bring the benefits of genetics into mainstream practice, £15 million to support the development of five genetics knowledge parks over five years, and £2.5 million for pharmacogenetic research into existing medicines. The Government also made a commitment to ensure that the necessary infrastructure (such as informatics and laboratory services) was in place and that training was available to support translational research. In April 2008, the Government published a review of the 2003 White Paper—*Genetics White Paper Review 2008* (“the 2008 Review”). (The White Paper and Review are considered further in Chapter 4.)
- 3.8. Although the Government has now fulfilled many of the objectives set out in the 2003 White Paper, a number of witnesses expressed concern about whether the funding commitments were sufficiently long-term. The Research Councils UK (RCUK), for example, warned that the “high level of investment [set out in the White Paper] ... will need to be maintained to ensure that the developing understanding feeds through into benefits for clinical care and public health” (p 1). According to Oxford Nanopore: “It is essential that the investment in genetics is part of a long-term strategy to support innovation in the field and not a one-off event” (p 325); and the Wellcome Trust Sanger Institute referred to the importance of having a

⁸ A Report to Government by the Bioscience Innovation and Growth Team, *The Review and Refresh of Bioscience*, January 2009, p 2.

“strategic vision and sustained investment” (p 328). It is perhaps reassuring therefore that the need for sustained funding was acknowledged in the 2008 Review that genetics is still a relatively new area of work, and the review recognises that developments need to be considered over a longer timeframe, and will require sustained support.⁹

- 3.9. When asked about the Government’s plans to extend the programmes set out in the 2003 Genetics White Paper, the Minister of State for Public Health, Dawn Primarolo MP, said:

“Both the MRC and NIHR have new funding streams supporting ... translational research ... We have also invested more money in the NIHR’s health technology investment programme, and that programme has recently put out a themed call for the evaluation of diagnostic tests, and on top of that the Department of Health, with the Wellcome Trust, has the Health Innovation Challenge Fund, which will have a big part to play ... [we have] recently appointed Professor John Burn from the Newcastle Centre for Life as Chair of the National Clinical Genetics Specialty Group ... responsible for facilitating and encouraging timely development and, building on this, we plan to award £100,000 a year to the University of Newcastle under the direction of Professor Burn to enable clinical geneticists to come together and to identify current research activity and new funding opportunities” (Q 857).

- 3.10. Although we welcome these initiatives, we question whether they amount to a sufficiently strategic, long-term approach to funding translational research into genomic science. Recognising this deficiency, Professor Sir Alex Markham, Chair of OSCHR Translation Medicine Board, suggested that OSCHR had a role to play in remedying it:

“OSCHR should be charged to make sure that there is some strategic thinking going on constantly about genetics and its place in the health system. The structures that have been built over the last 12–18 months in and around OSCHR are well designed to do that ... I think we have an oversight capacity now that we have never had in this country before to take the hot science into the clinic when appropriate” (Q 474).

- 3.11. On 4 November 2008, the Prime Minister, Gordon Brown MP, asked OSCHR to work with the Department of Health (DoH) and the Department for Innovation, Universities and Skills (DIUS), through the MRC, NIHR and the research community, to identify a set of National Ambitions for Translational Health Research, with a view to developing an overarching set of national objectives to encourage the translation of major research breakthroughs into new NHS treatments and services within a decade. As part of this initiative, **we recommend that OSCHR should take the lead in developing a strategic vision for genomic medicine in the UK with a view to ensuring the effective translation of basic and clinical genomic research into clinical practice.**

- 3.12. **This strategic vision should form the basis of a new Government White Paper on genomic medicine which should outline:**

⁹ The 2008 Review, p 26.

- **the measures the Department of Health will take in order to facilitate the translation of advances in genomic science into clinical practice;**
- **a roadmap for how such developments will be incorporated into the NHS; and**
- **proposals for a programme of sustained long-term funding to support such measures.**

Strategies to facilitate translational research in the NHS

Culture change within the NHS

- 3.13. In his Foreword to OSCHR's first progress report, Professor Sir John Bell suggested that real commitment to research was still lacking in most NHS trusts, something that had to change if a culture of innovation in the NHS were to develop. The final report of Lord Darzi of Denham's NHS Next Stage Review, *High Quality Care for All* ("the final report"), published in June 2008, proposed placing a legal duty on Strategic Health Authorities (SHAs) to foster and promote innovation which, in addition to other initiatives to encourage translation in the NHS, was intended to encourage cultural change. Commenting on that report, Professor Sir John Bell told us that although it was helpful that the NHS constitution was going to have within it a commitment with regard to research, "there needs to be central management to make sure that it is a main pillar of the whole organisation" (Q 453). Whilst acknowledging this caution, we are encouraged by recent developments with regard to cultural change within the NHS.

Making the conduct of clinical trials less burdensome

- 3.14. The UK Clinical Research Collaboration was established in 2004 to streamline applications for clinical trials. It has led to significant improvements in the applications process. These include setting up an infrastructure to conduct clinical research in the NHS through the national clinical research networks and the provision of an advisory service and model agreements for clinical trials. The establishment of the Integrated Research Application System in 2008, in conjunction with the National Research Ethics Service, which provides for one data entry point for applications, has also received positive feedback from the research community.
- 3.15. However, it appears that the process for the establishment of clinical trials in the NHS remains burdensome, in particular because of the way in which the EU Clinical Trials Directive has been applied in the UK, and also because of the complexities surrounding confidentiality and consent in the sharing of medical data for research purposes (see Chapter 6). *The Review and Refresh of Bioscience 2015* report noted that the proportion of UK patients in global trials fell from six per cent in 2002 to two per cent in 2006, and suggested that, although the EU Clinical Trials Directive aimed to simplify and harmonise the rules governing clinical trials in the EU, the opposite had in fact been achieved; and, it was further suggested, differences amongst member states in applying the Directive had made the UK an increasingly unattractive location for biotechnology businesses to conduct research.¹⁰

¹⁰ See footnote 8 above, pp 1–2.

3.16. The Association of the British Pharmaceutical Industry (ABPI) also referred to difficulties with the clinical trials process, including the “slow start-up of trials and recruitment of patients.” (p 369); and Professor Collins told us:

“The regulatory obstacles to the use of medical records, and the regulatory burden for clinical trials as a consequence of the EU Directive on clinical trials and its implementation into UK law, have pushed research and research funding out of the UK ... The consequence of these, and also of NHS research governance, is that our ability to do this kind of research has been made increasingly difficult and costly, and research is being slowed substantially” (Q 527).

3.17. We recommend that the Government revises the UK implementation of the EU Clinical Trials Directive, in consultation with the research community, to make it less burdensome for researchers.

3.18. The European Commission is currently considering whether the EU Clinical Trials Directive should be reviewed in 2010. *The Review and Refresh of Bioscience 2015* report urges the UK to take a leadership role in any revision of the Directive to ensure consistency and to prevent the UK continuing to be an unattractive place, for both regulatory and financial reasons, to conduct research.¹¹ **If the European Commission decides in favour of a review of the EU Clinical Trials Directive in 2010, we urge the Government to participate fully in discussions in order to ensure that the revised Directive is less burdensome for researchers.**

Promoting collaborative translational research between industry, academia, the charitable sector and the NHS

3.19. According to a recent ABPI survey, “the volume of collaborations declined between 2003 and 2007”. From the industry’s perspective, the ABPI cited “escalating cost, increasing international competition for research funds, difficulty in contract negotiation and lack of incentives available for academics to collaborate more closely with industry” as barriers to collaborative research and noted that “if the UK is to have the best chance to lead in genomic medicine, these issues should be addressed” (p 367).

3.20. With regard to the involvement of academia, the Human Genetics Commission (HGC) noted that “certain conditions—such as the cost of postdoctoral funding in the UK and level of incentive for academics to collaborate with industry on research projects under the proposed Research Excellence Framework—are not currently optimised for collaboration between the pharmaceutical industry and academia” (p 161). This view was echoed in a recent *Nature* article in which the University of Oxford stated that “it is not financially viable” to participate in the Innovative Medicines Initiative, a major new initiative to fund European public-private partnerships, due to the funding terms of the initiative.¹²

3.21. Professor Pirmohamed agreed that escalating costs inhibited collaboration with industry. He suggested that recent changes in funding mechanisms were part of the problem. The move to Full Economic Costing in April 2006 has meant that industry has had to pay for 100 per cent of the direct costs (for example, laboratory supplies for a project or the salary of a scientist to run it)

¹¹ *Ibid*, p 14 (recommendation 5).

¹² Natasha Gilbert, “European finding plan ‘unviable’”, *Nature*, vol 456, 4 December 2008, p 551.

and the indirect costs (for example, a proportion of the maintenance cost for university facilities) for each individual project, or their proportionate share of the direct and indirect costs of a collaborative project. According to Professor Pirmohamed, “it has made a difference to us in terms of full economic costing in that certain companies have walked away because of the additional costs” (Q 746).

3.22. There is also a lack of incentive for the NHS to take part in research collaboration. The Institute of Medical Genetics (IMG) told us:

“Co-operation between industry and the NHS is essential, but NHS resources to collaborate with industry are at best miniscule, if only because actual and perceived rules, such as commissioners not being allowed to fund ‘R&D’, create huge barriers to progress. If R&D were regarded more as R, D & S, indicating ‘Research, Development and Service’, that might help break down this barrier. Research then would be thought more of the remit of research funding bodies, and D&S rightly the remit of the NHS” (p 247).

3.23. The charitable sector is also discouraged from collaborating. We were told by the Breast Cancer Campaign that “there is presently no initiative to involve all funders of research in collaboration, and we believe that this will continue to slow down advancement across all areas of research” (p 500).

3.24. Although there seem to be so many practical disincentives to collaboration, the industry and others acknowledge its significance in principle. For example, the pharmaceutical company, Astrazeneca, said:

“Progress in genomic medicine and translation to clinical practice will require an integrated approach between stakeholders; including scientists to discover and develop biomarkers, diagnostic companies to develop enabling technology to test the biomarkers, pharmaceutical companies to conduct clinical trials demonstrating the clinical utility of the diagnostics and the healthcare system to translate the linked drugs and diagnostics to clinical practice” (p 477).

The Academy of Medical Sciences (AMS) endorsed this view:

“Extensive collaboration is required between pharmaceutical companies, academia and the regulatory authorities to validate new technologies [for genomic medicine]. This will require companies to share safety data and to engage in new pre-competitive joint research in the UK and internationally” (p 467).

3.25. The DoH and the ABPI have worked closely to develop the concept of “joint working” between the NHS and the pharmaceutical industry, and have issued best practice guidelines for NHS staff and a supporting best practice “toolkit”. The Royal College of Physicians is also preparing a report on promoting collaborative working; and the Minister for Science and Innovation, Lord Drayson, told us:

“[It is] central to the effect and development of innovative medicines and ... in particular in the case of developments from the field of genomics is the vital importance of this public/private partnership and the relationship between the academic research base, the NHS and the early stage development into the large pharmaceutical industry ... The MRC ... just this week ... is launching a new collaborative scheme”.

But, he concluded, “we need to do more” (Q 903).

- 3.26. Whilst we welcome the new MRC collaborative scheme, we are aware that the 2006 Cooksey Review recommended that OSCHR should also encourage greater collaboration to facilitate the translation of scientific advances into clinical applications. **We recommend that the proposed White Paper on genomic medicine (see paragraph 3.12 above) and the Strategic Vision of the Office for the Strategic Co-ordination of Health Research should identify barriers to collaborative working between academia and the pharmaceutical and biotechnology industries, and ways of removing them and also address the need for incentives for collaboration so as to promote translational research in the UK.**

Assessment, evaluation and regulation of diagnostic tests

Research to demonstrate the clinical utility and validity of genomic tests within the NHS

- 3.27. Genetic tests are essential for the diagnosis of single-gene disorders and genomic tests are becoming increasingly useful for differentiating treatments of particular groups of patients in common diseases. The development and assessment of such tests require research to prove their clinical utility and validity. But whereas clinical validity is tested as part of any assessment of the risks and benefits of new diagnostic tests—partly for funding reasons, clinical utility, which looks at the benefit to the patient, tends not to be. As a result, there is currently little data on which to assess the clinical utility of genetic and genomic tests in the NHS (pp 108, 136–7 and 395). The Royal College of Pathologists further suggested that research into clinical utility was inadequate because of “the organisational difficulty of conducting this type of research; its relative lack of ‘prestige’ amongst the scientific community; and a traditional reluctance of the major grant-giving bodies to fund ‘mundane’ research into such practical matters” (p 108).
- 3.28. Other than tests for single-gene disorders, genetic tests (such as pharmacogenetic tests and gene expression profiling) are entering the NHS on an *ad hoc* basis, often without a proper assessment of their clinical utility or validity. As a result, there is a risk that some tests may be used without good evidence of their clinical utility, and others with clinical utility may fail to get through the process due to funding difficulties. Dr Christine Patch, Genetic Counsellor Manager of the Clinical Genetics Department of Guy’s and St Thomas’ NHS Foundation Trust, referred to there being “a sort of technology creep” and commented that tests were being introduced “prior to really detailed evaluation”. She suggested that these problems arose because “at the moment there is a funding and policy gap in that area” (Q 292). The HGC made a similar comment:
- “There is a need to assess clinical validity and utility in specific clinical pathways, as a recent PHG Foundation/Royal College of Pathologists report has recommended. However, proper evaluation of clinical utility takes time and may require large-scale studies; the provision of government funding for this sort of work would help to ensure that the benefits that could derive from further development of some types of genetic testing might be realised” (p 163).
- 3.29. The IMG also said that, as part of the assessment of clinical utility and validity, “an individual accredited service laboratory has to do a considerable

amount of work in, often, completely redesigning an analytical method used in research to suit it for patient diagnostics. This is a crucial area of activity for which the NHS makes minimal provision in support and funding” (p 247). The Joint Committee on Medical Genetics (JCMG) told us that “the exclusion of research proposals including novel laboratory testing from the current funding calls of the NHS National Institute for Health Research (NIHR) is significantly exacerbating this problem” of developing such tests, and that other sources of funding were not bridging the gap (p 550). Dr John Crolla, Chairman of the JCMG, told us (in June 2008) that the Joint Committee had tried to have discussions with the NIHR “because several members have reported that there is a funding gap”—and the “NIHR would be the place that we would look to create specific funding streams” (Q 192).

- 3.30. Although many other funding organisations cover the assessment of innovations generally (such as the National Horizon Scanning Centre and the Centre for Evidence-based Purchasing), none of them have a specific remit to fund development research into the utility and validity of genomic tests. The Royal College of Pathologists noted that “all these agencies are selective in the topics they will address, and many new innovations are not covered by the remit of any of them” (p 109). Under the current system, the development of genomic tests is often funded through the Primary Care Trust itself, through charitable grants or the MRC, rather than through the NIHR. The arrangements are informal and usually developed through the interest of individuals or patient groups. In the view of the IMG, “clear direction needs to be given that funding for the development of diagnostics is included in the remit of governmental research-granting bodies” (p 247).
- 3.31. Given the evidence we received of a funding gap, it was in some respects reassuring to hear from the NIHR Chief Scientific Adviser, Professor Dame Sally Davies (in January 2009) that NIHR’s Health Technology Assessment programme (HTA) and the Health Services Research Network did have a responsibility for the assessment of genetic tests and their translation into clinical practice, and that the DoH were “putting vastly more money into the Health Technology Assessment programme so that people can apply for grants to look at ... clinical utility” (Q 858). However, we remain concerned. The HTA programme does not cover genetic or genomic diagnostic tests alone, but all diagnostic tests. We are also aware that research proposals on genomic tests have been declined. The UK Genetic Testing Network (UKGTN) expressed concern that genetics was not a high enough priority for research within the HTA, and they noted with disappointment that the “HTA did not take up a proposal to examine microarrays and their introduction into clinical practice” (p 212).
- 3.32. Professor Sir John Bell suggested that a specific HTA programme for diagnostics was “essential” as the problems associated with diagnostics were very different from those associated with therapeutics and “such a programme would provide information ... for the regulatory decision as to whether or not to license such technologies in the NHS” (p 226). We agree. **We recommend that the National Institute for Health Research ring-fence funding, through a specific Health Technology Assessment programme, for research into the clinical utility and validity of genetic and genomic tests within the NHS.**

The evaluation of clinical utility and validity of genomic tests for use within the NHS

- 3.33. At present, genetic tests for single-gene disorders which are developed within the NHS are evaluated by the UKGTN. The UKGTN is a collaborative group of NHS laboratory scientists, clinical geneticists, NHS commissioners and patient representatives. Tests that pass the UKGTN evaluation process, the “Gene Dossier Process”, are recommended to commissioners for funding within the NHS.
- 3.34. The UKGTN system works well for tests for single-gene disorders. In contrast, it is unclear how genomic tests for common diseases, including pharmacogenetic and microarray-based tests, are evaluated. The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for assessing the safety of new “in vitro diagnostic devices” including genomic tests, but this task is largely limited to ensuring compliance with EU regulations. It does not address the clinical validity or utility of tests. NICE and NHS QIS (Quality Improvement Scotland) have a remit to evaluate innovations in laboratory diagnostic techniques but in practice, according to the Royal College of Pathologists, “they have evaluated only a very small number” (p 109). It appears, therefore, that there is no body at present with a specific remit to evaluate pharmacogenetic tests or genomic tests for common diseases.
- 3.35. Professor Peter Furness, President of the Royal College of Pathologists, suggested that the UKGTN Gene Dossier Process could be adapted to evaluate genetic tests for multifactorial disorders, but believed that the UKGTN was “vastly too small” to take on the task of running the process (Q 193). Professor Sir John Bell took a similar view: “I am not persuaded that the structure [of UKGTN] ... is necessarily transferable into this rather more complicated, complex world where clinical utility testing will have to be done on thousands of patients in large prospective cohorts” (Q 448).
- 3.36. The position with regard to the evaluation of genomic tests contrasts with the evaluation system for new drugs which, after clinical trials, have to pass through a rigorous independent evaluation within the National Institute for Health and Clinical Excellence (NICE) to assess their utility, validity and cost-effectiveness. According to Roche Applied Sciences, “the pathway for approval of new drugs in the UK is well-established ..., but there is no NICE equivalent for diagnostics. The lack of clarity regarding both the regulatory and commissioning pathways presents a serious barrier to making novel molecular diagnostics available for clinical evaluation and use” (p 565).
- 3.37. We note that Lord Darzi of Denham’s final report included a commitment to creating a single evaluation pathway for new clinical technologies; and we were told by the Minister for Public Health, Ms Primarolo MP, that the DoH were already working closely with NICE to develop a new evaluation pathway which would include genetic testing. She also noted that the Ministerial Technology Strategy Group was considering the establishment of a diagnostic evaluation programme, due to start in June 2011 (Q 882).
- 3.38. We welcome DoH’s consideration of a diagnostic evaluation programme within NICE—but more needs to be done now. We note Professor Sir John Bell’s view that there is a “need to identify a new agency that can handle the clinical utility evaluation of diagnostics” and that the NHS should “utilise NICE for this purpose” (p 226). We agree. **We therefore recommend that**

the Department of Health extends the remit of the National Institute for Health and Clinical Excellence to include a programme for evaluating the validity, utility and cost-benefits of all new genomic tests for common diseases, including pharmacogenetic tests.

The evaluation and regulation of genetic and genomic tests developed outside of the NHS

- 3.39. Tests are developed both within the NHS and by independent laboratories (including tests for single-gene disorders, genetically complex diseases and pharmacogenetic tests). Those developed by independent laboratories are used within the NHS, in private healthcare services and directly by the consumer. Although these tests are regulated through the EU In Vitro Diagnostics Directive, the Directive does not require their clinical utility to be proved and nor are they subject to evaluation by an independent body (Q 299). Under the Directive most genetic tests are classified as “low risk”, which means that the manufacturer of the test is responsible for ensuring that the test fulfils the requirements of the Directive rather than a regulatory body such as NICE or UKGTN.
- 3.40. Ms Primarolo told us that the MHRA had acknowledged the concerns raised by Member States, including the UK, over the classification of genetic tests and that there was overwhelming support for moving genetic tests to the second highest risk category. This would require them to be subject to a more stringent assessment than they are at present. Ms Primarolo told us: “The Commission are currently assessing the results of the public consultation and I hope that this will produce some sort of proposal on the way forward as quickly as possible” (Q 879).
- 3.41. **We recommend that the Government support the re-classification of genetic tests to “medium risk” in the current review of the EU In Vitro Diagnostic Medical Devices Directive so as to ensure that all genomic tests on the market have been subject to pre-market review before their use either by the consumer directly or by the NHS and private healthcare services.**

The development of stratified or personalised uses of medicines

- 3.42. Stratified or personalised use of medicines entails matching therapies to specific patient groups using clinical biomarkers to target more effective treatments, for example by taking account of patient susceptibility to particular drugs or to adverse drug reactions. The stratification of patient groups for the purposes of prescribing involves using tests—often genetic tests—to separate patient groups according to their likely response to a particular therapy. Such tests are required for certain treatments under NICE guidelines. The number of drugs for which such tests are recommended is currently small but is likely to increase in the future. In its 2007 report, *Optimizing stratified medicines*, the Academy of Medical Sciences noted a consensus amongst researchers, economists, healthcare providers and the pharmaceutical industry that “stratification is desirable for patients, healthcare systems and companies”.
- 3.43. Stratified use of medicines is the area of genomic medicine which is predicted to hold the greatest potential for the healthcare sector in the near-term. It has the potential to cut the cost of ineffective drug treatments within the NHS and also reduce life-threatening adverse reactions. However it also

presents one of the biggest translational challenges—not only because of the complexities of developing and assessing a medicine and a genetic test at the same time but also because of the lack of incentives within the pharmaceutical and biotechnology industries to develop stratified medicines.

- 3.44. Given that the current blockbuster model for drug development is not considered to be sustainable in the longer term and that the industry is under pressure due to the economic downturn, there is a pressing need for the industry to develop new business models for personalised medicines and it is vital to ensure that Government provides industry with incentives to do so.

Incentives to develop stratified uses of medicines

Flexible pricing

- 3.45. At present there is little incentive for the pharmaceutical industry to develop the genomic tests necessary for the application of stratified medicines. Under existing business models for drug development, drugs are targeted at a large number of patients. This ensures a return on the substantial research and development investment needed to bring the drugs to market. But stratified use of medicines is targeted at much smaller patient groups, and also requires the development of an accompanying test. For stratified medicines therefore the return on investment and the cost for treatment will have to be higher for each patient.
- 3.46. Professor Sir John Bell suggested that “the delivery of a new set of genetic tools into the clinic has proved really difficult in every jurisdiction”. One reason for this was that diagnostic companies could not be relied on “to do what is done in therapeutics, which is to demonstrate clinical utility” and this was “because the cost of a clinical utility programme is such that, at the prices paid for diagnostics, they would never get the money back” (Q 444).
- 3.47. Pricing of medicines for use within the NHS is governed by the Pharmaceutical Price Regulation Scheme (PPRS). It is a non-contractual scheme aimed at ensuring that safe and effective medicines are available on reasonable terms to the NHS, in the context of a strong, efficient and profitable pharmaceutical industry. Despite this recognition of the needs of the industry, the pharmaceutical companies, Roche and Astrazeneca, were critical of PPRS. They told us that it failed to reflect the therapeutic value of the drugs that companies were supplying to the NHS (thereby endorsing the findings of an Office of Fair Trading market study of the PPRS in 2007)—“a situation” they warned “that is likely to become even more acute as personalised medicine develops” (p 360).
- 3.48. Roche suggested that “a new model” was required “consisting of flexible pricing for personalised medicines and intellectual property protection and value-based reimbursement for both targeted drugs and companion diagnostics” (p 360). This would allow the price of a medicine to be amended retrospectively if the value of the medicine to patient care had proved to be higher than first anticipated. In November 2008, the PPRS was revised to introduce a more flexible pricing scheme which took into account the possibility of retrospective price change. According to the report, *The*

Review and Refresh of Bioscience 2015, this development was welcomed by industry.¹³

- 3.49. Whilst, as Professor Dame Sally Davies told us, value-based or flexible pricing was now an option under the new PPRS and therefore medicines targeted at a stratified group of patients could be submitted for consideration under the scheme (Q 906), problems remain. **We recommend that the Government continue to work with the pharmaceutical industry to extend value-based pricing for the stratified use of medicines under the PPRS to reflect the value of drugs sold for stratified use and the increasing use of genetic tests to accompany such treatments.**
- 3.50. In light of the evidence we received about existing medicines (Q 719 and pp 360–61), **we recommend further that, with regard to medicines for common diseases which are already in use in the NHS, the National Institute for Health Research should target funding to encourage the development of pharmacogenetic tests to stratify use of these medicines in order to improve their efficacy and to reduce the frequency of adverse reactions.**

Intellectual property rights

- 3.51. Whereas the 2003 Genetics White paper acknowledged the importance of protection of intellectual property (IP) to encourage innovation and to ensure that innovations are transferred into clinical practice, the 2008 Review made no mention of how IP could be managed in the development of the stratified use of medicines and their accompanying diagnostics. We are aware that recent reports on IP—by the Department of Trade and Industry (DTI) in 2004 and the Gowers Review of Intellectual Property in 2006—concluded that the current law on IP was appropriate, but we believe that more work needs to be done on the management of intellectual property rights and the development of stratified medicines.
- 3.52. We were told by the UK Intellectual Property Office (UK IPO) that the 2004 DTI report “supported the view that the current law and practice in the UK met the needs of researchers” and that “while the Gowers Review highlighted some historical concerns about the patenting of genes”, it had “indicated that current policies for the scope of patents in this area were set at the right level and recommended that these should be maintained” (p 581). However, the UK IPO noted also that, although the UK has a strong IP track record in the academic sector, “there appears to be very little patent filing activity from the hospital sector”, and that “given the importance of clinical research in developing and understanding disease conditions, it would be worth considering why this situation arises” (p 592).
- 3.53. Dr Stuart Hogarth, member of the Society for Genomics Policy and Population Health, also questioned whether the current IP arrangements met the needs of researchers involved in stratified medicines. He told us that “it has been quite clear in our research [on the regulatory framework for genetic tests] ... that because the industry’s traditional business model is that it has intellectual property in testing platforms, not in biomarkers, it is poorly incentivised to do clinical studies that develop the evidence base for the clinical validity” or utility of new biomarkers. He explained this was because

¹³ See footnote 8 above, p 4.

a company “that puts the investment into such a study”, unless it has intellectual property in the biomarker, “will immediately have multiple other companies riding on that investment” (Q 338).

- 3.54. **We recommend that the Department for Innovation, Universities and Skills¹⁴ address the issues relating to the management of intellectual property rights within the healthcare sector to improve incentives for stratifying uses of new and existing medicines and for development of pharmacogenetic tests necessary for stratification.**

The co-development and evaluation of stratified uses of medicines and genetic tests

- 3.55. A further disincentive to the stratified use of medicines arises from the separate development and authorisation processes for therapies and diagnostic tests. We received evidence, for example, that the health technology assessment for new diagnostics happens too late in the drug development process. According to the Bioindustry Association (BIA), “it is widely accepted by drug developers that, as long as the disease and response biomarkers are known, the earlier they are integrated and analysed in the clinical development programme, the better. Integration of biomarkers as early as in Phase I studies gives the opportunity to build the necessary knowledge to allow personalised medicine to be implemented at a later stage in clinical practice” (p 487). The BIA also commented that “timescales for the approval of genetic tests should not exceed those for drug approval, and medicines which employ pharmacogenetic information during prescribing must be assessed in a timely and appropriate manner during reimbursement decisions by NICE” (p 483).
- 3.56. The ABPI suggested that “an integrated regulatory framework for the co-development of a medicine with a diagnostic or predictive test should be a priority” for the future. They suggested further that “OSCHR should take leadership in developing a UK national strategy on stratified medicines”, taking into account “emerging science in drug discovery and diagnostics; e-Health; clinical application; regulatory environment; and health economics” (p 368). *The Review and Refresh Bioscience 2015* report also called for the Government to develop a stratified disease strategy, involving industry, academia and a wide-range of relevant organisations.¹⁵
- 3.57. We share the view that there should be a national strategy on stratified medicines to promote the development and use of such medicines. **We therefore recommend that the Department of Health set out a national strategy on stratified uses of medicines (as part of the proposed White Paper on genomic medicine recommended in paragraph 3.12 of this report). The purpose underlying this strategy should be to streamline the co-development of stratified uses of medicines and of pharmacogenetic (or other) tests.** This should achieve better value for money through effective targeting of pharmaceuticals by removing the current barriers to translation and encouraging the development and uptake of stratified uses of medicines.

¹⁴ We are aware that on 5 June 2009, after this report was ordered to be printed by the House, the Department for Innovation, Universities and Skills (DIUS) and the Department for Business, Enterprise and Regulatory Reform (BERR) were merged to form the Department for Business, Innovation and Skills (BIS).

¹⁵ See footnote 8 above, p 48 (recommendation 15).

Encouraging innovation in the biotechnology and healthcare sectors

- 3.58. As we have said (see paragraph 2.5 above) the UK is well placed to capitalise on the huge potential market for genomic medicine because of the leading role played by UK scientists in the field, the availability of charitable and Government funding, and the ability to conduct genome-related clinical trials and research within the NHS. However, innovation in the sector is currently poor, with little uptake by the NHS of innovative medicines. The BIA told us that “currently the UK is one of the lowest adopters of innovative medicines in the EU” (p 486). To address this issue, the ABPI suggested the creation of an Innovation Platform by the Technology Strategy Board (TSB),¹⁶ co-sponsored by DoH and DIUS.
- 3.59. The Minister for Science and Innovation, Lord Drayson, explained: “The Technology Strategy Board is the mechanism within Government which identifies those areas where it is regarded that the UK has strategic competitive advantage in the scientific area and where there is both significant growth potential but also meeting what is regarded as the key demand facing the country” (Q 857). With regard to genomic science, in particular, he said “as yet the Technology Strategy Board has not identified genomics as a key platform and it could be argued that it should, and this is something which I am interested in looking into.” (Q 857). He continued:
- “... [genomic medicine is] clearly an area where the United Kingdom has real global leadership; it is an area where the United Kingdom also has this unique advantage of the assets of the NHS and the structures which we have in the Department of Health. The question is: can we find better ways to support the development of innovative medicines and wealth in this country through the exploitation of those assets and that is certainly something into which I am urging the Technology Strategy Board to look further” (Q 907).
- 3.60. **We recommend that genomic science is adopted as a key technology platform by the Technology Strategy Board, to drive forward commercial development and clinical application in this area over the next five years and to maintain the UK lead in genomic medicine.**

¹⁶ The Technology Strategy Board invests in and manages a range of delivery mechanisms and programmes to drive technology-enabled innovation. To guide their work, technology areas are identified, with Innovation Platforms targeting specific areas of challenge.

CHAPTER 4: IMPLEMENTATION AND SERVICE DELIVERY THROUGH THE NHS

Introduction

- 4.1. Advances in genomic science have already led to some new developments in clinical practice (see Chapter 2). Further changes to patient care are likely to include:
 - advances in diagnostics and treatments both for rare genetic diseases and for single-gene subtypes of more common diseases;
 - improved efficacy of treatments through stratification of patient groups;
 - improved safety of treatments, with a reduction in adverse reactions;
 - more effective screening for an increasing number of diseases; and, eventually,
 - preventative healthcare through predictive tests for common diseases.
- 4.2. Although these advances will lead to improvements in the delivery of healthcare services in the NHS, they will also present significant challenges. As genomic medicine develops, commissioning systems for genetic tests, the structure of laboratory services for the provision of genetic (and other) tests and patient care pathways will need to adapt in order to ensure that appropriate additional steps are integrated into the healthcare service (for example, carrying out a genetic test as part of a patient's care, interpreting and communicating the results appropriately and adjusting treatments accordingly). This has significant cost implications for the NHS and will require careful planning for the provision of such services in the future. We have therefore—where possible—considered changes to the current service configurations with a view to cost savings in the long run.
- 4.3. We are aware that, at present, some genetic tests which are available now have not been integrated properly into the healthcare service—for example, diagnostic tests to identify and personalise treatments for single-gene subtypes of common diseases (such as diabetes (see paragraphs 2.18–2.19)) and pharmacogenetic tests to stratify the use of medicines and personalise treatments to certain subgroups of the population (see paragraphs 3.42–3.50). According to Professor William McKenna, Professor of Cardiology, University College London, “we have not taken advantage of the knowledge that we have to implement gene testing” even for single-gene disorders” (Q 537). Professor McKenna gave an example:

“The disease causing genes for ... sudden death [disorders], have been identified going back more than 20 years and being able to perform gene testing in the family would have, and does have when it is available to us, a major impact on being able to make an early diagnosis in the family ... Recently NICE have recommended in their guidance that there should be gene ... testing for the monogenic disorders that cause sudden death in the young, and yet on a clinical level that is not readily available” (Q 531, 537).
- 4.4. We are also aware that advances in genomic science will lead to a need for education and training of the healthcare workforce (see Chapter 7). The Wellcome Trust Sanger Institute told us that the efficient use of diagnostics

for single-gene disorders would require “further development of clinical diagnostic laboratories and specialised training of clinicians and health care providers” and that developments enabling “predictive testing for susceptibility to late onset common diseases” would lead to a “substantial” demand for “adequate education, training and counselling of healthcare providers, test providers and the public” (p 333). Professor Finbarr Cotter, Professor of Experimental Haematology, Barts and the London School of Medicine, also referred to the need for “educated clinicians who know how to use the tests, what is appropriate to order and how to apply [them]” (Q 125).

- 4.5. Professor Donnelly foresaw that the availability of direct to consumer tests (DCTs) would also have implications for the NHS: “people will be arriving at the door of their GPs or their health professionals saying, ‘I’ve had this test and I’ve got these SNPs; I’ve learned that my risk of prostate cancer is increased by 30 per cent; what should I do?’” (Q 134). Dr Imran Rafi of the Royal College of General Practitioners thought that it would be “a time-consuming affair” and that there were “going to have to be service models set up to look at what is the most effective way of being able to provide patients with the necessary support that they need” (Q 196).
- 4.6. The Minister for Public Health, Ms Primarolo MP, told us that, in her view, her role as Minister was “to make sure that we have the framework and the necessary levers to deliver the strategic objective” and this involved ensuring “that ... scientific developments ... can be delivered into real patient benefits” (Q 855). We welcome this statement. But the Minister’s belief that the real benefit for patients was at least ten years away (Q 855) contrasts with other evidence which we received (see Chapter 2). It also fails to acknowledge both the developments in genomic science that have taken place (particularly those identifying single-gene subtypes of common diseases) and the rate at which new developments are likely to occur in the future. **We recommend that the Government should reconsider how they will prepare NHS commissioners and providers for the uptake of genomic medicine in the NHS. We also recommend that the National Institute for Health Research, as part of its remit, regularly monitors developments in genomic medicine and their implications for the NHS now and in the future.**

The 2003 Genetics White Paper

- 4.7. In the 2003 Genetics White Paper, the Government set out a plan of action for “taking advantage ... of the new genetic knowledge and technologies” and made a commitment to invest £50 million to achieve that aim through activities to strengthen the existing healthcare service, to mainstream genetics into clinical practice and to educate the workforce (see Chapter 3). The Government also sought to ensure that genetics permeated all branches of medicine by supporting new initiatives in genetics-based care in key disease areas, in secondary and primary care and in national screening programmes. The initiatives included several pilot projects for genetic disorders and additional screening for genetic conditions.
- 4.8. In addition, the White Paper included a commitment to invest in strengthening existing hubs of NHS expertise. Measures included: earmarking substantial capital investment (over £18 million capital in 2003–06) for a major programme of modernisation of genetics laboratories;

expanding the workforce within specialised genetics services; and investing in genetics training and information and communications technology budgets. It also included commitments with regard to developing NHS informatics, start-up funding for building genetics into mainstream practice, training and education of the workforce, and setting out strategies for communication and engagement with the public on the ethical and social issues surrounding genomic medicine.

The 2008 Review

- 4.9. In April 2008, the Government published a review of the 2003 White Paper which set out progress since 2003. It also reported the views of key stakeholders on what has been achieved and the opportunities and challenges they anticipated.

Integration of genetics into mainstream practice

- 4.10. The Government has developed a number of models to integrate genetics expertise into mainstream practice. These include:

- pilots to test new patient pathways designed to give easier access to genetics services (including Teesside Cancer Family History Service and Poole Familial Cancer project);
- ten service development pilots to bring specialist genetics advice into mainstream NHS services (such as Oxford Ophthalmic Genetics Service); and
- a project to implement and evaluate cascade testing in families with familial hypercholesterolaemia (London IDEAS knowledge park).

Significant progress has also been made on the screening commitments, including Down's syndrome screening (available to almost all maternity units to women of all ages) and the roll-out of newborn hearing screening and sickle cell and cystic fibrosis screening (now offered to all babies).

- 4.11. These pilots demonstrated that non-specialist NHS staff, with appropriate training and support, are able to develop sufficient expertise to provide genetics services within mainstream practice; and, as a result, recommendations have been made within the Department of Health (DoH) for extending such services in the future. Diana Paine of the DoH NHS Genetics Team told us that the evaluation reports from these projects, along with an external evaluation by Nottingham University looking at the operational issues of embedding new technologies and services in the NHS, would be reporting later in the year and that they would be looking at how they could share some of the lessons learnt from the pilots within the NHS (Q 72).
- 4.12. In Chapter 3 we have recommended a new White Paper on genomic medicine. **We envisage that the proposed White Paper will address the operational changes needed as a result of bringing genetic aspects of treatments for common disorders into mainstream clinical specialities (including changes to commissioning arrangements, processes for providing genetic tests within the NHS and arrangements for NHS laboratories to conduct such tests).**

Infrastructure investment

- 4.13. Both the 2008 Review and the evidence that we received highlighted a need for continued capital investment to ensure that advances in genomic medicine are brought into clinical practice. The Joint Committee on Medical Genetics (JCMG) suggested that, although the Review confirmed that the Government were “committed to bringing new genetic advances to bear wherever they can be used to benefit patients”—“matching these aspirations with a long-term commitment to infrastructure, funding and support, remains one of the greatest challenges facing the delivery of genomic medicine and technology via the NHS” (p 549). Similarly, the British Society for Human Genetics (BSHG) said that “the Genetics White Paper helped modernise and network specialised genetic services but a new and resourced plan is needed if genomic medicine is to be successfully exploited in the NHS” (p 130). And Dr Elles, Chairman of the BSHG, stressed that “if we are to realise the benefits that have rolled on since then from our knowledge of the human genome sequence then we need to continue that investment stream. Genetics is not a box that has been ticked” (Q 284).
- 4.14. Although the 2008 Review outlines a number of significant achievements since 2003, it gives no indication of the Government’s plans for future funding of activities or for the next steps in taking forward the lessons learnt either from the pilots or from the Nottingham University review. If the NHS is “to lead the world in taking maximum advantage of ... new genetic knowledge and technologies as soon as they become available” (the 2003 Genetics White paper), the Government will have to strengthen their commitment to investing in this area of medicine.

Provision of genetic services in the NHS

Integrating genomic medicine into mainstream practice

- 4.15. At present genetics services in the NHS focus on the specialised provision of clinical genetics services to families and individuals at risk of single-gene disorders. In the future, genetic tests to target treatment and prescription for both single-gene disorders and single-gene subtypes of common diseases are likely to become more routine. Dr Frances Flinter, a Member of the Human Genetics Commission (HGC), described how “more and more genetic tests are being requested by physicians outside genetic centres”. Clinical geneticists, she said, were few in number and worked in a very specialised area, concentrating on the management of single-gene disorders. In the face of this increase in demand for genetic tests, she suggested that clinical geneticists worked with colleagues in other specialities “to help them develop clear guidelines, or protocols, which identify the subgroup of their patients for whom genetic testing may be indicated” (Q 336).
- 4.16. The UK Genetic Testing Network (UKGTN) warned about the implications of this increase in demand: “as the number of appropriate genetic tests increases, the current role of the specialised genetic services in ‘gate-keeping’ will need to be reconsidered. Some colleagues in other specialties increasingly will want to use genetic testing. Funding will need to take account of test costs within these specialties and there will also be a need for education and information” to allow for the effective commissioning and interpretation of such tests (p 215). The Foundation for Genomics and Population Health (“the PHG Foundation”) suggested that “as genomics is

increasingly applied in mainstream medicine, new service models are needed in which appropriately trained health professionals from other clinical specialties take responsibility for routine genetic aspects of care, with access to specialist genetics referral where necessary” (p 135).

- 4.17. Following a request from the JCMG, the PHG Foundation established an expert group to review the use of genetic testing as a means of non-invasive prenatal diagnosis to inform a strategy for the implementation of diagnostics within clinical services. Their report was published in January 2009.¹⁷ The PHG Foundation and JCMG told us that the technology provided “an exemplar of the development, evaluation and implementation of new genetic technologies into healthcare” (p 155). The report identified a number of significant challenges associated with the need to adapt current prenatal and antenatal healthcare pathways, specifically of screening and testing, to accommodate such developments. Recommendations of the report included “development and implementation of appropriate clinical pathways, laboratory standardisation and infrastructure development, continuing professional oversight, and formal evaluation and long-term monitoring of prenatal testing”.¹⁸ The report also highlighted an urgent need for professional education (p 158).
- 4.18. Lord Darzi of Denham’s final report (see paragraph 3.13 above) outlines plans to develop the NHS and its workforce in the coming years with a move towards more local control and provision of services. Whilst the report includes proposals to encourage innovation in the NHS (including efforts to streamline the pathways for diagnostics), it does not acknowledge the challenges that application of new developments in genomic medicine will present to the NHS. The evidence we received has caused us to question whether these challenges would in fact be better met by centralised, rather than local, assessment of the impacts of genomic medicine on clinical practice, in order to address some of the broader issues affecting healthcare service delivery.
- 4.19. Although specialised genetic services are important for the diagnosis and treatment of single-gene disorders, we share the view of UKGTN that their role as “gatekeepers” for the increasing application of genomic medicine within mainstream medicine needs to be reconsidered. **We recommend that, on the basis of the monitoring activity of the National Institute for Health Research recommended in paragraph 4.6 above, the Secretary of State for Health should ensure that any necessary NHS operational changes, as a result of a shift in the provision of genomic services to mainstream medicine in the NHS, are implemented in the NHS. In order to facilitate the process the Secretary of State should identify whether the NHS is fit to handle such changes and also what new service models are needed if health professionals from other clinical specialties are to take routine responsibility for genomic aspects of healthcare (with referral to specialist genetics services only where necessary).**

¹⁷ Wright, C., *Cell-free fetal nucleic acids for non-invasive prenatal diagnosis*, Report of the UK expert working group, PHG Foundation, 2009.

¹⁸ *Ibid*, p 53.

Commissioning of genetic services

- 4.20. The need to revise the framework for the assessment and evaluation of clinical validity and utility for all types of genetic tests (see Chapter 3) coupled with mainstreaming the use of genetic tests and stratified prescribing in the NHS have implications for the commissioners of genetic tests. Inevitably, they will need to change their commissioning practices to meet changes in arrangements for the assessment, evaluation and provision of specialised diagnostics. The commissioning structure will need to be reviewed as genetics spreads further into the mainstream NHS. We agree with the UKGTN that “it is important that the commissioning and funding of genetic testing and genetic services are explicitly considered when national policies are developed that affect all aspects of health care” (p 211).

Single-gene disorders

- 4.21. Genetic services are currently commissioned by specialised commissioning groups (SCGs). The UKGTN was set up to co-ordinate the evaluation of genetic tests for single-gene disorders and to provide advice to commissioners about such tests with the objective of promoting delivery of a consistent service. There is a consensus that the current system for single-gene disorders and the service that UKGTN provides in assessing the tests work well (although, we note that the UKGTN is not responsible for monitoring the uptake or use of genetic tests, or the extent to which funding is available for their use in the NHS.)

Genetically complex diseases and single-gene subtypes

- 4.22. Genetic tests that are used to quantify risks of common disorders, to treat single-gene subtypes of common diseases, and pharmacogenetic and other tests used to stratify therapeutics are not included in the same commissioning category as single-gene disorder tests. They are outside the SCGs’ remit. Dr Mark Bale, Deputy Director of Scientific Development and Bioethics at the DoH, made reference to this gap in the system: “we have acknowledged in the review [of the White Paper] recently that there is an issue around how to ensure that commissioners and commissioning can cater for the new tests, which may have different approaches from the way you have managed certain sub-sets of the population” (Q 64).
- 4.23. **We recommend that the Department of Health should conduct a review with the aim of establishing appropriate commissioning structures for pharmacogenetic tests, tests for management of genetically complex diseases and tests for diagnosing single-gene subtypes of common diseases, as the use of such tests spreads further into the mainstream NHS.**

Commissioning across the NHS

- 4.24. A second commissioning issue which has been drawn to our attention is that it appears that genetic services are not provided consistently across the NHS—as regards both tests for single-gene disorders and for single-gene subtypes of common diseases. We are particularly concerned about the latter because they are poorly represented at present and a positive diagnosis has important implications for family assessment and individual treatment.

- 4.25. Jacqui Westwood, Director of Specialised Services for South East London, Bexley Primary Care Trust (PCT), told us that “at the moment there is no proper understanding of the way that genetic services are commissioned nationally. They are all dealt with differently in the different areas and there is no structure to that and therefore the tariffs are inconsistent because everybody is doing it differently” (Q 401). Dr Crolla of the JCMG noted the “very patchy uptake by PCTs” of genetic tests and highlighted a number of reasons for this, including the low priority given to such tests by Health Service Managers compared to other interventions. Dr Crolla suggested that PCTs were at the wrong level to commission genetic services because of the complexities of evaluating the benefit of genetic tests, and also because of the “enormous pressure” that commissioners were under to assess other interventions (Q 208).
- 4.26. For this reason, the JCMG recommended that “this specialist commissioning should go back to a national level so that when agreed nationally there should be provision for the rolling out of these tests” (Q 208). Dr Crolla suggested that “this would be the ideal” and likened the present system to “a postcode lottery”. He went on: “I think it needs to be ring-fenced and national” (Q 209).
- 4.27. Professor O’Rahilly gave an example of inequity in the current system:

“Jenny Taylor ... was involved in Oxford in the development of a service whereby people who died young and suddenly of sudden cardiac death, of which there are a number of genetic causes, would have their post-mortem DNA analysed and family members would be screened and then those individuals who carried the risk factors were given implantable defibrillators, et cetera, to prevent sudden cardiac death. That was accepted pretty much everywhere in the UK apart from the Oxford region and it could not be implemented there because of financial pressures on the PCT, so there you had an example of the very place that was developing and leading internationally in the area of development was unable to find funding. There are numerous such anomalies within the Health Service” (Q 209).

Professor McKenna supported this point:

“It is very much ... down to the postcode. If you happen to live in one area you can access gene testing, but in general it is a real struggle to access mutation analysis for your patients. We have about 4,000 patients a year with inherited forms of sudden death and heart failure and we do not have routine gene testing, we have to do this through research grants and international collaborations” (Q 537).

- 4.28. We recommend that the Department of Health should conduct a review of current genetic test service provision within the NHS both for single-gene disorders and for single-gene subtypes of common disorders. This should aim to eliminate what are serious inconsistencies in the provision of genetic services across the NHS.**

Uptake of pharmacogenetic tests in the NHS

- 4.29. There are differences not only in the provision of pharmacogenetic tests across the NHS, but also in the way in which they are applied by different practitioners. There are two main reasons for this: first, a lack of clarity of appropriate funding streams (or tariffs) for the use of such tests as part of

treatments within non-genetic specialties; and, secondly, inconsistencies in the actual prescribing of such tests by healthcare workers during patient consultations.

Funding streams

4.30. We have already noted that an increasing number of genetic tests are now ordered by specialties other than genetics. This can cause problems as there are no specific funding mechanisms within the non-genetic specialty for the use of such tests as part of a patient's treatment. For example, Professor Peter Farndon, Director of the UKGTN, told us that:

“The tension we have got is if an ophthalmologist wants to send a test in, they have no funding stream in ophthalmology to pay for it unless they pay for it out of their budget. The funding stream for the majority of these tests is through the genetics services; that is another policy tension. If we try to roll out equity of genetic testing into other specialties, we have to come to some re-think about how that might occur” (Q 396).

4.31. As new tests develop, national tariffs or local prices will need to adjust for these costs. We are aware that the UKGTN is working to develop tariffs for genetic tests that are separate from clinical service provision (UKGTN). In December 2008, the report of the second phase of the *Independent Review of NHS Pathology Services in England*, chaired by Lord Carter of Coles (the second Carter Report), was published. The report noted that the DoH was considering the feasibility of a tariff for pathology and recommended that further work should be undertaken to develop tariff commissioning guidance for community-based and specialist (for example, genetics) pathology.¹⁹

4.32. We recommend that the Department of Health should develop a national set of standards and tariff guidance for the commissioning of genetic tests, taking into account the recommendations from the second phase of the Carter Review of NHS Pathology Services that there should be tariff guidance for community-based and specialist pathology, particularly relating to DNA and RNA-based genetic tests.

Prescribing practices

4.33. Professor Pirmohamed gave an example of inconsistent use of pharmacogenetic tests within the NHS by practitioners during the patient consultation process which involved genetic testing to assess whether patients might be susceptible to certain risks associated with the use of the drug azathioprine. “If you look at the different physicians who actually use this drug in this country, you find that there is a great deal of variability in terms of uptake” (Q 726). An extension of the current “red flag system” could alert healthcare workers to the need to use pharmacogenetic tests as part of the prescribing process where appropriate.²⁰ Professor Pirmohamed commented that, “as the new NHS IT system develops, then it may be possible to build [testing] into the prescribing process” (Q 728). Dr Hilary Harris, a GP and former member of the HGC, supported this:

¹⁹ The second Carter Report, p 24.

²⁰ The red flag system is an electronic prescribing system that alerts the practitioner to the need to take a certain treatment option during a consultation process by flashing up a red flag on the practitioner's computer screen.

“It is perfectly possible to flag up prescribing so that some of the warnings will come up, as they do now, or the instruction to have a test allied to a particular pharmaceutical preparation” (Q 834).

- 4.34. **We recommend that the Department of Health should commission the National Institute for Health and Clinical Excellence to issue guidance on the use of genetic tests by non-genetic specialties; and that the NHS should consider the expansion of the “red flag system” to alert healthcare workers to the need to conduct a specific test, in some cases a pharmacogenetic test, before deciding on treatment or prescription.**

Provision of laboratory services

- 4.35. It appears that a further cause of inconsistent provision of genetic services across the NHS has been the control of laboratory services at the level of the NHS Trust. This is partly due to the rapid advances in the field and developments in technology—many laboratories now need to replace equipment and replacement has varied across NHS Trusts—and partly because of variations in the availability of tests across laboratories. This is compounded by challenges in recruitment and retention of highly trained staff to run the service.

Re-capitalising of laboratories

- 4.36. As a result of the speed of technological developments in genomic sequencing and informatics, according to the BSHG, “[laboratory] services will be faced with a need to re-capitalise in the next three to five years”. They advised that “the Government should consider recurrent mechanisms to ensure that the NHS maintains cost effective access to appropriate technology platforms” (p 130). Oxford Nanopore made a similar point:

“At the time of the 2003 Genetics White Paper, the funding structure for new technology assumed that it should be considered for replacement after five years. The existing technology pipeline indicates that a two-year cycle would be more appropriate for one technology to be replaced by the subsequent generation. Planning of the infrastructure and funding of genomic medicine would need to take this into account” (p 345).

- 4.37. The provision of laboratory services varies across the UK because of commissioning arrangements and also because of differences in the investment decisions of PCTs. Professor Furness told us that:

“it was anticipated that when the [Genetics] White Paper introduced new developments and new equipment that commissioners would have arrangements to replace that equipment in due course. My understanding is that in some areas a lifetime of five years has been agreed in the budgets over which such equipment will be written off, and that is probably too long, but there are certainly other areas where commissioners have made no provision whatsoever for writing off and replacing the equipment, so we are getting differences of funding in different parts of the country which I think is regrettable” (Q 229).

- 4.38. Other witnesses, including Sir Alex Markham, Professor Sir John Bell, Professor Martin Bobrow and Professor Furness, suggested that the combination of molecular pathology (that is, DNA or RNA-based tests, in

the context of mainstream specialities) and clinical genetics services should be combined within a single clinical service structure. This would help to address these variations and to ensure a more coherent and streamlined approach to genetic testing within the NHS. Professor Sir John Bell suggested that:

“Pathology and laboratory services in NHS hospitals are severely fragmented and there is a serious risk that introduction of a range of new technology platforms will lead to further duplication in multiple different laboratory settings. Many of the technologies necessary for moving pathology into a new era are the same as those that would be used in clinical genetics laboratories and will also have applicability to both microbiology and haematology. There is an urgent need therefore to rationalise the management of these, either at an NHS Trust level or through large regional laboratories. These tools need careful technical support, bioinformatics and quality control and it seems unlikely that these can be developed in multiple sites within a hospital without undue costs. I think the coalescence of these platforms within a single clinical service structure is imperative to ensure that there is a coherent approach to these methodologies within the NHS. We have achieved this in Oxford using the Clinical Research agenda to drive integration of laboratory services. It should be replicated elsewhere” (p 226).

4.39. Professor Sir John Bell, citing developments in Oxford, referred to Figure 5 below.

FIGURE 5

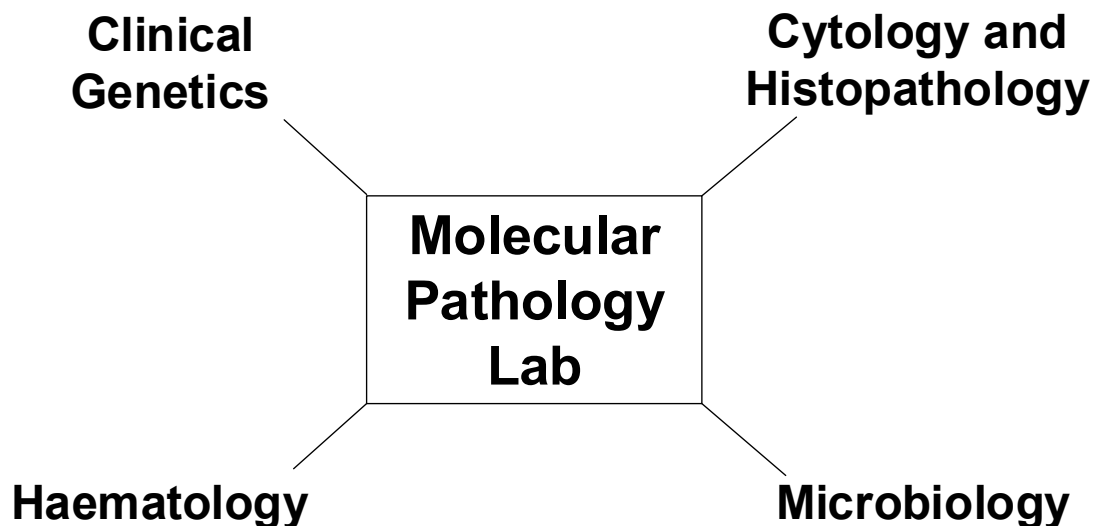
Laboratory Structures

Current laboratory structure (a) in which pathology services are funded and delivered separately; and suggested new arrangements (b) with the coalescence of molecular diagnostics into a centralised ‘hub’ with more locally positioned ‘spokes’ of specialised services

a



b



4.40. The view expressed by Professor Sir John Bell was supported by Professor Martin Bobrow, former Head of the Department of Medical Genetics, Cambridge University, who stressed the need to “consider a much greater degree of integration of the laboratory disciplines and [to] break down this now century old division into haematology and histopathology and so forth and start bringing the processes together” (Q 285).

“Hub and spoke” arrangement

4.41. Reconsideration of pathology services is already underway. The second Carter Report, endorsing a Healthcare Commission report on pathology services published in 2007, argued that there was

“... a strong case for consolidation of pathology to improve quality, patient safety and efficiency. Driving up standards, quality and patient care at the same time as reducing costs by between £250 and £500 million a year for reinvestment in the service which is necessary to deliver and assure service quality and to support the rapid adoption of innovative new technology and new approaches to the delivery of pathology services”.²¹

4.42. We envisage that for genomic medicine the “hub and spoke” system would mean that rapid specialised services would remain in local laboratories and highly technical DNA and RNA tests with expensive equipment would be in a hub. Professor Furness, for example, said that:

“There are aspects of providing molecular biology systems that are very expensive and nowadays rely on very large expensive machines where you only have [to] look at the economics and it is absolutely obvious that it is more efficiently done with a small number of those machines analysing samples from all over the country ... However, on the other hand, the people who actually interact with patients ... have to be where the patients are. To that extent you are potentially talking about a hub and spoke arrangements to make it most efficient. How many hubs you have around the country is a difficult question and will probably depend on the tests that you are talking about” (Q 219).

4.43. Although Professor Furness anticipated savings from such a reorganisation, he thought that funding would be a problem:

“The barrier to [the hub and spoke arrangement] is, first of all, the need for capital investment to do it and, secondly, the current structure of NHS funding. We have ‘silo’ funding where this amount of money goes to this service to keep doing what it has been doing year in, year out, irrespective largely of new demands and new developments, and it is very difficult to get agreement to change that pattern. The expense of that sort of reorganisation ..., I personally suspect it would not be enormous and I think the savings could be greater than the expense if it is done logically; but we have this hump, this barrier of organisational inertia to get over to make it happen” (Q 219).

4.44. The 2008 second Carter Report followed this model and recommended that specialist services should be consolidated through referral to specialist testing centres. It also recommended that pathology networks should be developed

²¹ The second Carter Report, pp 5–7.

with a single, integrated management structure, with only urgent testing carried out on-site. It suggested that Strategic Health Authorities (SHAs) should draw up implementation plans for consolidating services in their regions, requiring the PCTs to take the lead with local providers in drawing up cost-effective plans for implementation.²²

- 4.45. The Minister for Public Health, Ms Primarolo MP, said that the Government was working with some SHAs to explore how the second phase of the Carter Review could be taken forward (Q 875)—although she also said that it was “for the NHS to make the decisions on the spend and their equipment in the light of circumstances” (Q 871). Following this work, the DoH intend to publish an impact assessment of possible changes to the provision of laboratory services in the early summer 2009.
- 4.46. The first Carter Report, *Report of the Review of NHS Pathology Services in England*, published in 2006, made a range of recommendations about pilot projects to evaluate how to integrate pathology services. Two years and a second report later, a further recommendation about pilot projects was made and the impact of potential change to the service is still being assessed. The pace of change towards consolidation—a key recommendation of the first and second phase of the Carter Review—has been disappointingly slow. Consolidation of pathology services is essential to the cost-effective spread of genomic medicine across the NHS.
- 4.47. **We recommend that the Government centralise laboratory services for molecular pathology, including genetic testing, in line with the recommendations of the second phase of the Carter Review of NHS Pathology Services. The aim should be to organise effective laboratory services for molecular pathology and genetics by bringing together the whole range of DNA and RNA-based tests for pathology and medical specialties to ensure that services are cost effective. This would have the potential to free up funds, for example, for the highly specialised technical equipment that is needed.**

²² *Ibid*, p 23.

CHAPTER 5: COMPUTATIONAL USE OF MEDICAL AND GENOMIC DATA: MEDICAL INFORMATICS AND BIOINFORMATICS

Introduction

- 5.1. Realising the potential of genomic medicine will require the storage and interpretation of very large amounts of genetic information within the NHS, in turn requiring skills and facilities in bioinformatics and the establishment of information management systems to link genomic databases with medical patient records (see paragraphs 2.32–2.36).
- 5.2. The 2003 Genetics White Paper recognised the challenges to bioinformatics posed by new genome technologies: “the prospect of cheap whole-genome scanning could bring entirely new opportunities. In theory, a patient’s whole genome could be scanned once and the results interrogated later. The need to store and interpret such vast quantities of computerised data will produce real challenges in bioinformatics”.²³
- 5.3. Although the Government’s undertakings in the White Paper (that is, to ensure that genetics was included in developments in NHS informatics and to develop a genetics portal on the National Electronic Library for Health) have been met, the scale of the genomic datasets now being generated in clinical practice, and the resulting informatics requirements in clinical genetics and across the NHS, were largely unanticipated. Professor Sir John Bell told us that:

“Even research labs that have a hold of the new sequencing technologies are finding it almost impossible to manage the data ... There are two problems. One is that there is a hardware issue about having the kit to store the information on. There is also a human capacity problem. Despite the fact that we all sat around 15 years ago and said that the really crucial thing to train in the UK will be bioinformaticians—people who can handle data—the truth is we have now hit the wall in terms of data handling and management” (Q 461).

The emergence and growth of bioinformatics

- 5.4. Bioinformatics uses computational methods to analyse biological data. The discipline has arisen because of the very large scale of the datasets. A single genome is three billion nucleotides (see Box 1 in Chapter 2) in length; a typical genetic experiment analyses a million or more nucleotide sequence variants or quantitative variation in 25,000 genes. Interpretation requires not only sophisticated software to format and visualise the data generated in a particular experiment, but expert programmers and biologists to work together to develop a comparison with other data sources, to assess the significance, for example, of a new sequence variant found in a patient or biological sample. In a clinical setting, the data need to be presented to clinicians in a format that will be usable in a near-patient context.
- 5.5. Bioinformatics is a relatively new discipline, less than 20 years old. Professor Dame Janet Thornton described the growth of the European Bioinformatics Institute (EBI):

²³ The 2003 Genetics White Paper, p 28, para 2.22.

“There are now about 400 people in the EBI. This has grown from a size of about 70 when it was started ten years ago, so this is a huge expansion” (Q 713).

She added:

“within Europe we have an ESFRI (European Strategic Forum for Research Infrastructures) project called ELIXIR, which is trying to address the funding for bioinformatics within Europe and this is a major challenge for us still. We only have half of our money secured” (Q 712).

5.6. Although the EBI is the European hub for bioinformatics, these comments highlight the difficulty of securing sustainable funding for this emerging field. There is a sharp contrast with the equivalent of the EBI in the United States—the National Centre for Biotechnology Information (NCBI)—which “is funded by a direct subvention from Congress. This is therefore funded at the very highest level and they have a mandate about what they do there which overrides the biases of individual clinicians or individual researchers or individual hospitals” (Q 715).

5.7. The importance of sustainable funding for the EBI was emphasised by Dr Sir Mark Walport, Director of the Wellcome Trust:

“In the United Kingdom the holder of much of [the genomic] information is the European Bioinformatics Institute. Much of the funding of the EBI is in fact charitable and the European Union does not provide adequate support for the European Bioinformatics Institute ... It is extremely important that there is national funding for this enormously important database ... I think one of the major things that this Committee could actually be helpful on is to point out the need for there to be proper and sustained funding for databases such as the European Bioinformatics Institute which will otherwise become unsustainable and would put Europe in a weak competitive position” (Q 149).

5.8. We recognise the rapid growth in bioinformatics and its key role in supporting national and European genetics and genomics activities. Its dependence on charitable and cyclical EU funding jeopardises the data and the skills base which have accumulated at EBI over the last ten years. On our visit to the National Institutes of Health in the United States, we heard that the large majority of funding for the NCBI was intramural, government funding.

5.9. **We recommend that the Government show leadership on leveraging sustainable funding to the European Bioinformatics Institute (EBI), through the European Research Infrastructure (ESFRI) instrument and through the UK Research Councils. This would reduce the dependence of the EBI on charitable and cyclical funding and allow further growth of the Institute commensurate with the recent growth in genomic databases and the value of the EBI to the UK science base.**

Linking informatics with electronic medical records

5.10. One of the major challenges of utilising genomic information within the NHS is linking genomic databases and informatics platforms with electronic medical records. This will have benefits both for patients directly by improving patient care and decision making and indirectly by enabling

research for the public good to unravel the role of genetic, environmental and lifestyle factors in disease.

- 5.11. Setting up good electronic patient records is the first challenge. Dr Kári Stefánsson, President and Chief Executive Officer of deCode Genetics, told us that “if you want to let genetics have an impact on your health care system and if you want to contribute ... in advancing personalised medicine and the use of genetics in medicine, you have to introduce good electronic medical records into all your hospitals [and] into your primary care” (Q 548).
- 5.12. In the UK there has been considerable investment in creating electronic health records for all patients in the NHS through the National Programme for IT (NPIIT). In some respects, progress has been extremely good. Professor Sir Alex Markham noted that “effectively 100 per cent of NHS patients in primary care have their records held electronically” (Q 465).
- 5.13. Electronic patient records hold great value for research purposes, prescribing practice, pharmacovigilance and public health. Linking genomic data to electronic patient records offers additional benefits for patient care and for research. The Wellcome Trust told us that “the NHS provides a unique research resource—offering potential to link large-scale genomic data with information on health outcomes and responses to treatments captured in electronic patient records” (p 68). The new Research Capability Programme within Connecting for Health, the NHS computer programmes that store patients’ information, will help to establish systems to ensure that information is stored in an appropriate format for research purposes (see QQ 153, 154 and 670).
- 5.14. Linking these databases will also allow clinicians to access genomic information to aid their decision-making. The Wellcome Trust told us that “as genomics research advances and more clinically-relevant findings result, there will be a need for resources that collate and present information in a way that can support clinicians in their decision making. One example of an existing project is the DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources) initiative at the Sanger Institute, which uses genomic array technologies to identify chromosome abnormalities in children with developmental defects and presents this alongside clinical information about chromosomal abnormality” (p 74).
- 5.15. But joining electronic health record data to genetic or genomic data presents considerable challenges. These were highlighted by the EBI. They include the need to have adequate safeguards in place to ensure personal data security during data-sharing (see Chapter 6), the need to consider how to manage and handle complex genomic datasets within NHS IT systems, and also how the curators of such databases will handle information on the interpretation of such data for clinical purposes. Finally, genetic data will need to be linked to personal medical records to aid decision-making which will require a complex informatics component. Professor Dame Janet Thornton told us:

“We feel that genomic medicine is very exciting and does have enormous potential, and it is really critical, I think, at this time that the UK addresses the question of how best to translate this knowledge into the health sector. For us the informatics challenges that this poses are enormous ... Biomedical informatics ... has new aspects that we have not had to consider within bioinformatics, such as the translation to the

patient, the security of the data, all those aspects are not a part of our current role, and I think that for the research at this stage and for the future for the medicine it is clear that we really do need to strategically plan how to handle these informatics since it will underpin the future of the translation into the clinics” (Q 695).

- 5.16. Dr Ewan Birney, Senior Scientist at the EBI, drew attention to cultural differences between IT in the health service, which worked on an “IT procurement kind of model”, and biomedical informatics which is “complex and ... will move and evolve over years requiring more ‘a research style of investment’” (Q 702). Professor Dame Janet Thornton said that “there are two communities. There are the bioinformaticians and at the EBI, ... we have a very strong cadre of scientists who address this. We then have the medical health records area and the electronic health records ... and I do believe that there is something of a gap between the two and there needs to be a bringing together of these two different aspects” (Q 696).
- 5.17. Dr Sir Mark Walport told us of the excellent organisation of the Tayside healthcare database and the way in which this has contributed to clinical care and research: “In Tayside they have a very good electronic database around diabetes care where the purpose of the database is to provide better patient care, but that information can also be used in individuals who have given consent alongside genetic information” (Q 153). “I have visited the set-up in Dundee and it is a very powerful set-up in terms of informatics, providing better patient care and in doing so doing very good research” (Q 172).
- 5.18. Professor Dame Janet Thornton believed that, although challenging, it was technically feasible to use genomic data linked to healthcare records and that a single body should be tasked with computerising the health records and linking them to genomic data: “In terms of the investment, I think it ultimately will be very large ... I think we need somewhere in the UK which has a clear mandate to handle the biomedical records with that as their priority. This should be linked to the research, both the clinical research and the biological research, perhaps in a new institute or in a new unit which would address this” (Q 701).
- 5.19. Although it may take time for electronic health records to become fully established in the UK, the progress already made, together with evidence of the, albeit smaller, model in Tayside indicate to us the exceptional long-term value of linking health records to personal, clinically relevant genetic data, both for the benefit of basic and clinical research, and for the long-term value to healthcare of UK citizens.
- 5.20. The linking of UK electronic patient health records to personal genetic data would have substantial long-term value for the health of UK citizens. Given the importance of the NHS as a resource for clinical trials and genetics research, we believe that the Government should, as a matter of priority, take steps to bring together NHS expertise in electronic health records with the UK’s international leadership in genome informatics.
- 5.21. **We recommend the establishment of a new Institute of Biomedical Informatics to address the challenges of handling the linking of medical and genetic information in order to maximize the value of these two unique sources of information. Such an institute would bridge the knowledge, culture and communications gap that currently exists between the expertise in NHS IT systems and bioinformaticians**

working on genome research. The Institute would guide the NHS in the creation of NHS informatics platforms that will interface with databases containing personal genetic data and with publicly available genome databases.

Developing expertise in bioinformatics

- 5.22. Given the importance of bioinformatics to realising the full potential of genomic medicine, it is a cause for concern that there is reported to be a shortage of expertise in this area. Dr Elles asked the question: “where are we going to get the expertise in order to be able to access that data, to integrate it, and to interpret it at the laboratory level. We need a whole generation of bioinformatics-trained people ... from the world of bioinformatics to come into healthcare and to help us interpret this genomic data” (Q 264).
- 5.23. Professor Sir John Bell drew attention to the need for “a much more concerted and systematic approach to making sure that bright young people are brought into this arena and trained up at a variety of different levels” (Q 461). Professor Dame Janet Thornton also recognised the lack of expertise and training in biomedical informatics, commenting that at the EBI “we run extensive training programmes in the UK for students and post-docs, and some training of clinical geneticists has been undertaken, but just a very little bit so far” (Q 699).
- 5.24. **We recommend that the Department of Health should establish a centre for national training in biomedical informatics (within the Institute of Biomedical Informatics) with the aim of providing training that bridges the gap between health records information technology and genome informatics, and ensuring the delivery of an expert workforce for the NHS.**
- 5.25. An important aim of this national training programme should be to develop, implement and train the healthcare workforce in the use of secure and stable informatics software and databases that are suitable for the practice of Genomic Medicine. (Broader issues relating to the workforce requirements for bioinformatics within the NHS are considered in Chapter 7.)

Immediate informatics needs of NHS Regional Genetics Centres and laboratories

- 5.26. In addition to the long-term need to develop platforms to interface clinical information with genomic databases, there is an immediate need to improve the IT and bioinformatics facilities within the Regional Genetics Centres and laboratories across the UK in order to store and interpret the enormous amount of data generated from genetic tests, to aid communication between laboratories and to allow the comparison of non-personal genetic information from genomic databases to aid patient care.
- 5.27. The IT infrastructure of Regional Genetics Centres was greatly improved by funding following the 2003 Genetics White Paper. Informatics was not, however, a high priority in the White Paper, and there is now an urgent requirement for more bioinformatics expertise and tools.
- 5.28. Dr Elles told us that the need was immediate:
- “Increasingly ... we find variants in the DNA sequence of patients and we are not always sure what that variant means so it is the task of the

laboratory scientist to try and interpret that by comparing whether for example that variant has been seen in another laboratory in the UK ... [or] ... much further afield ... The tools which we have [to do this] ... have been developed for research use ... often there is very little quality assurance in the data ... Yet we are starting to need to use them for healthcare in the patient care pathway. [The] tools ... are often unstable, by which I mean the research funding ends ... and we are left high and dry in terms of not having a tool that is useful for healthcare” (Q 264).

- 5.29. Other witnesses, for example, the Institute of Medical Genetics (IMG) and UKGTN, pointed out that software for clinical genetics needs to be developed since there is no nationally available software for displaying family history. Although progress has been made in Wales and the National Genetics Reference Laboratory in Manchester has done some good work, “funding for the local implementation of LIMS [Laboratory Information Management Systems] is left up to individual Trusts, so it is patchy, and risks inefficiency and inequality” (p 248). Also, network communication speeds needed urgent improvement. Dr Crolla commented on his work with Connecting for Health:

“The problem was that through the NHS N3, the band width out to the Internet was 250 kb/sec speed width for the whole of the NHS, for all 1.2 million users ... [I understand that it is currently] one megabit per second, ... [but] it urgently needs upgrading to much faster, ten or 20, or as the French are now installing in Paris 100 megabits per second as a standard broadband band width ... This technology infrastructure improvement should [not] only be in the reference laboratories. I think it should be in all laboratories which are accessing genomic information” (Q 210).

- 5.30. We see clear deficiencies in the informatics tools and communication bandwidth available to the Regional Genetics Centres and National Genetics Reference Laboratories and note that funding for informatics in this area is patchy due to local implementation.
- 5.31. **We recommend that the Department of Health should implement a programme of modernisation of computing and information technology within the Regional Genetics Centres and laboratories, including an upgrade in computer hardware, software tools and communication bandwidth, in order to manage current needs of clinical and genome informatics in the Regional Centres.**

CHAPTER 6: PUBLIC ENGAGEMENT AND ETHICAL, SOCIAL AND LEGAL ISSUES

Introduction

- 6.1. With the advance of genomic science and its application in both clinical and non-clinical settings, a range of ethical, social and legal issues have emerged.
- 6.2. The 2003 Genetics White Paper dealt with a number of these issues and contained a commitment by the Government to engage with the public as a means of encouraging confidence in these new developments. Measures included:
 - efforts to support public understanding of genetics;
 - negotiation with the insurance industry of a moratorium on the use of genetic data;
 - a commitment to consider the issue of unfair discrimination based on genetic characteristics—a commitment underpinned by the principle that “no one should be unfairly discriminated against on the basis of his or her genetic characteristics”;²⁴ and,
 - a commitment to ensure that the current regulatory framework anticipated public concerns about developments in genetic science.

Public engagement

- 6.3. Public engagement is a vital element in achieving the full potential of genomic medicine. The Wellcome Trust told us that “continued support for public engagement activities will be crucial in order to ensure that patients are equipped to understand genetic risk information, and to foster a supportive public environment that allows the healthcare benefits of genomic medicine to be realised” (p 68). The Economic and Social Research Council Centre for Social and Economic Research on Innovation in Genomics (INNOGEN) suggested that there was an “increasingly important role for public consultation and engagement in informing ... [policy] decisions” and that consideration needed to be given to issues concerning human rights, informed consent, ownership, accessibility and confidentiality (p 18).
- 6.4. A number of bodies are charged with considering the ethical, legal and social implications of genomic medicine, each with a different role in engaging the public and improving public understanding. For example, the Human Genetics Commission (HGC), an independent advisory body to the Government, was set up in 1999 to look at the ethical, legal and social issues surrounding developments in human genetics and how they impact on individual lives. The Nuffield Council on Bioethics also examines ethical issues raised by new developments in biology and medicine. Both organisations include the promotion of debate amongst their activities.
- 6.5. In 2002, the Government set up a national network of six Genetics Knowledge Parks, with initial Government funding for five years. Their purpose was “to bridge the understanding gaps that exist between scientists and healthcare

²⁴ This principle was demonstrated by the inclusion in the Human Tissue Act 2004 of a provision making it an offence to test a person’s DNA without his or her knowledge or consent.

professionals and the general public in relation to genetics” (Q 525). The concept underlying them was to create multi-disciplinary environments where clinicians and laboratory workers could meet teachers, lawyers, politicians, ethicists, industrialists, patient groups and the general public to explore the ways in which genetic technologies could best be deployed in healthcare settings. Although the British Society for Human Genetics (BSHG) criticised the Government for not continuing funding for the Parks—describing the decision as “short-sighted and damaging” (p 132)—the Government defended their position on the ground that the work which the Parks had begun was “continuing within the separate institutions and wider networks” through Best Research for Best Health, the National Genetics Education and Development Centre (NGEDC), Sciencewise (within the Department for Innovation, Universities and Skills (DIUS)) and the Economic and Social Research Centre (ESRC) Genomics Network (p 426).

- 6.6. The BSHG and Oxford Nanopore suggested that it was the responsibility of the Government to promote public engagement. The BSHG recommended that the Government should “facilitate an adequately resourced programme of engagement between health professionals, policy makers and the public” to ensure transparency in genetic policymaking and public confidence (p 132). Oxford Nanopore argued that “the complex and controversial issues that surround genomic medicine warrant extensive debate which must be facilitated by Government” and welcomed Government support for the HGC to expand its work in this area (p 324).
- 6.7. **We welcome the public engagement activities that have been undertaken so far. We urge the Government and others to continue them, building on the successful dialogue models developed by Sciencewise. We have some concern, however, that these activities have focused primarily on public understanding of single-gene disorders. We urge the Government and other relevant bodies to extend the scope of their public engagement activities to include more detailed consideration of the implications of genetic tests for common complex diseases.** To this end, we welcome the launch in October 2008 of a study by the Nuffield Council for Bioethics into the ethical issues raised by new technologies that involve more personalised healthcare. The study is due to report in 2010. **We recommend in particular that the Human Genetics Commission should promote a wide-ranging debate on the ethical and social issues relating to genetic tests and gene associations for genetically complex diseases and how they contrast with genetic tests for single-gene disorders. The debate should aim to improve public understanding of genetic risk and predictive testing in common complex disorders.**
- 6.8. **We recommend further that the Department of Health should establish a comprehensive and regularly updated public information web site which would review the most recent science on the genetics of common diseases, to help the public to understand and interpret results of genetic tests.**

Ethical aspects particular to genomic research and medicine

Confidentiality and consent and use of personal genetic information in research studies

- 6.9. Central to the ethical debate on the implications of genetic science is the tension between, on the one hand, protecting individual privacy and

preventing the misuse of personal data held on genetic databases and, on the other hand, achieving the beneficial potential of genetic science through researchers linking genetic and medical data in order to find associations between genes and disease. The Genetic Interest Group (GIG) added to this dichotomy of interest the public “disbenefit” of not conducting research: we need “an ethical and regulatory framework that not only [takes] account of the potential harms arising from doing genomic research, but also of the harms associated with not doing it—notably the balance that needs to be struck between individual risk and lost opportunities” (p 199).

Public benefit of data-sharing

- 6.10. Both the 2006 report of the Academy of Medical Sciences (AMS), *Personal Data for Public Good*, and the 2002 report of the HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data*, highlighted the public benefit of researchers using personal medical data. Based on a large-scale survey of public attitudes, the HGC report concluded that there was strong public support for research in human genetics and for the benefits which this research could bring, provided that appropriate consent was given to use and store the information on genetic databases.²⁵ Professor Sir John Bell drew our attention to the level of public support for UK Biobank: “Biobank had recruited a very large number of people by the time the disk from the Treasury with all the data of the 22 million women on child support got lost in the post or whatever happened. I immediately called and I said, ‘Trouble coming. Let us watch the pace at which people pull out of this study because they will say we just cannot trust you guys.’ We did not have a single person withdraw” (Q 471).
- 6.11. In July 2008, Richard Thomas, the Information Commissioner, and Dr Sir Mark Walport published a report on data-sharing, the *Data Sharing Review* report, which recognised the importance of “sharing personal information for the purposes of research and statistical work” as “the third [most] important category of sharing” which “has produced benefits in almost all areas of life”.²⁶ It was further noted that “the foundation of modern medicine is research [which] depends on the study of individuals and populations” and that research “depends on the use of aggregated personal data”.²⁷
- 6.12. Given the public benefits of data-sharing, the question is how these benefits can be achieved without intruding upon individual privacy. The answer lies in part in the adequacy of the regulatory framework.

The current regulatory framework

- 6.13. In the UK, research on human subjects, including genetic research, is governed by a regulatory framework which seeks to protect personal information. It requires the informed consent of participants, research ethics committee approval and compliance with relevant legislation and conventions (for example, the EU Clinical Trials Directive and the regulations transposing the Directive into domestic law, the Human Tissue

²⁵ Human Genetics Commission, *Inside Information: Balancing Interests in the Use of Personal Genetic Data*, 2002, p 7.

²⁶ Richard Thomas and Mark Walport, *Data Sharing Review*, 11 July 2008, para 2.28.

²⁷ *Ibid*, para 2.31.

Act 2004 and the Human Tissue (Scotland) Act 2006, the European Convention on Human Rights, the Council of Europe Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data, the EU Data Protection Directive and the UK Data Protection Act 1998).

- 6.14. A number of witnesses, speaking from a researcher's perspective, were critical of the regulatory framework and in particular of the number of sources of regulation. The Association of Medical Research Charities said that it was "in danger of having a negative impact on research" and that it would "hamper progress in a number of areas by hindering the use of existing samples, lowering recruitment rates, and increasing the cost and complexity of studies" (p 472) (see Chapter 3). The 2006 AMS report, *Personal Data for Public Good*, highlighted the constraints on the use of personal health data, which arose through "confusing legislation and professional guidance, bureaucracy of process and an undue emphasis on privacy and autonomy".²⁸
- 6.15. Professor Collins of UK Biobank told us that "it is the bureaucratic obstacles to [the] linkage [of genetic datasets to medical records] that are the concerns" (Q 506) and that if he were able to make one recommendation to the Committee "it would be to remove the bureaucratic obstacles to using health records to improve the health of people in the UK" (Q 527). He told us that "the legislation is not clear [and that] it can be interpreted in a variety of different ways" (Q 507). Professor Andrew Morris, Chairman of the Generation Scotland Scientific Committee, also commented on the regulation governing a project such as Generation Scotland:

"The Department of Health guidance suggests that this domain is affected by 43 relevant pieces of legislation. There were 12 sets of relevant standards and eight professional codes of conduct. What this has bred is a culture of caution, confusion, uncertainty and inconsistency ... so for us to interpret it and to have consistent interpretation from legal bodies who have data protection responsibilities is absolutely key. Currently this is *the* major issue in terms of the ability to safely link data in a way which is in the public good with appropriate security. This was a major focus of the [*Data Sharing Review*] report, which was broadly welcomed" (Q 507).

The *Data Sharing Review* report said: "the complexity of the law, amplified by a plethora of guidance, leaves those who may wish to share data in a fog of confusion".²⁹

- 6.16. We were struck by the weight of evidence about the difficulties arising from the bureaucratic burden imposed by the current regulatory framework. Our recommendations in this chapter are intended to meet these concerns and to reduce this bureaucratic burden.

Anonymising personal data

- 6.17. Sharing genetic data of individuals must be regulated because they are personal data and are therefore subject to the demand for protection of

²⁸ Academy of Medical Sciences, *Personal Data for Public Good: using health information in medical research*, 2006, p 3.

²⁹ Richard Thomas and Mark Walport, *op cit*, p i.

personal privacy. Given that the identity of a patient will usually³⁰ be irrelevant to a researcher—the researcher will usually simply wish to link genetic data from patient A with medical data on patient A to associate some other variable with genetic factors—it would appear that the fundamental tension created by genetic data sharing could be resolved by anonymising the data. Put simply, this could be achieved by linking data from a patient in two separate databases with personal identifiers replaced by a code, the encryption for which would be held by a third party.

- 6.18. But the issue of anonymising data is more complicated than that. There are different forms of anonymising, some more helpful to researchers than others. If, say for example, there were a requirement to “de-link” or “de-identify” personal data, that is severing all links that make it possible to link them to other data from the same person, then a great many sorts of research into genetic associations would be impossible. Confusingly, as the *Data Sharing Review* report indicates, what counts as legally acceptable levels of anonymisation remains unclear.
- 6.19. A difficulty in designing an appropriate anonymisation mechanism was brought recently to the fore by the development of new methods for analysing genomic databases. An article published on 28 August 2008 in the *Public Library of Science Genetics Journal* suggested that an individual’s inclusion within a cohort of anonymised genetic profiles may be identified by those with access to his or her genomic profile, even if that profile were only present in summary format amongst those of hundreds of other individuals (although it would only be possible to identify an individual from such a database if one had prior knowledge of the individual’s genetic profile).³¹ A consequence of the new method of analysis is that several DNA databases run by the US National Institutes of Health, the Wellcome Trust and the Broad Institute in Massachusetts have taken the precaution of ending public access to genomic databases.³² UK Biobank also told us that they would not be putting scientific data into the public domain but would make it “available only to researchers under strict control” (Q 521). These examples highlight the need for clarity with regard to issues associated with anonymisation of data.

Consent

- 6.20. UK Biobank and Generation Scotland are examples of “prospective” studies, where the consent of volunteers, who are carefully informed, is given in broad terms for projects which collect information that may be used in research that is only envisaged or undertaken many years later (see paragraph 6.24 below).
- 6.21. Different considerations apply to the use of data collected from patients in the NHS, where there will be uncertainty about the specific purposes for which information might be used in the future. Arguably, this could mean

³⁰ We acknowledge that, in some circumstances, researchers may need access to patient identification details, for example to collect samples from research subjects and their family members, or to identify and invite relevant people to take part in clinical trials. We have not addressed issues raised in these circumstances in this report.

³¹ Homer et al 2008, “Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays”, *PLoS Genet* 4:e1000167.

³² “DNA databases shut after identities compromised”, *Nature*, vol 455, 4 September 2008, p 13.

that some patients will have insufficient information to enable them to make an adequately informed choice when consenting to the use of their personal data. This issue was raised by the Information Commissioner. Professor Collins commented that “it is impossible to counsel people on what the implications will be of things we might do in 15 or 20 years time, or, indeed, what the relevance of the things that we find might be” (Q 516).

- 6.22. Other jurisdictions have used different approaches to this problem. For example, Denmark uses a system of broad consent and aims to promote legitimate research using genetic data on the basis of an “opt-out” system. Dr Birney told us that Denmark “has an opt-out system, not an opt-in system” whereby it is assumed that an individual wishes to consent unless he or she says otherwise. “Some of the researchers in Denmark have access to very broad population study data and seemingly the Danish population is happy with that ... Many people have the desire in that context to give very broad consents in the context of research, of course, as long as the data is only being used for research and as long as it is secure” (Q 708).

Developing systems that balance the needs of the individual and the general public

- 6.23. Recommendation 15 of the *Data Sharing Review* called for the development of “safe havens” to provide an environment for population-based research and statistical analysis by researchers who had been approved or accredited to work in those environments, whilst safeguarding the privacy of individuals. In response to the *Data Sharing Review*, the Department of Health (DoH) made a commitment to develop such a scheme through the Research Capability Programme, working with the Information Centre for Health and Social Care. The DoH also made a commitment to determine principles to enable the use of information derived from care records alongside other datasets under conditions that would protect identifiable personal and confidential information.
- 6.24. UK Biobank is a database that contains anonymised biological samples and medical and lifestyle information (that is, a collection of samples and information that are held in uninterpreted form). Volunteers give their consent after being informed about the range of uses to which the information collected, including genetic information, may be put and can withdraw from the Biobank studies at any time. Only accredited researchers may have access to information from the database. They may apply for access to specific types of anonymised information or samples, subject to review by the relevant Research Ethics Committee. According to the Wellcome Trust Sanger Institute, “the UK Biobank initiative has set a gold standard for ethical principles and guidelines concerning the large population studies” (p 333).
- 6.25. **When developing the “safe havens” for research, recommended by the *Data Sharing Review* report, we encourage the Department of Health to consider adapting the approach developed by UK Biobank for ensuring the protection of personal privacy as an exemplar.**

Data Protection Act (DPA) 1998

- 6.26. We agree with the Information Commissioner that “organisations must ensure that robust safeguards are in place so that individuals enjoy a proper level of privacy and data protection and their personal genetic information is handled in a way that inspires trust” (p 547). This is fundamental if the

public is to be encouraged to participate in genetic research. However, we question whether the correct balance between the protection of individual privacy and enabling data-sharing for the purposes of legitimate scientific research and patient benefit has been achieved. Part of the problem appears to derive from the application of DPA 1998. We note, for example, the conclusion of the *Data Sharing Review* report:

“A significant problem is that the Data Protection Act fails to provide clarity over whether personal information may or may not be shared. The Act is often misunderstood and considerable confusion surrounds the wider legal framework—in particular, the interplay between the DPA and other domestic and international strands of law relating to personal information. Misunderstandings and confusion persist even among people who regularly process personal information; and the specific legal provisions that allow data to be shared are similarly unclear” (paragraph 8.21).

- 6.27. **The *Data Sharing Review* report further suggested (in Recommendation 7(a) of the report) that a statutory duty should be put on the Information Commissioner to publish (after consultation) a data-sharing code of practice to remove “the fog of confusion”—which should include sector specific instructions where necessary. It also recommended (Recommendation 8(a)) that where there was a genuine case for removing or modifying an existing legal barrier to data sharing, “a new statutory fast-track procedure should be created”. We support these recommendations.**
- 6.28. **Further, we urge the Information Commissioner to publish a set of clear, feasible and proportionate guidelines, in accordance with the Data Protection Act 1998, specifically for researchers handling genetic data for the purposes of non-personal research in order to reduce the burden of data protection legislation on researchers.**
- 6.29. **The Data Protection Act 1998 is “tightly tied” to the EU Directive on the protection of personal data. The *Data Sharing Review* report recommended (Recommendation 6) strongly that, due to the need for clarity over when data-sharing is appropriate under the Data Protection Act 1998, although change may be a long way off, the Government should participate “actively and constructively in current and prospective reviews of the European Directive, and assume a leadership role in promoting the reform of European data law”. We agree.**
- 6.30. **We recommend that, meanwhile, the Government should seek to amend the Data Protection Act 1998 where possible (including amendments to bring into effect the recommendation in paragraph 6.28 above) so as to facilitate the conduct of non-personal research using genetic data.**

Use of genetic information for insurance and employment purposes— genetic discrimination

- 6.31. In May 2008, the United States Congress passed the Genetic Information Non-discrimination Act (GINA). The purpose of GINA is to protect American citizens against genetic discrimination in health insurance and employment. Other countries, including France, Sweden and Finland, have

also legislated against forms of genetic discrimination. In addition, the Council of Europe Convention on Human Rights and Biomedicine (Chapter IV, Article 11) prohibits any form of discrimination against a person on grounds of genetic heritage.³³ At present the UK is not a signatory to the Convention, although the HGC has recommended that the Government should take steps towards becoming one.

- 6.32. In the UK, discrimination in employment on the ground of any manifest genetic condition is regulated by laws with broader scope, in particular by the Disability Discrimination Act (DDA) 1995. A number of other statutes—the Human Tissue Act 2004, the DPA 1998, the Human Rights Act 1998—may also apply in certain circumstances. None the less, we received evidence in which concerns were raised about the risk of genetic discrimination in employment or for insurance purposes because of supposed gaps in the current legislation. Mr Michael Harrison, a barrister specialising in clinical negligence and member of the HGC, reviewed the scope of these various pieces of legislation and considered whether they provided a satisfactory alternative to consolidated, genetic discrimination legislation. He concluded that they “may cover many situations” but they are “unlikely to cover all of them”, stressing, for example, that the DDA 1995 would only cover genetic conditions once they had caused a manifest functional disability. “Late onset” genetic conditions would not therefore be covered until that time (Q 620). We note however that insurers typically already have access to information about such disorders in the form of medical information and family history and, at present, genetic tests for such conditions are not considered to be accurate enough to be used by the industry.
- 6.33. Mr Harrison suggested that there should be a statutory provision to the effect that “the default setting is that genetic discrimination would be unlawful, but that [if] a defence is provided for someone who seeks to treat a person differently on the basis of a genetic difference, they have to justify that differential treatment” (Q 620).
- 6.34. Mr Harrison further suggested that this statutory provision should be included in the single Equality Bill (currently before Parliament). In 2007, the Government published a consultation document entitled *A Framework for Fairness: Proposals for a Single Equality Bill for Great Britain*. The consultation asked, “Do you agree that there is no current justification for legislating to prohibit genetic predisposition discrimination?” Over 4,000 responses were received of which around 60 per cent said that legislation was needed. The HGC also responded in support of genetic discrimination being recognised explicitly in anti-discrimination legislation, in particular the single Equality Bill (p 161). On the basis of an email survey, the HGC believed that such discrimination was taking place.³⁴
- 6.35. In October 2008, the Government announced that, following their consultation, they did not intend to introduce specific statutory protection against discrimination on grounds of genetic predisposition given the safeguards in an established Concordat with the Insurance Industry on the use of genetic tests for insurance purposes (see paragraph 6.42 below). At that time, they proposed instead to continue with the present system of

³³ <http://conventions.coe.int/treaty/EN/Treaties/Html/164.htm>

³⁴ HGC response to the Discrimination Law Review consultation, *A Framework for Fairness: Proposals for a Single Equality Bill for Great Britain* (14 September 2007).

monitoring by the HGC and the Genetics and Insurance Committee (GAIC). The Minister, Ms Primarolo MP, has since told us, however, that the DoH propose to disband GAIC (see paragraph 6.48 below).

Employment

- 6.36. Genetic conditions may have considerable bearing on an individual's capacity for employment. Where a condition is already manifest, information about the condition and its effects will be known through ordinary medical assessments. New genetic tests, on the other hand, provide information about "late onset" conditions which are not yet apparent. But we have heard that these genetic tests do not predict when the disease will develop or its severity. So while information obtained through genetic tests is useful for medical purposes, it is, according to the Information Commissioner, "too intrusive and the information's predictive value is insufficiently certain to be relied on to provide information about a worker's future health".³⁵
- 6.37. In 2006, the HGC conducted a survey from which they concluded that "there was no significant evidence of genetic testing occurring in the workplace" (p 430); in contrast, an earlier survey of companies, in 2000, conducted by the Institute of Directors, had found that "50 per cent of respondents were in favour of using genetic tests to identify workers who were at risk from occupational hazards" (p 302). There is therefore a need to continue to monitor the situation. Sarah Veale of the TUC gave an example of why employers would want to use genetic tests: "if you ensure that you do not have any employees who are susceptible to particular, say, types of chemical use, it is rather cheaper than preventing the use of the chemicals in the first place" (Q 619). Also, employers would benefit from excluding a worker who "is predicted to need considerable time off due to ill health" (p 302). The TUC supported a law against genetic discrimination.
- 6.38. Other witnesses cautioned against creating "genetic exceptionalism" by making genetics a special case within discrimination and data protection laws. They also questioned whether it would be possible legally to define genetic discrimination. For example, the Foundation for Genomics and Population health ("the PHG Foundation") described calls to outlaw genetic discrimination as "misguided as it will not be possible to arrive at a consistent legal definition and such legislation would unfairly privilege DNA-based information over other types of information that may be equally or more predictive" (p 136).
- 6.39. We are not persuaded that there is sufficient evidence at this stage to warrant legislation against genetic discrimination in the workplace; added to which, the uncertain predictive value of tests for common complex disorders means that the information derived from them would be of little value in the employment context. We are also mindful of the fact that the US legislation, GINA, was passed because of links between employment and health insurance in the US which are not present in the UK because of the provision of free healthcare through the NHS.
- 6.40. **We do not believe that at present there should be specific legislation against genetic discrimination, either in the workplace or generally.**

³⁵ Information Commissioner's Employment Practices Data Protection Code under the DPA 1998. http://www.ico.gov.uk/upload/documents/library/data_protection/practical_application/coi_html/english/employment_practices_code/part_4-information_about_workers_health_2.html.

But rapid advances in genetic science mean that there is a continuing need to monitor the situation. This should be undertaken by a designated body, possibly the Human Genetics Commission.

Life Insurance

- 6.41. Insurance companies fear “adverse selection”—where high risk individuals, if not required to disclose the results of a genetic test, may insure themselves at unfairly low rates which could in turn have a disproportionate negative effect on the insurance market leading to higher premiums for everyone.
- 6.42. In 1999, an agreement was reached on a system of voluntary regulation. The Government set up the Genetics and Insurance Committee (GAIC); and the Association of British Insurers (ABI) published a Code of Conduct which was intended to be observed by all its members and which imposed a moratorium on the use of genetic tests for insurance purposes unless there was demonstrable evidence that they were actuarially significant. The moratorium has been revised and extended three times: in 2001, 2005 and 2008 (extended to 2014). The next review is due in 2011. In 2005 a Concordat between the Government and the ABI was incorporated into the moratorium. Under the Concordat companies are able to ask for the results of a predictive genetic test already undertaken by an individual only “if it has been approved by GAIC and if the policy is for more than £500k of life cover or £300k for other types of insurance” (p 430). Only one test is currently allowed—for Huntington’s disease for life insurance policies over £500k (p 431). Under the terms of the moratorium, insurers agree not to request individuals to undertake predictive genetic tests in order to obtain life insurance. GAIC told us that they had received only three legitimate complaints since 2004 about the use of genetic tests for insurance purposes, none of which concerned predictive genetic tests.
- 6.43. In 2007, 132 insurance applicants disclosed test results for Huntington’s disease, representing an increase of four per cent from 2006. Of those, 108 were normal (negative), 19 were adverse (positive) and five were ambiguous. Three of the applicants with adverse test results were declined insurance, two were accepted at ordinary rates and the rest were accepted with increased premiums or revised terms. Five of the applicants with normal test results were declined insurance, 66 were accepted at ordinary rates, seven did not complete the application and the rest were accepted with increased premiums or revised terms.³⁶
- 6.44. According to GAIC, “whilst we have the moratorium in place, this is probably sufficient”, although Professor David Johns, Chairman of GAIC, said that he was aware that this was “very temporary [and] ... only a partial solution” (Q 578) and that “people are very, very naturally concerned that somehow the insurance industry may say, ‘No moratorium and we are looking backwards’” (Q 587). As Chairman of GAIC, he spoke to patient groups and heard “their concerns” about the retrospective use of test results (Q 588). Other witnesses made a similar point. Dr Helen Wallace, Executive Director of GeneWatch UK, for example, referring to predictive testing for breast cancer genes, told us about “the issue of ‘test now, buy later’”—“There are women deciding whether to take the test now who do not know if

³⁶ http://www.abi.org.uk/BookShop/ResearchReports/080711_2007%20ABI%20Genetic%20Compliance%20Report_FINAL.pdf.

they buy insurance later on in their lives whether at that point the moratorium will have ended and there will be a requirement from the insurance industry to see the results ... Women do worry about the future insurance implications when they consider whether or not to take a test, so you have a specific circumstance where the medical decision that you take may be influenced by knowing whether or not the insurance industry will have access” (Q 361).

- 6.45. In the 2003 Genetics White Paper, the Government made a commitment to work with patient groups and with the industry to ensure a longer-term solution. The Minister for Public Health, Ms Primarolo MP, told us that if the “sunset clause” of the moratorium inadvertently gave an indication that genetic test results might become available at a later state, this would need to be addressed (Q 900).
- 6.46. Stephen Haddrill of the ABI felt that the moratorium was appropriate for current circumstances, although he would not “rule out legislation forever if the circumstances justified it” (Q 580). There were, however, downsides to legislation for the consumer: “legislation does not necessarily work to the benefit of the customer because it may create a kind of unfair level playing field” (Q 580). Currently, an individual can declare the negative results of a genetic test. This may have the effect of reducing premiums which could otherwise have been loaded by family history alone. If information from genetic test results had to be excluded altogether as a loading factor in calculating premiums, individuals might on occasions lose out.
- 6.47. Although we have concluded against specific legislation against genetic discrimination, we accept that action needs to be taken to address a concern that the “sunset clause” of the insurance moratorium may deter individuals from taking genetic tests for fear of not being able to purchase adequate insurance cover after 2014. **We recommend therefore that the Government should negotiate with the Association of British Insurers a new clause in the Code of Practice, Moratorium and Concordat on Genetic Testing and Insurance that prevents insurers from asking for the results of genetic tests which were carried out while the Moratorium was in place.**
- 6.48. **We recommend that the Government, together with the Association of British Insurers, should establish a longer-term agreement about the use of genetic test results for insurance purposes. The moratorium is next due to be revised in 2011. This would provide a good opportunity to take this recommendation further.**
- 6.49. We were recently informed in a letter from Ms Primarolo to the Committee dated 28 April (p 463) that the DoH have decided to disband GAIC, to reassess how to address genetics and insurance in the future and to put in place alternative arrangements.
- 6.50. **Given that the Genetics and Insurance Committee is to be disbanded, we recommend further that the Government should put in place arrangements for monitoring the use of genetic tests for insurance purposes. These arrangements should be part of the longer-term agreement on the use of genetic testing in insurance envisaged in paragraph 6.48 above.**

Direct to Consumer Tests (DCTs)

Value of information derived from DCTs

- 6.51. When using DCTs, the usual arrangement is that an individual provides a saliva sample using a home test kit and a few weeks later the genetic test results are delivered back, often electronically. DCTs are used to test for various genetic features. Some focus on the “social” aspect of genetic testing, such as information about ancestry, while others promote the idea of empowering individuals to take control of their health by learning about their susceptibility to common diseases such as heart disease, diabetes and cancer. Witnesses held wide-ranging views about the value of DCTs.
- 6.52. Professor Bobrow commented on DCTs:
- “If you look at things like deCODEme and the 23andMe website, a lot of their emphasis is on doing your genome so that you can go and find out whether some chap you have met is your second cousin and other things of that nature. It is scientifically valid, it is medically irrelevant and I think it is very much a question of if you want to blow £1,000 on that, it is your business” (Q 260).
- 6.53. Dr Ron Zimmern, Executive Director of the PHG Foundation, thought that that companies should not be prevented from selling DCTs and said that he could “see nothing in a free society to suggest that we should stop people from knowing that they have a two per cent higher risk of asthma or a four per cent lower risk of heart disease”. But, he believed that the type of data derived from DCTs was “totally useless information” (Q 256).
- 6.54. Dr Bale told us that “many of the companies that provide over-the-counter services or direct-to-the-public services steer very well clear of the single-gene, highly penetrative disorders, those that may have a dramatic impact on a person’s health. They look to provide a service which focuses on the weaker associations that might help people to adopt a better diet or maybe to consider the most effective way of stopping smoking or losing weight” (Q 107).
- 6.55. Professor Donnelly spoke positively about DCTs and suggested that they might be the best way to ensure that technology develops to a point where it becomes useful for public healthcare. They would also be beneficial for the small number of individuals who had a high risk of developing a disease due to the additive effects of having several low risk gene markers. He thought that DCTs were the first step to a service that would eventually be incorporated into routine clinical practice. He said:
- “There is a possibility ... for people to be able to say, ‘there’s a whole range of diseases, I know from my genetics that [for] two or three [diseases] I am [at] particular high risk, let me focus on the lifestyle changes which will make a difference to those’. That is the upside and it could have non-trivial consequences in terms of prevention ... In the short term I think the main way in which that information will get to individuals is through the commercial organisations who are offering direct to consumer testing ... Over the long term the picture is clear. It is hard to predict the timescale of this but I think we would all guess that at some time in the future—which might be ten years or more—genetic information will be a routine part of many aspects of medical care” (Q 134).

Risks of DCTs

- 6.56. Some witnesses highlighted their concerns about the consequences of the limited predictive value of DCTs and the inaccuracy on occasions of the advice given to the public. For example, according to Dr Wallace, some companies made claims about future health “which are not substantiated by the scientific evidence”; and she referred to the absence of a “routine system for analysing the clinical utility or validity of the tests” (Q 344).
- 6.57. There is also a worry about the format in which results are delivered. In most cases results are delivered via the Internet. They are therefore received without the supervision of a health professional who would be able put the results in context and offer advice. This could result in unnecessary anxiety and unnecessary further conventional tests. Given that tests for genetically complex diseases cannot be used as a basis for accurate prediction of an individual’s risk of disease, the likely inability of an individual to understand fully the implications of test results in these circumstances, particularly if these are not supported by genetic counselling and advice, is worrying.
- 6.58. Dr Wallace went as far as suggesting that “there is a case for a ban on offering tests directly to the public without medical support” (Q 349) although Alistair Kent, Director of GIG, thought that a ban risked creating “a black market of people operating from unregulated territories” (Q 349). Dr Flinter warned of the implications for the NHS: individuals “take those tests, they are then confused, they may be falsely reassured, they may be falsely worried, they then go and see their GP and the NHS has to try and pick up the pieces” (Q 307). This need for advice has implications for the training of medical students and existing primary care doctors (see Chapter 7).
- 6.59. Of particular concern are reports of companies offering DCTs that purport to be of diagnostic value in certain psychiatric disorders (Q 350), despite, as the ERSC Genomics Network CESAGEN pointed out, the fact that “providing individuals with the likely risk of developing psychiatric disorders is not straightforward, and may not account for the complex interaction of genetic and environmental factors” (p 29).
- 6.60. Recent OECD (Organisation for Economic Co-operation and Development) guidelines recommend that informed consent should be sought prior to customers purchasing a DCT and that genetic counselling should be available prior to, and after, testing.³⁷ Such counselling should be appropriate to the characteristics of the test including its limitations, the potential for harm and the relevance of test results to individuals and their families.
- 6.61. The PHG Foundation and other witnesses suggested that it was possible for companies to be transparent about their work and to provide the public with more evidence on the accuracy of such DCTs. For example, they could place information about the clinical validity and utility of commercially available genetic tests in the public domain, including documentation of the standards to which a laboratory complies, the scientific basis of any tests offered and any consideration of ethical, social or legal issues. This would ensure that consumers could make an informed decision about the value of the test.

Advertising

- 6.62. A number of press reports have recently highlighted the shortcomings of DCTs, including variations between companies as to the interpretation of

³⁷ OECD Guidelines for Quality Assurance in Molecular Genetic Testing, 2007, p 13.

individual test results. The HGC warned of the risk that DCT providers might “undermine the credibility of genomic medicine, by making inflated or misleading claims in marketing their products” (p 163). But, as most of the companies that offer DCTs are based abroad, the Advertising Standards Agency “has no remit to regulate claims made by companies on their own websites” (p 469).

Regulation and guidance

- 6.63. There are no regulations in the UK governing the sale of DCTs. The EU has limited regulation of DCTs under the In Vitro Medical Devices Diagnostic Directive but this extends to regulation of the test kits sent to the customer to produce the saliva sample and, in most cases, not to the tests themselves or to the interpretation of the results. Importantly, under the Directive, genetic tests are classified as being of “low risk” and DCTs are therefore not subject to pre-market assessment. The re-classification of such tests is currently being considered by the European Commission and, in paragraph 3.41 above we have called for them to be re-designated as “medium risk” (see Chapter 3).
- 6.64. Some witnesses favoured a mandatory regulatory code for DCTs, with a requirement to provide medical advice to consumers when delivering test results. In May 2008, the Council of Europe approved the final version of an Additional Protocol to the Convention on Human Rights and Biomedicine on Genetic Testing for Health Purposes: “the Protocol reinforces the OECD Guidelines for Quality Assurance in Genetic Testing, and includes further provisions on clinical utility, medical supervision and genetic counselling. Extensive consideration is given to issues related to consent, and genetic screening programmes have also been addressed”.³⁸
- 6.65. In contrast, in June 2008, the HGC hosted a seminar on DCTs the purpose of which was to explore the merit of a voluntary code of practice in the UK and develop guidelines on good practice and ethical conduct for companies providing DCTs. Dr Flinter reported that “there was pretty general agreement that a code of practice would be helpful; particularly the companies that are providing these tests felt that at the moment it was very unclear to them what the framework was in this country, what the rules and regulations were, and they said that they would welcome a code of practice” (Q 306). Following the seminar, the HGC undertook to develop a draft code.
- 6.66. We favour a voluntary code of practice. It would, we believe, offer safeguards for the consumer by encouraging test providers to be open about the limitations of the tests offered, enabling consumers to make an informed decision about purchasing DCTs. **We support the Human Genetics Commission’s work on developing, with the industry, a voluntary code of practice for selling genetic tests directly to consumers. The code should include a requirement for companies to place in the public domain information about the standards adhered to and the national accreditation status of the company’s laboratory, and the clinical validity and utility of the tests offered. The code should also include guidelines for provision of appropriate pre- and post-test counselling and an ethical code of conduct for the sale of such tests.**

³⁸ <http://www.phgfoundation.org/news/4213/>.

6.67. Further to our recommendation in paragraph 6.8 above, we recommend that the proposed Department of Health web site should set out the following:

- up-to-date information on the national or international accreditation schemes with which the “direct to consumer” test (DCT) laboratories are registered, including the laboratories’ registration status;**
- the quality assurance schemes in which these laboratories participate; and**
- the extent to which the DNA sequence variants used by DCTs for predicting risk of future disease have been validated in genome-wide association studies, and shown in prospective trials to have utility for predictive genetic testing.**

CHAPTER 7: TRAINING, EDUCATION AND WORKFORCE PLANNING

Introduction

- 7.1. As more genetic tests, either for single-gene disorders or for single-gene subtypes of common diseases, are requested by physicians in mainstream specialties, so the need for education and training in genetics, genomics and information technology across a broad cross-section of the healthcare workforce will increase.
- 7.2. Predictive tests for single-gene disorders are carried out principally within Regional Genetics Centres, using the services of clinical geneticists and genetic counsellors. Clinical expertise in this specialty is well-developed and appears to function efficiently. As a result, we do not take the view that a fundamental change in the current practice of clinical genetics is called for at present. But genetic testing outside of the Regional Genetic Centres and outside the specialty of clinical genetics is increasing, and in this area we have concluded that action does need to be taken to meet the educational needs of the wider healthcare workforce. Our recommendation that pathology services should be consolidated will also have training implications (see paragraph 4.47 above).

Genetic testing in common diseases—educational and training needs across the NHS

- 7.3. The Minister for Public Health, Ms Primarolo MP, recognised the significant educational and training needs of non-genetic specialties within the mainstream of the NHS: “developing the genetic competence of both new and existing NHS staff is a huge undertaking ... This is a task that is going to take some time” (Q 886). Dr Sir Mark Walport made a related point:

“The clinical genetics community up to now has largely been trained in the universe of monogenic disorders, single-gene abnormalities, but actually we are moving into a whole new area ... [The trainees] are not all going to be clinical geneticists ... I think it is also about training people who are gastroenterologists with a genetic interest or training respiratory physicians who have an interest in genetics” (QQ 139–41).

- 7.4. With regard to the increasing availability of, and demand for, tests for single-gene subtypes of common disorders, the Foundation for Genomics and Population Health (“the PHG Foundation”) told us that

“the current paradigm of joint clinics involving clinical genetics departments and other specialist departments (cardiology, oncology, ophthalmology etc) is likely to become untenable as the number of available tests for single-gene diseases increases and their cost drops. This means that patients will largely be looked after in the relevant specialty by health professionals knowledgeable in aspects of genetics relevant to that specialty ... This model for integration of genetics into mainstream services requires a substantial investment in education and training” (pp 137–8).

The PHG Foundation also said:

“As genomic tests and information are incorporated into strategies for the routine diagnosis and management of common disease and the estimation of disease risk, many—if not most—health professionals will need to understand how to interpret test results and risk information and to be able to explain the implications to patients. They will also need to be able to make informed judgements about which tests are appropriate for different patients and clinical situations. General practitioners are likely to find themselves in the ‘front line’ of these developments and will need appropriate training” (p 138).

- 7.5. The Human Genetics Commission (HGC) commented that “the implications of genetic test results that are intended to identify susceptibility to disease are, in general, poorly understood, and more information and education at all levels, and in particular an increase in capacity of genetic counselling services, are required ... Ensuring that this information is provided to the patient (and, if appropriate, their family) in a manner that is easily understood and will be remembered is a complex process, requiring specific skills on the part of the clinician involved” (p 159).
- 7.6. Furthermore, as we have already noted (see Chapter 6), we anticipate that the availability of direct to consumer tests (DCTs) is likely to lead to consumers putting increasing demands on general practitioners to advise on the interpretation of results. According to the Wellcome Trust, “there will ... be an increasing number of patients who will seek advice from physicians based on results of DCTs. There is, therefore, an urgent need to ensure that professionals across the health service are educated on genetics and the ethical and social issues it raises” (p 77).

Medical students

- 7.7. Responsibility for setting standards for the knowledge, skills, attitudes and behaviour of UK medical students rests with the General Medical Council (GMC). The GMC publication *Tomorrow's Doctors* sets out the standards for undergraduate medical education in the UK. It states that doctors “must ... have an understanding of the genetic, social and environmental factors that determine disease and the response to treatment” and must understand “the effective and safe use of medicines as a basis for prescribing including ... genetic indicators” (p 517). The current edition of *Tomorrow's Doctors* was published in 2003. It is now under review. In 2003, use of genomic tools in diagnosis and management of common diseases was at a very early stage of development. It is not surprising therefore that these subjects are not mentioned in the generic standards for undergraduate medical education.
- 7.8. **We believe that understanding the use of genomic tools for diagnosis, stratification of patients and choice of treatment in common diseases should form an important part of the undergraduate medical curriculum and urge the General Medical Council to take this aspect of disease management into account in their current review of *Tomorrow's Doctors*.**

Doctors in primary and secondary care

- 7.9. As we have already noted, there is a range of different genetic tests in use in clinical practice. They include predictive tests for single-gene disorders and single-gene subtypes of common diseases, genetic tests for guidance in the

management of established diseases and pharmacogenetic tests to assist drug prescribing. There are also predictive tests for common diseases, which are mostly sold as DCTs, and are as yet of unproven predictive value.

- 7.10. In the NHS, 70 to 80 per cent of genetic tests are ordered directly by physicians, rather than through clinical geneticists (Q 401). If they are to be ordered and interpreted appropriately, the medical workforce must be able to understand their benefit and use. Professor McKenna referred to the challenges in interpreting and delivering the results to general practitioners and specialists other than clinical geneticists. To do this we “are going to have to invest in training and teaching of general practitioners in relation to genetic risk in general” (Q 548).
- 7.11. The Royal College of General Practitioners told us that they “anticipate that genomic medicine will have a major impact on healthcare ... General practice must accept this and [that] ... the potential interventions ... may differ depending on disease state. As with all developments in medical technology, training will need to follow the emerging evidence base, and GPs will have to feel confident to give patients the relevant advice” (p 113). Dr Flinter noted that, in terms of the extent of the requirement to educate other professionals,
- “we are aware that there is a very great need and I suspect at the moment that we are not quite meeting it in that some of our colleagues are beginning to use genetic tests, perhaps not always appropriately, perhaps sometimes requesting a very great long list of tests all at once when it might be more appropriate to go through a staged process and, sometimes asking for a genetic test when actually a simple x-ray might give them the same answer much more cheaply and much more quickly.” (Q 336).
- 7.12. In the 2003 Genetics White Paper, the Government made a commitment to provide funding to improve training and education in genetics. We were told by Dr Rafi that in primary care ten GPs were funded nationally “to promote education and raise awareness of the value of primary care genetics”; he added, “there is a realisation now that GPs and GP trainers who are involved in training GPs locally need to gain genetic knowledge” (Q 194). Research had shown, however, that confidence was low amongst existing GPs in their overall expertise in genetics and their ability to understand enough to be able to order, interpret and counsel on genetic tests appropriately (Q 195). According to the ESRC Genomics Policy and Research Forum, “there will ... be a need not only to increase provision of specialist training, but also to integrate appropriate training in providing genetic health care into the core medical and nursing curriculum” (p 12).
- 7.13. Within secondary care, genetic testing for diagnosis and management of established disease is mostly carried out in pathology laboratories. The Royal College of Pathologists said that both clinical scientists and medically-trained genetic pathologists were needed. The College had therefore explored how genomic and molecular pathology might be brought into the curricula for trainee pathologists and clinical scientists, with a core level of understanding for all pathologists and more advanced training and curricula for specialists. Providing this training on such a large scale had, however, proved difficult: “In the UK a mere five individuals are qualified in the application of genomics to ‘acquired’ disease ... Only one of these is in NHS employment as a genetic pathologist (in Cardiff) ... There are nominally just two Genetic

Pathology Specialist Registrar posts in the UK” (p 110). We were told that a number of junior doctors were interested in training in the specialty in 2007 (p 252), but in the absence of any consultant posts to absorb trainees the Royal College of Pathologists had recently had to conclude that training for the specialty should be suspended. This, the College suggested, was “surely a bizarre development, driven by the reality of short-term economics rather than any logical assessment of future need” (p 110). We have recommended the centralisation of laboratory services. We believe that centralisation could enable such expertise to be consolidated within a centralised “hub” of services for the NHS.

- 7.14. The evidence demonstrates a clear need for training in genomic medicine for doctors in primary and secondary care. As to the appropriate level of training and whether it should be part of the core curricula or form part of specialist training, Paul Streets, Chief Executive of the Postgraduate Medical Education and Training Board (PMETB), did not favour the former. He said that “from our work to-date, we are not receiving a lot of evidence that suggests that genomic medicine is an area of deficit in the current curricula” (Q 817). He continued: “the question we have to look at is the balance between core curricula and specialist content in an area, and ... when there is huge pressure on training doctors, where do we draw the line? ... For us to consider genomic medicine as being a core content of any curricula we need a very strong evidence base because something would have to give” (Q 834).
- 7.15. We need to ensure that genomic medicine education and training for those in primary and secondary care keep pace with the developments in the field. Given that genomic medicine is predicted to have an impact across primary and secondary care, we believe that basic training in genomic medicine should form part of the undergraduate and postgraduate curricula.
- 7.16. **We recommend that the Royal Colleges of Pathologists, Physicians and General Practitioners, after consultation with other relevant bodies, should develop a joint national strategy for undergraduate and postgraduate education and training in genomic medicine, with a clear timetable for implementation.**
- 7.17. **We recommend that the General Medical Council should introduce training in genomic medicine as a core competency in the Certificate of Completion of Training of all junior doctors training in the medical and pathological specialties.**
- 7.18. **We recommend that general practitioners should be trained to be able to provide general advice to patients on the implications of the results of predictive tests for common diseases. Planning how this might be done should be part of the review by the Royal Colleges recommended in paragraph 7.16 above.**
- 7.19. **We recommend that the Postgraduate Deans of Medicine and Medical Education for England, together with the relevant Royal Colleges and the Postgraduate Medical Education and Training Board, reinstate the currently suspended training programme in genetic pathology with a view to reintroducing a viable programme for the intended small number of pathologists (perhaps up to five at any one time) training in this specialty. This training may need to be overseen by both pathologists and clinical geneticists and could lead to the possibility of dual accreditation in genetics and pathology.**

- 7.20. **We also recommend that the Department of Health should work with the Postgraduate Deans of Medicine and the relevant Royal Colleges to reinstate consultant posts in genetic pathology capable of absorbing a sustainable number of registrar training posts.**
- 7.21. Genetics training is needed not only for those who are in training posts but also for those currently in established consultant or general practice posts or in other non-training posts. The ESRC Genomics Network, CESAGEN, referred to a need for adequate resources for continuing professional development (CPD) for existing practitioners (CESAGEN) (p 31). Mr Streets of the PMETB raised the issue of “the extent to which we might want to credential doctors in areas outside of the specialty in which they trained”. He thought that “clinical genetics could well be an area in which we would be looking to credential doctors who may not have done genetics within their training because they may have trained 20 or 30 years ago” (Q 821). Dr Harris also supported genetics as part of CPD: “It seems to me that it would be very good if we could have a [postgraduate education] curriculum that included genetics, or at least have some nucleus of a curriculum that had genetics in it” (Q 823).
- 7.22. **We recommend that genomic medicine is included as a clinical competency within continuing professional development (CPD) for clinicians in primary and secondary care, and that this is recognised by the Royal Colleges which monitor CPD.**

Genetics education for nurses

- 7.23. Nurses play an important role in the delivery of genetic services in the NHS, both in nursing practice and as genetic counsellors within genetics centres. Speaking about the current provision of genetic education for nurses, Professor Maggie Kirk, Leader of the Genomics Policy Unit at the National Genetics Education and Development Centre (NGEDC), described it as “patchy” (p 412). As a result, she said, the NGEDC, with Skills for Health,³⁹ had developed “an education framework that sets out learning outcomes at pre-qualifying levels” which also included a requirement that all nurses at the point of registration “should be able to demonstrate a knowledge and understanding of the utility and limitations of genetic testing and genetic information” (Q 817). (The role of the NGEDC is considered in detail in paragraphs 7.34–7.37 below.) But although the education framework was leading to “a gradual but slow recognition of the relevance of genetics to nursing” that was “being translated into nursing faculty curricula”, the Nursing Team within the NGEDC stressed that “until the NMC [Nursing and Midwifery Council] or other body are able to set detailed standards across the curriculum, some areas that are critical to nursing practice will be sidelined in some HEIs [Higher Education Institutes]” (p 412). The NGEDC suggested that this was due to “a deficit in the current system of allowing pre-registration nursing curricula content and outcomes to be determined in partnership between those delivering, purchasing, providing learning in practice and potential employers” (p 411).
- 7.24. **We therefore urge the Nursing and Midwifery Council to set detailed standards across the curriculum on genetics and genomics for nurses,**

³⁹ “Skills for Health” is the Sector Skills Council for the UK health sector.

both for pre-registration nursing education and as part of post-registration education and practice.

Provision of genetic counsellors

Genetic counselling and single-gene disorders

- 7.25. Genetic counsellors advise and counsel individuals, and their families, affected by single-gene disorders. They work primarily through Regional Genetic Centres. They are in increasing demand. Dr Crolla of the Joint Committee on Medical Genetics (JCMG) said demand was “growing at the rate of the number of tests and scenarios which require interpretation of diagnostic tests” (Q 206). The JCMG also commented that more genetic counsellors needed to be trained because it was “difficult to fill posts” and demand was “increasing year on year” (p 551). The Academy of Medical Sciences (AMS) made a similar point and saw a need for “significant investment ... in training more specialist genetic counsellors” (p 468).
- 7.26. The 2003 Genetics White Paper included a commitment to increase training capacity for genetic counselling and the 2008 Review of the White Paper recorded that training for the first tranche of 50 new genetic counsellors had been completed with a second tranche on the way. None the less, Dr Harris remained of the view that “there are simply not enough genetic counsellors” (Q 838). CESAGEN made the same point: “At present the only advanced training for genetic counsellors in the UK is provided through Masters courses at Manchester and Cardiff Universities ... [which] currently produce c. 25 graduates per annum ... It is clear that such small numbers are insufficient to meet the needs of the public” (p 31).

Genetic counselling and single-gene subtypes of genetically complex diseases

- 7.27. To date, the role of genetic counsellors has not been well defined outside the specialty of clinical genetics. But as genetic testing within mainstream specialties increases, more genetic counsellors will be needed in the general medical setting to provide support to the mainstream specialties—in the same way that they are currently providing support within the specialty of clinical genetics with regard to single-gene disorders. This point was made by the HGC:
- “As the relevance of genetic information moves beyond specialist genetic services ... substantial efforts will need to be made to incorporate this meaningfully into practice, on the one hand, and to absorb a new area of demand for health advice on the other ... A significant amount of this requirement is likely to fall on genetic counsellors to support families in which new disease-predisposing genetic variations are identified and for which tests are developed, and we recognise the need to support additional posts to meet this demand” (p 164).
- 7.28. The JCMG supported this view with specific reference to single-gene causes of breast cancer: “in Poland ... they have screened their population for 3 *BRCA1* mutations and have 3930 carriers—[this will require] a lot of counselling ... If similar screening for genetic risks occurs in the UK we [will] need a lot of trained counsellors to cope” (p 551).
- 7.29. The number of predictive and diagnostic genetic tests for single-gene disorders and for single-gene subtypes of common diseases is increasing (see

paragraphs 2.18–2.19), and these tests are, in turn, increasingly being requested by physicians outside the Regional Genetics Centres. This will undoubtedly have an impact on the NHS. We believe that genetic counsellors would be well placed to meet the challenges created by these developments and, after appropriate training, would be able to apply their skills effectively in discussing with patients and their families the implications of positive genetic tests for single-gene subtypes of common diseases.

- 7.30. Dr Patch, a nurse and genetic counsellor herself, raised another important point about the provision of genetic counsellors when she told us that “there is no statutory professional regulation for genetic counsellors” (Q 336). We note, however, that the voluntary Association of Genetic Nurses and Counsellors plan to submit an application for genetic counsellors to be registered with the Health Professional Council (Q 336).
- 7.31. **We recommend that the Department of Health should review provision of genetic counselling with regard to single-gene disorders, single-gene subtypes of common diseases and common diseases.**
- 7.32. **On the basis of the findings of the review, we recommend further that the Department should take steps to ensure that adequate provision for genetic counselling is made available within the Regional Genetic Centres and also outside the Centres. The review should take account of the increasing need to support non-specialist physicians in giving accurate and informed advice to patients, and their families, following diagnosis of a single-gene subtype of a common disease.**
- 7.33. **The review should also consider the content and scope of training courses for genetic counsellors to ensure that they are able to provide advice on single-gene subtypes of common diseases as well as single-gene disorders; and give consideration to statutory professional regulation of genetic counsellors.**

The role of the National Genetic Education and Development Centre

- 7.34. The National Genetics Education and Development Centre (NGEDC) was set up in Birmingham in 2004, following the 2003 Genetics White Paper, to address the educational needs of health professionals who are not genetic specialists, with the aim of incorporating genetics into core curricula and CPD. The work of the NGEDC includes a series of programmes: to develop resources to support the knowledge base for learners and trainers; to enable workforce competencies to be integrated into job roles and assessment; and to train and support educators and to develop training materials.
- 7.35. We commend the NGEDC for developing valuable educational resources to integrate genetics into training for non-specialists. But, at present, those resources appear to relate principally to single-gene disorders. We were told by NGEDC’s Professor Kirk about several case studies on genetically complex diseases and we acknowledge Professor Kirk’s wish to conduct further work on these diseases (QQ 832 and 843); but we question whether sufficient NGEDC resources can be applied to work on genetically complex diseases or to work on the management of single-gene subtypes of common diseases. We are not convinced that the existing mechanisms within the NGEDC are capable of delivering education and training on the scale that is required.

- 7.36. The NGEDC contract was for five years and the 2008 Review of the 2003 White Paper confirmed funding until August 2009. We were pleased to be told by the Minister for Public Health, Ms Primarolo MP, that the DoH were in discussions with the NGEDC about a new contract that would take “key initiatives through to 2014” (Q 886). However we are concerned that the NGEDC contract is currently being renewed without issues relating to common complex diseases being addressed. Generalising the structures put in place for training relevant to single-gene disorders will not be appropriate for educating the general medical and nursing workforce about the use of genetic tests in the context of common diseases.
- 7.37. **We recommend that the Department of Health reviews the National Genetics Education and Development Centre’s (NGEDC) role, to establish whether it has the appropriate structure and mechanisms in place to provide national leadership in training the general medical and nursing workforce in the practice of genomic medicine and the use of genetic testing in the context of common diseases. The aims of the review should be to establish a national programme of training in genomic medicine for the non-genetic medical and nursing specialties, either under the auspices of the NGEDC or another body.**

Laboratory scientists, modernising scientific careers, workforce planning and re-training

- 7.38. In November 2008, the DoH published a consultation paper entitled *The Future of the Healthcare Science Workforce: Modernising Scientific Careers* (“the workforce review”). It acknowledged that the development and implementation of new diagnostics would require transformation of healthcare science career pathways, supported by new education and training programmes, and the development of new treatment service models. Genetics and molecular science would form part of these new training programmes. Under the workforce review, it was proposed that, during pre-registration (first three to four years), a modular inter-disciplinary approach to training should be introduced.
- 7.39. The JCMG warned that “the impact of this model needs careful scrutiny in the context of the need for greater flexibility in recruitment of scientific staff with appropriate genomic and bioinformatic backgrounds” (p 550). Dr Elles similarly gave a warning: “one problem which we perceive is that the current reform of training for healthcare scientists is to an extent making a straitjacket which I hope will not preclude us from being able to employ within the NHS bioinformatic specialists and turn them to the task of using their skills for healthcare. This is of real concern amongst BSHG [British Society for Human Genetics] members” (Q 264).
- 7.40. Furthermore, scientists and technicians who are already in post may not have the necessary skills to work on new genetic testing technologies. Professor Sir John Bell told us: “we probably have 1,000, maybe 2,000, cytogeneticists. We have a variety of cytopathologists. There may be 3,000 or 4,000 people in the NHS who are doing jobs today that, within a very few years, may be completely redundant. How do you take those people and retrain that workforce?” (Q 467).
- 7.41. Dr Crolla suggested that cytogenetics had been transformed by the introduction of array technologies. But there was now a need to train the current workforce in new skills to match the new technologies:

“We are right at the beginning of the roll-out phase of that technology, and so I think where the investment needs to go is really in the restructuring of the workforce and the retraining of the workforce because people will no longer be looking down microscopes primarily. We must not get rid of that skill, we must hold on to that skill, but they will not be looking down microscopes, they will be sitting in front of PCs doing bioinformatic interpretation and generating other tests as a result of the results that they are getting. That is where I think the investment very much needs to go at this particular point in time” (Q 228).

- 7.42. The 2006 Carter Review of the NHS Pathology Services in England (see Chapter 5) noted that the age profile of the current pathology workforce meant that it would shrink and be unable to sustain services in their present form. The report also suggested that the workforce was not deployed to best effect, and that the gap between the functions and skills of pathology staff was widening due to increasing automation. We believe that our recommendation to centralise laboratory services for molecular pathology (see paragraph 4.47 above) would help to ensure that the most effective use is made of the pathology expertise within the NHS.
- 7.43. **We recommend that, as part of the current review of the healthcare scientific workforce, the Department of Health should consider how members of the current healthcare science workforce can be trained to enable them to use the new genomic technologies and, bearing in mind the recommendation at paragraph 7.47 below, how to develop bioinformatics skills in particular.**

Workforce planning and delivery

- 7.44. Continuing advances in the application of genomic medicine will impact on healthcare services delivery at all levels, with clear implications for workforce planning. We have considered whether the current workforce in the NHS will be able to adapt to the integration of genomic medicine into mainstream specialties.
- 7.45. Dr Zimmern expressed some doubts:

“I have for some years been concerned by the fact that ... nobody is responsible for the manpower planning of genetic epidemiologists, bioinformaticians, biostatisticians, health technology assessment experts and health economists who have an understanding of genomics ... I suggest we do need some idea of how many we need five or ten years down the line, because ... without these people ... who understand genomics we are not going to get that translational shift” (Q 264).

We share Dr Zimmern’s particular concern about recruiting bioinformaticians (see Chapter 5).

- 7.46. As for the most effective way to integrate genomic testing into mainstream specialties, Dr Zimmern suggested that “we might have in every single strategic health authority one public health physician who is skilled in [genomics]” (Q 271). The Royal College of General Practitioners also recognised the need for assistance for primary and secondary healthcare workers:

“In order to disseminate expertise on this rapidly developing technology, it may be necessary to provide community based genetics advisory

services. Involving close collaboration between regional genetics departments and primary care, they will act as a centre where local primary care physicians can access help and information when faced with clinical problems or issues associated with the ethical, legal and social aspects of genome based medicine” (p 113).

- 7.47. The Minister for Public Health, Ms Primarolo MP, referred us to the DoH report entitled *A High Quality Workforce: NHS Next Stage review*, published in June 2008, which sets out the Government’s commitments to planning, education and training for primary and secondary healthcare workers. Following the *A High Quality Workforce* review, the DoH has made a commitment to set up a Centre of Excellence to help organisations within the NHS to respond quickly to changing service requirements and to encourage effective workforce planning. The Centre will be responsible for horizon-scanning and gathering intelligence for workforce planning and will act as an arena for new ideas, gathering and exploiting new information and best practice drawn from national and international experience. **We support the Department of Health’s commitment to establish a Centre of Excellence for national planning and commissioning of workforce supply and demand. We recommend that the Centre is the appropriate body to provide advice to the NHS on what measures can be taken to address the pressing need to recruit bioinformatic expertise into the service.**
- 7.48. We have some concern that the *A High Quality Workforce* review does not identify changes in workforce planning that will be needed in response to the wider use of genetic testing within the NHS or to the development of genomic medicine. **We recommend therefore that the Centre should be asked also to evaluate the workforce planning implications of an expansion of genetic and genomic test services into mainstream specialties.**

CHAPTER 8: LIST OF RECOMMENDATIONS AND CONCLUSIONS

Translating human genomic research into clinical practice (Chapter 3)

The framework for translational research in the UK

- 8.1. Since its creation, the Office for the Strategic Co-ordination of Health Research (OSCHR) has been responsible for the co-ordination of public sector health research in the UK, estimated to be worth £1.7 billion a year by 2010–11. We commend the strategic and co-ordinated approach of OSCHR to translational research and the work of OSCHR in achieving this co-ordination. (paragraph 3.5)

Funding and translational research

- 8.2. We recommend that OSCHR should take the lead in developing a strategic vision for genomic medicine in the UK with a view to ensuring the effective translation of basic and clinical genomic research into clinical practice. (Recommendation 1). This strategic vision should form the basis of a new Government White Paper on genomic medicine which should outline:
- the measures the Department of Health will take in order to facilitate the translation of advances in genomic science into clinical practice;
 - a roadmap for how such developments will be incorporated into the NHS; and
 - proposals for a programme of sustained long-term funding to support such measures (paragraphs 3.11 and 3.12). (Recommendation 2)

Making the conduct of clinical trials less burdensome

- 8.3. We recommend that the Government revises the UK implementation of the EU Clinical Trials Directive, in consultation with the research community, to make it less burdensome for researchers (paragraph 3.17). (Recommendation 3)
- 8.4. If the European Commission decides in favour of a review of the EU Clinical Trials Directive in 2010, we urge the Government to participate fully in discussions in order to ensure that the revised Directive is less burdensome for researchers (paragraph 3.18). (Recommendation 4)

Promoting collaborative translational research

- 8.5. We recommend that the proposed White Paper on genomic medicine (see Recommendation 2) and the Strategic Vision of the Office for the Strategic Co-ordination of Health Research should identify barriers to collaborative working between academia and the pharmaceutical and biotechnology industries, and ways of removing them and also address the need for incentives for collaboration so as to promote translational research in the UK (paragraph 3.26). (Recommendation 5)

Research to demonstrate the clinical utility and validity of genomic tests within the NHS

- 8.6. We recommend that the National Institute for Health Research ring-fence funding, through a specific Health Technology Assessment programme, for

research into the clinical utility and validity of genetic and genomic tests within the NHS (paragraph 3.32). (Recommendation 6)

Evaluation of the clinical utility and validity of genomic tests for use within the NHS

- 8.7. We recommend that the Department of Health extends the remit of the National Institute for Health and Clinical Excellence to include a programme for evaluating the validity, utility and cost-benefits of all new genomic tests for common diseases, including pharmacogenetic tests (paragraph 3.38). (Recommendation 7)

Evaluation and regulation of genetic and genomic tests developed outside of the NHS

- 8.8. We recommend that the Government support the re-classification of genetic tests to “medium risk” in the current review of the EU In Vitro Diagnostic Medical Devices Directive so as to ensure that all genomic tests on the market have been subject to pre-market review before their use either by the consumer directly or by the NHS and private healthcare services (paragraph 3.41). (Recommendation 8)

Incentives to develop stratified uses of medicines

- 8.9. We recommend that the Government continue to work with the pharmaceutical industry to extend value-based pricing for the stratified use of medicines under the PPRS to reflect the value of drugs sold for stratified use and the increasing use of genetic tests to accompany such treatments (paragraph 3.49). (Recommendation 9)
- 8.10. We recommend further that, with regard to medicines for common diseases which are already in use in the NHS, the National Institute for Health Research should target funding to encourage the development of pharmacogenetic tests to stratify use of these medicines in order to improve their efficacy and to reduce the frequency of adverse reactions (paragraph 3.50). (Recommendation 10)

Intellectual property rights

- 8.11. We recommend that the Department for Innovation, Universities and Skills address the issues relating to the management of intellectual property rights within the healthcare sector to improve incentives for stratifying uses of new and existing medicines and for development of pharmacogenetic tests necessary for stratification (paragraph 3.54). (Recommendation 11)

Co-development and evaluation of stratified uses of medicines and genetic tests

- 8.12. We recommend that the Department of Health set out a national strategy on stratified uses of medicines (as part of the proposed White Paper on genomic medicine (Recommendation 2 above)). The purpose underlying this strategy should be to streamline the co-development of stratified uses of medicines and of pharmacogenetic (or other) tests (paragraph 3.57). (Recommendation 12)

Encouraging innovation

- 8.13. We recommend that genomic science is adopted as a key technology platform by the Technology Strategy Board, to drive forward commercial development

and clinical application in this area over the next five years and to maintain the UK lead in genomic medicine (paragraph 3.60). (Recommendation 13)

Implementation and service delivery through the NHS (Chapter 4)

Introduction

- 8.14. We recommend that the Government should reconsider how they will prepare NHS commissioners and providers for the uptake of genomic medicine in the NHS. We also recommend that the National Institute for Health Research, as part of its remit, regularly monitors developments in genomic medicine and their implications for the NHS now and in the future (paragraph 4.6). (Recommendation 14)

Integration of genetics in mainstream practice

- 8.15. We envisage that the proposed White Paper (Recommendation 2 above) will address the operational changes needed as a result of bringing genetic aspects of treatments for common disorders into mainstream clinical specialities (including changes to commissioning arrangements, processes for providing genetic tests within the NHS and arrangements for NHS laboratories to conduct such tests) (paragraph 4.12). (Recommendation 15)

Provision of genetic services in the NHS

- 8.16. We recommend that, on the basis of the monitoring activity of the National Institute for Health Research (see Recommendation 14 above), the Secretary of State for Health should ensure that any necessary NHS operational changes, as a result of a shift in the provision of genomic services to mainstream medicine in the NHS are implemented in the NHS. In order to facilitate the process the Secretary of State should identify whether the NHS is fit to handle such changes and also what new service models are needed if health professionals from other clinical specialties are to take routine responsibility for genomic aspects of healthcare (with referral to specialist genetics services only where necessary) (paragraph 4.19). (Recommendation 16)

Commissioning of genetic services

- 8.17. We recommend that the Department of Health should conduct a review with the aim of establishing appropriate commissioning structures for pharmacogenetic tests, tests for management of genetically complex diseases and tests for diagnosing single-gene subtypes of common diseases, as the use of such tests spreads further into the mainstream NHS (paragraph 4.23). (Recommendation 17)

Commissioning across the NHS

- 8.18. We recommend that the Department of Health should conduct a review of current genetic test service provision within the NHS both for single-gene disorders and for single-gene subtypes of common disorders. This should aim to eliminate what are serious inconsistencies in the provision of genetic services across the NHS (paragraph 4.28). (Recommendation 18)

Uptake of pharmacogenetic tests in the NHS

- 8.19. We recommend that the Department of Health should develop a national set of standards and tariff guidance for the commissioning of genetic tests, taking

into account the recommendations from the second phase of the Carter Review of NHS Pathology Services that there should be tariff guidance for community-based and specialist pathology, particularly relating to DNA and RNA-based genetic tests (paragraph 4.32). (Recommendation 19)

- 8.20. We recommend that the Department of Health should commission the National Institute for Health and Clinical Excellence to issue guidance on the use of genetic tests by non-genetic specialties; and that the NHS should consider the expansion of the “red flag system” to alert healthcare workers to the need to conduct a specific test, in some cases a pharmacogenetic test, before deciding on treatment or prescription (paragraph 4.34). (Recommendation 20)

Provision of laboratory services

- 8.21. We recommend that the Government centralise laboratory services for molecular pathology, including genetic testing, in line with the recommendations of the second phase of the Carter Review of NHS Pathology Services. The aim should be to organise effective laboratory services for molecular pathology and genetics by bringing together the whole range of DNA and RNA-based tests for pathology and medical specialties to ensure that services are cost effective. This would have the potential to free up funds, for example, for the highly specialised technical equipment that is needed (paragraph 4.47). (Recommendation 21)

Computational use of medical and genomic data: medical informatics and bioinformatics (Chapter 5)

Emergence and growth of bioinformatics

- 8.22. We recommend that the Government show leadership on leveraging sustainable funding to the European Bioinformatics Institute (EBI), through the European Research Infrastructure (ESFRI) instrument and through the UK Research Councils. This would reduce the dependence of the EBI on charitable and cyclical funding and allow further growth of the Institute commensurate with the recent growth in genomic databases and the value of the EBI to the UK science base (paragraph 5.9). (Recommendation 22)

Linking informatics with electronic medical records

- 8.23. We recommend the establishment of a new Institute of Biomedical Informatics to address the challenges of handling the linking of medical and genetic information in order to maximize the value of these two unique sources of information. Such an institute would bridge the knowledge, culture and communications gap that currently exists between the expertise in NHS IT systems and bioinformaticians working on genome research. The Institute would guide the NHS in the creation of NHS informatics platforms that will interface with databases containing personal genetic data and with publicly available genome databases (paragraph 5.21). (Recommendation 23)

Developing expertise in bioinformatics

- 8.24. We recommend that the Department of Health should establish a centre for national training in biomedical informatics (within the Institute of Biomedical Informatics) with the aim of providing training that bridges the

gap between health records information technology and genome informatics, and ensuring the delivery of an expert workforce for the NHS (paragraph 5.24). (Recommendation 24)

Immediate informatics needs of NHS Regional Medical Genetics Centres and laboratories

- 8.25. We recommend that the Department of Health should implement a programme of modernisation of computing and information technology within the Regional Genetics Centres and laboratories, including an upgrade in computer hardware, software tools and communication bandwidth, in order to manage current needs of clinical and genome informatics in the Regional Centres (paragraph 5.31). (Recommendation 25)

Public engagement and ethical, social and legal issues (Chapter 6)

Public engagement

- 8.26. We welcome the public engagement activities that have been undertaken so far. We urge the Government and others to continue them, building on the successful dialogue models developed by Sciencewise. We have some concern, however, that these activities have focused primarily on public understanding of single-gene disorders. We urge the Government and other relevant bodies to extend the scope of their public engagement activities to include more detailed consideration of the implications of genetic tests for common complex diseases (paragraph 6.7). (Recommendation 26)
- 8.27. We recommend in particular that the Human Genetics Commission should promote a wide-ranging debate on the ethical and social issues relating to genetic tests and gene associations for genetically complex diseases and how they contrast with genetic tests for single-gene disorders. The debate should aim to improve public understanding of genetic risk and predictive testing in common complex disorders (paragraph 6.7). (Recommendation 27)
- 8.28. We recommend further that the Department of Health should establish a comprehensive and regularly updated public information web site which would review the most recent science on the genetics of common diseases, to help the public to understand and interpret results of genetic tests (paragraph 6.8). (Recommendation 28)

Data-sharing

- 8.29. When developing the “safe havens” for research, recommended by the *Data Sharing Review* report, we encourage the Department of Health to consider adapting the approach developed by UK Biobank for ensuring the protection of personal privacy as an exemplar (paragraph 6.25). (Recommendation 29)

Data Protection Act 1998

- 8.30. The *Data Sharing Review* report suggested that a statutory duty should be put on the Information Commissioner to publish (after consultation) a data-sharing code of practice to remove “the fog of confusion”—which should include sector specific instructions where necessary. It also recommended that where there was a genuine case for removing or modifying an existing legal barrier to data-sharing, “a new statutory fast-track procedure should be

created”. We support these recommendations (paragraph 6.27). (Recommendation 30)

- 8.31. Further, we urge the Information Commissioner to publish a set of clear, feasible and proportionate guidelines, in accordance with the Data Protection Act 1998, specifically for researchers handling genetic data for the purposes of non-personal research in order to reduce the burden of data protection legislation on researchers (paragraph 6.28). (Recommendation 31)
- 8.32. The *Data Sharing Review* report recommended strongly that, due to the need for clarity over when data-sharing is appropriate under the Data Protection Act 1998, although change may be a long way off, the Government should participate “actively and constructively in current and prospective reviews of the European Directive, and assume a leadership role in promoting the reform of European data law”. We agree (paragraph 6.29). (Recommendation 32)
- 8.33. We recommend that, meanwhile, the Government should seek to amend the Data Protection Act 1998 where possible (including amendments to bring into effect Recommendation 31 above) so as to facilitate the conduct of non-personal research using genetic data (paragraph 6.30). (Recommendation 33)

Genetic discrimination

- 8.34. We do not believe that at present there should be specific legislation against genetic discrimination, either in the workplace or generally. But rapid advances in genetic science mean that there is a continuing need to monitor the situation. This should be undertaken by a designated body, possibly the Human Genetics Commission (paragraph 6.40). (Recommendation 34)

Life insurance

- 8.35. We recommend that the Government should negotiate with the Association of British Insurers a new clause in the Code of Practice, Moratorium and Concordat on Genetic Testing and Insurance that prevents insurers from asking for the results of genetic tests which were carried out while the Moratorium was in place (paragraph 6.47). (Recommendation 35)
- 8.36. We recommend that the Government, together with the Association of British Insurers, should establish a longer-term agreement about the use of genetic test results for insurance purposes. The moratorium is next due to be revised in 2011. This would provide a good opportunity to take this recommendation further (paragraph 6.48). (Recommendation 36)
- 8.37. Given that the Genetics and Insurance Committee is to be disbanded, we recommend further that the Government should put in place arrangements for monitoring the use of genetic tests for insurance purposes. These arrangements should be part of the longer-term agreement on the use of genetic testing in insurance envisaged in Recommendation 36 above (paragraph 6.50). (Recommendation 37)

Direct to Consumer Tests (DCTs)

- 8.38. We support the Human Genetics Commission’s work on developing, with the industry, a voluntary code of practice for selling genetic tests directly to consumers. The code should include a requirement for companies to place in the public domain information about the standards adhered to and the

national accreditation status of the company's laboratory, and the clinical validity and utility of the tests offered. The code should also include guidelines for provision of appropriate pre- and post-test counselling and an ethical code of conduct for the sale of such tests (paragraph 6.66). (Recommendation 38)

8.39. Further to Recommendation 28 above, we recommend that the proposed Department of Health web site should set out the following:

- up-to-date information on the national or international accreditation schemes with which the "direct to consumer" test (DCT) laboratories are registered, including the laboratories' registration status;
- the quality assurance schemes in which these laboratories participate; and
- the extent to which the DNA sequence variants used by DCTs for predicting risk of future disease have been validated in the genome-wide association studies, and shown in prospective trials to have utility for predictive genetic testing (paragraph 6.67). (Recommendation 39)

Training, education and workforce planning (Chapter 7)

Medical students

8.40. We believe that understanding the use of genomic tools for diagnosis, stratification of patients and choice of treatment in common diseases should form an important part of the undergraduate medical curriculum and urge the General Medical Council to take this aspect of disease management into account in their current review of *Tomorrow's Doctors* (paragraph 7.8). (Recommendation 40)

Doctors in primary and secondary care

8.41. We recommend that the Royal Colleges of Pathologists, Physicians and General Practitioners, after consultation with other relevant bodies, should develop a joint national strategy for undergraduate and postgraduate education and training in genomic medicine, with a clear timetable for implementation (paragraph 7.16). (Recommendation 41)

8.42. We recommend that the General Medical Council should introduce training in genomic medicine as a core competency in the Certificate of Completion of Training of all junior doctors training in the medical and pathological specialties (paragraph 7.17). (Recommendation 42)

8.43. We recommend that general practitioners should be trained to be able to provide general advice to patients on the implications of the results of predictive tests for common diseases. Planning how this might be done should be part of the review by the Royal Colleges recommended in Recommendation 41 above (paragraph 7.18). (Recommendation 43)

8.44. We recommend that the Postgraduate Deans of Medicine and Medical Education for England, together with the relevant Royal Colleges and the Postgraduate Medical Education and Training Board, reinstate the currently suspended training programme in genetic pathology with a view to reintroducing a viable programme for the intended small number of pathologists (perhaps up to five at any one time) training in this specialty. This training may need to be overseen by both pathologists and clinical

geneticists and could lead to the possibility of dual accreditation in genetics and pathology (paragraph 7.19). (Recommendation 44)

- 8.45. We also recommend that the Department of Health should work with the Postgraduate Deans of Medicine and the relevant Royal Colleges to reinstate consultant posts in genetic pathology capable of absorbing a sustainable number of registrar training posts (paragraph 7.20). (Recommendation 45)
- 8.46. We recommend that genomic medicine is included as a clinical competency within continuing professional development (CPD) for clinicians in primary and secondary care, and that this is recognised by the Royal Colleges which monitor CPD (paragraph 7.22). (Recommendation 46)

Genetic education for Nurses

- 8.47. We urge the Nursing and Midwifery Council to set detailed standards across the curriculum on genetics and genomics for nurses, both for pre-registration nursing education and as part of post-registration education and practice (paragraph 7.24). (Recommendation 47)

Genetic counselling

- 8.48. We recommend that the Department of Health should review provision of genetic counselling with regard to both single-gene disorders, single-gene subtypes of common diseases and common diseases (paragraph 7.31). (Recommendation 48)
- 8.49. On the basis of the findings of the review, we recommend further that the Department should take steps to ensure that adequate provision for genetic counselling is made available within the Regional Genetic Centres and also outside the Centres. The review should take account of the increasing need to support non-specialist physicians in giving accurate and informed advice to patients, and their families, following diagnosis of a single-gene subtype of a common disease (paragraph 7.32). (Recommendation 49)
- 8.50. The review should also consider the content and scope of training courses for genetic counsellors to ensure that they are able to provide advice on single-gene subtypes of common diseases as well as single-gene disorders; and give consideration to statutory professional regulation of genetic counsellors (paragraph 7.33). (Recommendation 50)

National leadership and the role of the NGEDC

- 8.51. We recommend that the Department of Health reviews the National Genetics Education and Development Centre's (NGEDC) role, to establish whether it has the appropriate structure and mechanisms in place to provide national leadership in training the general medical and nursing workforce in the practice of genomic medicine and the use of genetic testing in the context of common diseases. The aims of the review should be to establish a national programme of training in genomic medicine for the non-genetic medical and nursing specialties, either under the auspices of the NGEDC or another body (paragraph 7.37). (Recommendation 51)

Workforce planning

- 8.52. We recommend that, as part of the current review of the healthcare scientific workforce, the Department of Health should consider how members of the

current healthcare science workforce can be trained to enable them to use the new genomic technologies and, bearing in mind Recommendation 53 below, how to develop bioinformatics skills in particular (paragraph 7.43). (Recommendation 52)

8.53. We support the Department of Health's commitment to establish a Centre of Excellence for national planning and commissioning of workforce supply and demand. We recommend that the Centre is the appropriate body to provide advice to the NHS on what measures can be taken to address the pressing need to recruit bioinformatic expertise into the service (paragraph 7.47). (Recommendation 53)

8.54. We recommend that the Centre should be asked also to evaluate the workforce planning implications of an expansion of genetic and genomic test services into mainstream specialties (paragraph 7.48). (Recommendation 54)

APPENDIX 1: MEMBERS AND DECLARATIONS OF INTEREST

Members:

- Lord Broers
- Lord Colwyn
- † Baroness Finlay of Llandaff
- Lord Krebs
- Earl of Northesk
- † Baroness O'Neill of Bengarve
- † Lord Patel (Chairman)
- † Baroness Perry of Southwark
- Lord Sutherland of Houndwood
- † Lord Taverne
- Lord Warner
- † Lord Winston

- † Co-opted Members

Specialist Adviser

Professor Tim Aitman, Professor of Clinical and Molecular Genetics, MRC Clinical Sciences Centre and Imperial College London

Declared Interests:

- Lord Broers
 - Fellow, Academy of Medical Sciences*
 - Member Council, Foundation for Science & Technology*
 - Fellow, Royal Society*
- Lord Colwyn
 - None*
- Baroness Finlay of Llandaff
 - Previously a member of UK Bio-Bank Ethics and Governance Council*
 - Hon Professor at Cardiff University, School of Medicine*
- Lord Krebs
 - None*
- Earl of Northesk
 - None*
- Baroness O'Neill of Bengarve
 - Trustee, Sense About Science*
 - Member Council, Foundation for Science & Technology*
 - Chair of the Nuffield Foundation*
 - Societal Issue Panel EPSRC (member)*
 - Fellow, Academy of Medical Science*
- Lord Patel
 - Chancellor at the University of Dundee*
 - Fellow, Academy of Medical Sciences, Royal Society of Edinburgh*
 - Member, Council, Medical Research Council*
 - Vice President, Life Sciences RSE*
 - Chairman of UKNSN & Stemcell Oversight Committee*
 - Chairman, National Patient Safety Agency*
 - Members, National Quality Board*

Baroness Perry of Southwark

*Was a member of the Select Committee on Stem Cell Research
Chair of Research Governance Committee in Addenbrooke's and Cambridge
University Clinical School
Patron of Alzheimer's Research Trust*

Lord Sutherland of Houndwood

Chair of the Advisory Board of Generation Scotland

Lord Taverne

Chairman, Sense About Science

Lord Warner

None

Lord Winston

*Director, Atazoa Ltd (company involved in transgenic & genomic research)
Trustee Institute of Obstetrics and Gynaecology Trust
Trustee UK Stem Cell Foundation
Professor of Science and Society, Imperial College London (Remunerated)
Member of EPSRC Council*

A full list of Members' interests can be found in the Register of Lords Interests:
<http://www.publications.parliament.uk/pa/ld/ldreg.htm>

Professor Tim Aitman, Specialist Adviser

*Receipt of research grant from Affymetrix inc (2002–2003)
Member of Scientific Advisory Board of London Genetics plc
Member Southern Atherosclerosis Advisory Board Merck, Sharpe & Dohme
Member of the Human Genetics Commission (starting January 2009)
Member of the British Society of Human Genetics
Fellow, Academy of Medical Sciences
Fellow, Royal College of Physicians
Research Collaboration with Life Technologies inc (from May 2009)*

APPENDIX 2: WITNESSES

The following witnesses gave evidence; those marked with * gave oral evidence:

- Academy of Medical Sciences
- * Professor Stephen O’Rahilly
- Advertising Standards Authority
- Almac Group
- Applied Biosystems
- * Mr Kevin McKernan
- Arts and Humanities Research Council
- * Professor John Dupré
- Association for Clinical Cytogenetics (ACC)
- Association of British Insurers
- * Mr Stephen Haddrill
- Association of the British Pharmaceutical Industry (ABPI)
- * Dr Philip Wright
- Association of Medical Research Charities (AMRC)
- AstraZeneca
- Bexley Care Trust
- * Mrs Jacquie Westwood
- BioIndustry Association (BIA)
- Biosciences Federation
- * Professor Martin Bobrow
- Professor Paula Boddington
- Breakthrough Breast Cancer
- Breast Cancer Campaign
- British Association for Applied Nutrition & Nutritional Therapy (BANT)
- British Heart Foundation
- British Society for Ecological Medicine
- British Society for Haematology (BSH)
- British Society for Human Genetics (BSHG)
- * Dr Rob Elles
- British Society for Human Immunology
- * Professor Anthony Brookes, University of Leicester
- Cancer Research UK
- * Professor Herbie Newell
- * Professor Peter Parker

- ★ Professor Finbarr Cotter, Leukaemia Research Fund
- Department of Health (DoH)
- ★ Dr Mark Bale
- ★ Professor Dame Sally Davies
- ★ Ms Diana Paine
- ★ Rt Hon Dawn Primarolo MP
- Department for Innovation, Universities & Skills (DIUS)
- ★ Rt Hon Lord Drayson
- ★ Dr Sivasegaram Manimaaran
- ★ Mr Paul Williams
- Economic & Social Research Council (ESRC)
- Centre for the Social and Economic Aspects of Genomics (Cesagen)
- Centre for Genomics in Society (EGENIS)
- Genomics Forum
- Innogen
- ★ Professor Joyce Tait
- European Bioinformatics Institute (EBI)
- ★ Dr Ewan Birney
- ★ Professor Dame Janet Thornton
- ★ Professor Anne Ferguson-Smith, University of Cambridge
- ★ Professor Amanda Fisher, Imperial College London
- Gen2phen
- General Medical Council (GMC)
- Generation Scotland
- ★ Professor Andrew Morris
- ★ Professor David Porteous
- GeneticHealth
- ★ Mr Brian Whitley
- ★ Dr Paul Jenkins
- Genetic Interest Group (GIC)
- ★ Mr Alastair Kent
- GeneWatch UK
- ★ Dr Helen Wallace
- GenoMed
- Genzyme UK & Ireland
- Professor Maggie Gregory
- ★ Mr Alistair Hall, Medichecks

- ★ Professor Mark Hanson, University of Southampton
- ★ Dr Hilary Harris, General Practitioner
- ★ Mr Michael Harrison, Human Genetics Commission
Harvard Medical School—Partners HealthCare Centre for Genetics and Genomics
The Hastings Center
- ★ Professor Andrew Hattersley, Peninsula Medical School
Health and Safety Executive (HSE)
- ★ Mr Stuart Hogarth, Loughborough University
Human Fertilisation & Embryology Authority
Human Genetics Commission (HGC)
- ★ Dr Frances Flinter
- ★ Dr Christine Patch
- ★ Sir John Sulston
- ★ Illumina
Dr Geoff Smith
Information Commissioner’s Office
Institute of Medical Genetics, Cardiff
- ★ Professor Julian Sampson
- ★ Professor David Johns, Genetics and Insurance Committee (GAIC)
Joint Committee on Medical Genetics (JCMG)
Laboratory of the Government’s Chemist (LGC)
- ★ Mr Thomas Lönnngren, European Medicines Agency (EMA)
- ★ Professor William McKenna, University College London
Medical Research Council (MRC)
- ★ Professor Veronica van Heyningen
- ★ Dr Declan Mulkeen
Medicines and Healthcare products Regulatory Agency (MHRA)
- ★ Mr Richard Gutowski
Professor David Melzer, Peninsula Medical School
- ★ Dr Colin Miles, Biotechnology & Biological Sciences Research Council (BBSRC)
National Genetic Reference Laboratory, Manchester (NGRL)
National Genetic Reference Laboratory, Wessex
National Genetics Education and Development Centre (NGEDC)
National Genetics Education and Development Centre, University of Glamorgan
- ★ Professor Maggie Kirk

- National Institute for Health and Clinical Excellence (NICE)
- * Professor Peter Littlejohns
- Office for Strategic Coordination of Health Research (OSCHR)
- * Professor Sir John Bell
 - * Professor Sir Alex Markham
- Oxford Nanopore Technologies
- * Mr Clive Brown
- Professor Marcus Pembrey
Pfizer
- * Dr Annette Doherty
- PHG Foundation (Foundation for Genomics and Population Health)
- * Dr Ron Zimmern
 - * Professor Munir Pirmohamed, University of Liverpool
 - * Professor Sir Bruce Ponder, Cancer Research UK Cambridge Research Institute
- Research Councils UK (RCUK)
Roche
- * Dr Chris Chamberlain
- Roche, 454 Life Sciences
Roche Applied Science (RAS)
Royal Academy of Engineering
Royal College of General Practitioners
- * Dr Imran Rafi
- Royal College of Pathologists
- * Professor Peter Furness
- Royal College of Physicians
- * Dr John Crolla
- Royal Pharmaceutical Society of Great Britain (RPSGB)
- * Professor James Scott, Imperial College London
- Sheffield Children's NHS Foundation Trust
- * Dr Kári Stefánsson, deCODE Genetics
 - * Mr Paul Streets, Postgraduate Medical Education and Training Board (PMETB)
- Trades Union Congress (TUC)
- * Ms Sarah Veale
 - * Professor Richard Trembath, King's College London
- UK Biobank
- * Professor Rory Collins

- UK Genetic Testing Network
- * Professor Peter Farndon
- UK Intellectual Property Office (UK-IPO)
- University de Montréal
- * Professor Albert Weale, Nuffield Council of Bioethics
- Wellcome Trust
- * Dr Sir Mark Walport
- Wellcome Trust Centre for Human Genetics
- * Professor Peter Donnelly
- Wellcome Trust Sanger Institute (WTSI)
- * Dr Richard Durbin
- Wyeth

APPENDIX 3: CALL FOR EVIDENCE

Call for Evidence: Genomic Medicine

The House of Lords Science and Technology Committee has appointed a sub-committee, chaired by Lord Patel, to look at genomic medicine. The inquiry will provide an assessment of genome technologies and their actual and potential impact on clinical practice in the post-genome era.

The Committee invites evidence on the following questions:

Policy Framework

- Who is in charge of setting and reviewing policy in this area?
- Who provides scientific advice on policy development? Who monitors and anticipates potential scientific developments and their relevance to future policy? How effective are these mechanisms?
- Does the existing regulatory and advisory framework provide for optimal development and translation of new technologies? Are there any regulatory gaps?
- In what way is science and clinical policy decision-making informed by social, ethical and legal considerations?
- How does the framework compare internationally?

Research and Scientific Development

- What is the state of the science? What new developments are there? What is the rate of change?
- Who is taking the lead in the consideration and co-ordination of research and the development of new technologies?
- How effective is the policy and investment framework in supporting research in this area?
- How does research in the UK compare internationally? How much collaboration is there?
- What are the current research priorities?
- What is the role of industry? How much cross-sector collaboration takes place?

Data Use and Interpretation

- Is genomic information published, annotated and presented in a useful way? Should there be a common, public database? If so, who should fund, and have responsibility for, such an initiative?
- Who should provide the framework for optimal evaluation of data and translational opportunities? What policy and funding mechanisms are in place for recognising and utilising potential opportunities?

- Is other medical information recorded in a suitable format to allow optimal interpretation of genomic data? How should genomic data be brought together with other health information?
- What are the implications of the generation and storage of genome data on personal data security and privacy, and on its potential use or abuse in employment and insurance? How should these be addressed?

Translation

- What opportunities are there for diagnostics, therapeutics and prognostics—now and in the future?
- Who is responsible for translation to clinical practice?
- Given the pace of technological advance, how ‘future-proof’ is healthcare investment in this area?
- How does the UK compare to other countries and what lessons can be learnt?
- How meaningful are genetic tests which use genome variation data? What progress has been made in the regulation of such tests?

Biomarkers and Epidemiology

- In what way do genome-wide association studies contribute to the identification of biomarkers? How is the study of genetic factors and biomarkers integrated for translational purposes?
- What impact will genomic data have on data emerging from projects such as UK Biobank, Generation Scotland and other biobanks?

Use of genomic information in a healthcare setting

- What impact will genomic information have on the classification of disease? How will it affect disease aetiology and diagnostic labels?
- How useful will genomic information be as part of individualised medical advice? What provisions are there for ensuring that the individual will be able to understand and manage genomic information, uncertainty and risk?
- Should there be a regulatory code (mandatory or voluntary) covering the provision of this advice?
- What are the implications of developments in genomic technologies for the training of medical specialists and other health professionals? Are there any gaps that need addressing? What is the assessment and planning for future needs in capacity?

APPENDIX 4: SEMINAR HELD AT THE HOUSE OF LORDS

19 March 2008

A seminar was organised at the House of Lords to give the Committee an opportunity to discuss the Genomic Medicine Inquiry with academic experts, representatives from the Department of Health, the Department of Innovation University and Skills, the Department for Business Enterprise and Regulatory Reform and other organisations.

Members of the Sub-Committee present were: Lord Broers, Lord Colwyn, Baroness Finlay of Llandaff, Earl of Northesk, Baroness O'Neill of Bengarve, Lord Patel (Chairman), Baroness Perry of Southwark, Lord Sutherland of Houndwood, Lord Taverne and Lord Warner. In attendance were: Professor Tim Aitman (Specialist Adviser), Elisa Rubio (Clerk), Christine Salmon (Clerk) and Dr Cathleen Schulte (Committee Specialist).

The speakers were: Professor Tim Aitman (Specialist Adviser to the Committee; Professor of Clinical and Molecular Genetics, MRC Clinical Sciences Centre and Imperial College London); Professor Sir John Bell (Regius Professor of Medicine, Oxford University; President, Academy of Medical Sciences; and Chair, Office for Strategic Coordination of Health Research (OSCHR)); Dr Ros Eeles (Reader in Clinical Cancer Genetics, Institute of Cancer Research); Professor Wolf Reik (Associate Director of the Babraham Institute in Cambridge; Professor of Epigenetics, University of Cambridge); Professor Peter Donnelly (Professor of Statistical Science and Director of the Wellcome Trust Centre for Human Genetics, Oxford; and Chair, Wellcome Trust Case Control Consortium); Dr Ewan Birney (European Bioinformatics Institute); Professor Graeme Laurie (Professor of Jurisprudence, University of Edinburgh; and Chairman, Ethics and Governance Council UK Biobank).

Other participants were: Dr Adrian Pugh (Strategy and Policy Support Officer, Biotechnology and Biological Sciences Research Council); Dr Steve Sturdy (Deputy Director, Genomics Policy and Research Forum, Economic and Social Research Council); Nancy Lee (Policy Adviser, Strategic Planning and Policy Unit, Wellcome Trust); Yvonne Gritschneider (Policy Officer, British Heart Foundation); Dr Louise Jones (Experimental Cancer Medicine, Cancer Research UK); Dr Peter Sneddon (Head of R&D Programmes, National Institute for Health Research); Professor Peter Furness (Vice-President, Royal College of Pathologists); Professor Peter Farndon (Consultant Clinical Geneticist; and Director, UK Genetic Testing Network); Dr Neil Ebanzer (Policy Manager, NHS Genetics Team, Department of Health); Diana Paine (Team Leader, NHS Genetics Team, Department of Health); Michael Davies (Research Councils Unit, Department of Innovation, Universities and Skills); Dr David Griffiths-Johnson (Bioscience Unit, Department for Business Enterprise and Regulatory Reform); Dr Frances Flinter (Clinical Director and Consultant Clinical Geneticist at Guy's and St Thomas' NHS Foundation Trust; and Commissioner at the Human Genetic Commission); Dr Rob Elles (Chairman of the British Society of Human Genetics; and Director of Molecular Genetics, National Genetics Reference Laboratory and Regional Molecular Genetics Service); Professor Richard Trembath (Head, Division of Medical Genetics, Kings College London); Professor Sandy Thomas (Head, Foresight Unit in GO-Science); Dr Helen Munn (Director, Medical Science Policy, Academy of Medical Sciences); Dr Sarah Bunn (Biology and Health Parliamentary Adviser, Parliamentary Office of Science and

Technology); Dr Hilary Burton (Programme Director, PHG Foundation); Dr Ian Frayling (Consultant in Genetic Pathology, University Hospital of Wales); and Dr John Crolla (Chair, Joint Committee on Medical Genetics).

Introduction to genetics and genomic medicine (Professor Tim Aitman)

Professor Aitman opened with a number of definitions. Genetics was the science of heredity and variation in living organisms, with the basic units of inheritance being called genes; and genomics was the study of an organism's entire genome, its whole hereditary information encoded in the DNA on the organism's chromosomes. The word genome derived from the fusion of "gene" and "chromosome".

There were two broad classes of genetic diseases:

- Mendelian diseases are rare diseases caused primarily by defects in a single gene. Examples include cystic fibrosis, haemophilia and Huntington's disease.
- Genetically complex diseases are more common, with a prevalence of up to 30 percent, and are caused by an interaction between genes and the environment. Examples include coronary heart disease, diabetes, obesity, arthritis and common cancers such as breast and prostate cancer.

Genome technologies had seen great advances in recent years, driven in part by large-scale sequencing projects such as the mapping and sequencing of the human genome. Automated DNA sequencing and high throughput genotyping technologies detected and measured sequence variations in the genome which were usually inherited. DNA microarrays were a powerful method of genomic investigation that allowed the expression of all the genes in the genome (20,000 – 30,000) to be measured in a single experiment. Use of DNA microarrays had led to new and more precise molecular classifications of disease states that were suggesting innovative treatment strategies for a range of diseases.

New genome technologies had dramatically advanced our ability to understand the inherited basis of common human diseases. New generation DNA sequencers introduced at the end of 2005 had led to spectacular increases in the quantity of data output, as they were able to sequence 1,000 million base pairs in a single run, often in a few hours. Similar increases in genotyping capacity had, in just the last two years, led to a revolution in identifying genes associated with common diseases. These technology advances had enabled a new strategic approach, the genome-wide association study, to be carried out. After the first publications of this type of study towards the end of 2006, there had been a flood of publications during 2007. Between 2005 and 2007 around 100 new genes for common diseases such as diabetes, arthritis and cancer were identified. By the end of 2008 it was predicted that another 400 will have been found.

Professor Aitman concluded that a new "genomic information" era had arrived and was increasingly touching healthcare professionals and the public. However, a number of questions arose: how clinically useful and reliable was genomic information in predicting and preventing common diseases? Were we ready to put genomic information to good use? Were the costs justifiable and affordable? And how should the UK take advantage of these potential advances in healthcare?

Translation of genomics into healthcare (Professor Sir John Bell)

Professor Sir John Bell described the impact of genomics on healthcare in two main areas: diagnostics and therapeutics. Advances in therapeutics were being driven by an increasing knowledge of disease genes and mechanisms and through an enhanced ability to predict drug efficacy and side effects. These advances were mostly at an early stage of development. On the other hand, advances in diagnostic testing using genomic tools were having a profound impact on clinical decision making and many new tests had already reached clinical practice.

Molecular diagnostic tests had led to an improved ability to stratify common diseases, to predict risk of future disease and to use drugs more effectively. For example, tests in cancer patients that use DNA microarrays to measure gene expression profiles and gene copy number could identify patient subgroups with very different prognostic outcomes, and treatment could be tailored to these different prognostic groups. This may not only improve treatment outcomes, but may also lead to more efficient use of existing therapies. The newly identified genes for common diseases could also be used to test healthy individuals for their risk of developing a range of common diseases, although these genes mostly have a small effect on disease susceptibility and the clinical utility of these tests in healthy subjects at present remained to be defined. In most cases it was anticipated that the range of new tests would be used in conjunction with existing means of risk prediction and disease classification. However in some specific diagnostic areas, such as the use of cytology screening for cervical cancer, molecular diagnostics were rapidly gaining ground as the method of first choice and may supersede conventional screening tests.

The new discipline of pharmacogenetics aimed to personalise drug treatment so as to optimise drug efficacy and to reduce the frequency of adverse drug reactions. It was well known that most drugs worked effectively in a minority of patients, and physicians frequently relied on a trial and error approach to prescribing. One way of improving drug efficacy was by using genetic tests to distinguish responders and non-responders, and examples existed where this approach had reached routine practice, for example in the use of Gleevec in chronic myeloid leukaemia and herceptin in breast cancer. Such genetic tests could be the most effective way of establishing personalised treatment programmes, and by increasing the proportion of patients who responded to a particular therapy may also be effective in reducing overall drug costs.

Sir John identified five main obstacles to translation of genetic testing more widely into the NHS:

- the hospital organisational structure, which was currently not set up to use genetic testing across medical specialties and different pathological disciplines;
- an increasing innovation gap in the NHS between new tests becoming available and their delivery into clinical practice;
- the commissioning system at the local level, which was not oriented to the introduction of new diagnostic tests and methods;
- the need to demonstrate clinical utility of new tests—not only must tests be reliable and accurate, but there should be evidence of clinical benefit and need; and
- costs.

These obstacles to translation would require innovative solutions. For example, Sir John described the establishment of a central Molecular Pathology laboratory in Oxford, where genetic testing was carried out for all the conventional pathological specialties. The requirement to demonstrate clinical utility of new diagnostic tests posed significant regulatory challenges, as present regulatory structures were not suited to adapting to rapid changes in diagnostic technologies. New regulatory bodies and procedures may therefore be required.

The Office for Strategic Coordination of Health Research (OSCHR), chaired by Sir John, was a body set up by the Government to oversee the translational agenda undertaken by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR). The MRC undertook research leading to the discovery of new diagnostics, but responsibility for proof of concept and clinical utility trials rested with NIHR.

In conclusion, the likely impact of genomics on healthcare was very large but a steady hand and clear vision would be required to use genomics to deliver clinically useful and cost-effective advances in healthcare across the NHS.

Genomics in cancer (Dr Ros Eeles)

There were about 300,000 cases of cancer per annum in the UK, of which approximately 16 percent were breast cancer, 13 percent lung cancer, 13 percent bowel cancer and 12 percent prostate cancer.

There were two types of common alterations in genome sequence that were relevant to cancer susceptibility: somatic changes, which took place in cancer cells only and were not heritable; and germline alterations, which were found in sperm and egg DNA, and were passed down from generation to generation. Major progress was being made in cancer care by genomic profiling and sequencing. The Cancer Genome Project which was being undertaken at the Wellcome Trust Sanger Institute was looking at genomic changes in cancer cells to determine patterns of DNA sequence changes that related to cancer diagnosis and treatment outcome. Gene expression microarrays were useful molecular tools to refine pathological diagnosis, determine prognosis, guide treatment and predict response to treatment. Dr Eeles gave two examples of ongoing genomic clinical trials in cancer care: MINDACT (Microarray In Node-negative Disease may Avoid Chemotherapy Trial) which was using microarray data in tumour cells in breast cancer to ascertain whether chemotherapy could be avoided; and a second study, being carried out in the USA, that was investigating how the genetic make-up of patients determined response to hormone therapy in prostate cancer patients.

Dr Eeles went on to talk about the genetic alterations that were having an impact on public health and may lead to new screening and treatment programmes.

There were several different types of DNA sequence alterations that individuals could inherit, and examples were cited for the breast cancer predisposition genes. Alterations in the *BRCA1* and *BRCA2* genes were rare but they convey a high cancer risk and a woman with alterations in one of these genes was approximately ten times more likely to develop breast cancer in her lifetime than women without such alterations. *BRCA1* and *BRCA2* were therefore known as high risk or “high penetrance” genes. By contrast, alterations in the *CASP8* and *FGFR2* genes were much more common but the relative risk of developing breast cancer for carriers of these genes was very small. These genes were therefore of “low penetrance”. It was of interest that prostate cancer patients who had alterations in the *BRCA2* gene were twice as likely to die from the disease as those who did not have *BRCA2* gene

alterations, suggesting a common role for *BRCA2* in breast and prostate cancer. It cost £962 to screen for mutations in the *BRCA1* and *BRCA2* genes in NHS Genetics laboratories. Tests for alterations in the *CASP8* and *FGFR2* genes were not currently available on the NHS, but could be bought by the public directly from genomic screening companies as part of a genomic screen that currently costs around £500. As the cost of sequencing and whole genome profiling had dramatically reduced, and continued to do so, it was likely that DNA sequence alterations would be detectable more quickly and cheaply in the future, permitting wider use of targeted screening of high risk groups.

In the past two years, there had been an explosion in genome-wide association studies in cancer that had identified low penetrance genes for a wide range of cancers and other diseases. Recently published studies covered breast, colon and prostate cancer and there were on-going studies in lung cancer, lymphoma, pancreatic, ovarian and testis cancer. However it was uncertain how these discoveries could be applied to the clinic, and it was also unknown how interaction of these low penetrance genes with the environment may impact on disease susceptibility. Dr Eeles and others had recently applied for a grant from the EU to investigate these issues.

One potential application of genomic testing was to guide the targeting of expensive screening tests to subsets of the population who may have a higher than average risk of developing a particular disease. For example, identification of individuals from the general population who carried a significant alteration in the *BRCA1* gene, who therefore have a greatly increased risk of developing breast cancer, could be used to target individuals for screening with magnetic resonance imaging which was more expensive and time-consuming, but also more sensitive than mammography.

Dr Eeles enumerated a number of issues to be considered at the clinical interface in efforts to bring genomic advances into health care. More research needed to be undertaken in risk prediction and gene-environment interaction. On the other hand, ongoing research should not stop clinical implementation in cases of clear benefit. Access to genetic testing by specialists and GPs needed to be clarified and the public and health professionals needed to be educated on the potential value and implications of genetic tests.

Dr Eeles finished with a word of caution, from herself and colleagues at the Cancer Genetics Group, against over-regulation of companies who sold genetic tests direct to the public. She offered the view that, at present, the information that these companies offered was of little value to consumers or healthcare professionals but that, with further research, such information would become useful in predicting disease in the future. Over-regulation may impair or stop progress towards this objective.

Epigenetic factors and their importance in genome-wide association studies (Professor Wolf Reik)

Professor Reik posed the question “who do we think we are?” The answer should be in our DNA. All the genes in the human genome were known but they were not used all at the same time. Different sets of genes were switched on or off during development of an organism to form different tissues and organs. Epigenetics was defined as gene expression states that were stable over rounds of cell division, but did not involve changes in the underlying DNA sequence of the organism.

Epigenetic modifications generally turned genes on or off, thus allowing or preventing the gene from being used to make a protein. As a result cells would differ in their protein content giving them different functions and forming diverse organs such as the brain and heart. Epigenetic factors started working as soon as the embryo was formed.

There were probably hundreds of epigenomes and what was really important was that epigenomes were not only influenced by genetic factors but also by the environment, nutrition, multigenerational inheritance and by pregnancy. All these factors played a major role in setting the shape that the multiple epigenomes had. There were many associations beginning to emerge between epigenetic marking and common diseases. Epigenetic factors had major influence in cancer, it was suspected they had a major role in obesity and psychiatric disorders and they were of key importance in the use of stem cell therapies. There were multiple examples of environmental influences resulting in altered epigenomes and possible disease such as maternal grooming resulting in anxiety and altered methylation of glucocorticoid receptors in children.

The challenge that we were facing was: if there were hundreds of epigenomes, how could we determine what they were? Given that the sequencing of a single genome took many years and vast sums of money, this may seem like an impossible task. However, next generation sequencing technology would make this a reality very soon.

The UK was a World leader in epigenetics research together with Japan and the US. However, we needed to build capability in epigenomics and combine genetic mapping with epigenome sequencing, as genetic variants interacted with epigenetic variants and the nature of this relationship was largely unexplored.

Population genomics and insights into the genetics of common diseases (Professor Peter Donnelly)

Professor Donnelly illustrated the pace of discovery of genes associated with common diseases by explaining that until October 2006 the number of common genetic variants that we knew reliably to be associated with common diseases was very low. At the end of 2006 the first results of a new generation of “genome-wide association studies” started to be reported. While in 2005 only a handful of common genetic variants were known reliably to be associated with common diseases, such as diabetes and macular degeneration, in the year up to September 2007 more than 50 were discovered that contributed susceptibility to a range of diseases including coronary heart disease, prostate cancer and inflammatory bowel disease. The pace of discovery was likely to continue to increase, owing to better ways of analysing the data generated in genome-wide association studies, to new and larger studies being carried out across a range of common diseases, and to finding ways of combining data from different studies.

Several factors had driven the current explosion of genetic variants associated with common diseases. At the beginning of the decade, the Human Genome Project provided a map where scientists could start placing variants. The SNP Consortium was a private-public partnership which aimed at finding single nucleotide polymorphisms (SNPs)—letters in the genetic code that varied between different human chromosomes. The International HapMap Project, a huge international collaboration, then looked at the correlation of patterns of genetic variation in different human populations. The most recent advance, and a direct cause of the recent explosion of data, was the ability to read as many as a million letters of the

genetic code in different positions in an individual's genome in a single chip experiment.

The Wellcome Trust Case Control Consortium (WTCCC) undertook genome-wide association studies in seven different common diseases, comparing the pattern of SNPs across the genome of 2000 people with each disease with the pattern in 3000 healthy people in order to find sequence variants associated with predisposition to each disease. This was the largest of the first generation of genome-wide association studies and led to the discovery and confirmation of more than 30 novel disease associations to date, and around 20 more when combining data with other studies. After decades of largely unsuccessful efforts, scientists had finally found a method which was robust in terms of finding genes associated with common diseases that could then be reliably reproduced in other samples. Whilst it was agreed that these sequence variants were robust markers of disease risk, at present it was not known how most of these variants functioned to increase the risk of disease development. Understanding the mechanism by which these SNPs underlie disease risk was the subject of major ongoing global research efforts.

Relative risk was a measure used to describe how much a person's risk of disease was increased by a particular genetic variant. For virtually all the loci found from association studies, the estimated effect sizes were modest in some cases and small in most cases. This supported the view that many genes were likely to play a role in inherited susceptibility to common diseases and that environmental risk factors, such as lifestyle and environmental exposures, also had a major part to play. However, since scientists estimated the effect sizes of the measured genetic markers rather than the causative DNA change itself, it was likely that the effect sizes had been underestimated. This underestimation had consequences in the ability to use relative risk in disease prediction, since relative risks at particular loci may increase once the causative variants themselves have been identified.

It was also important to appreciate that although the relative risk conferred by individual markers was not great, combining information from many genetic markers and from conventional measures of disease risk may identify segments of the population who were at very significantly increased risk of individual diseases. While most individuals would have an average risk for most diseases almost everyone would be at very high risk for some diseases. Professor Donnelly estimated that 95 percent of people would be in the top five percent of genetic risk for at least one disease, 40 percent of people would be in the top one percent of genetic risk for at least one disease and five percent of people would be in the top 0.1 percent of genetic risk for at least one disease.

Professor Donnelly drew two main conclusions. First, at a time when the new markers of common diseases had only very recently been discovered, it was true that reliable disease predictions were not possible, and therefore the clinical utility of this new knowledge was uncertain. Nonetheless this may change as we learn more about genetic variants, and when we were able to predict disease for a range of, say, 50 diseases, each individual was likely to be at a high relative risk for a few of those diseases. It may therefore be useful to think of genomic tests, including those sold "direct to consumers", as a tool for individuals to identify the diseases for which they had the highest genetic risk, based on current knowledge. However, in the context of tests sold direct to consumers, if the information were to be of value it was essential that suppliers of the tests were able to carry out genomic tests accurately, and that they explained to their prospective customers the pitfalls and limitations of such tests, as well as the potential benefits.

The second conclusion was that while there was ongoing uncertainty regarding the clinical utility of genomic tests for disease prediction, the most important outcome of this new research may be in advancing understanding of the molecular causes of disease development, which was already providing new leads for ways in which to prevent and treat common diseases.

Organisation and analysis of genomic data (Dr Ewan Birney)

Dr Birney explained the key components that would be required for an information infrastructure for Genomic Medicine: a fundamental biology reference, patient-related information and clinical knowledge. He further identified four basic principles for a successful informatics infrastructure: (1) research infrastructures were best constructed openly and should be coordinated on a national and international level. The human genome was an example of open infrastructure which was extensively used worldwide; (2) patient information was not appropriate for public release; (3) informatics hardware costs halved approximately every two years while the sequencing capacity doubled every year; and (4) like most IT projects, an information infrastructure for Genomic Medicine would require complex management with the added difficulty that most informatics developers were not trained in genetics and therefore the pool of people with the appropriate expertise was very small.

With regards to the fundamental biology reference, Dr Birney mentioned that the reference genome sequence would be updated approximately every two years with minor updates (less than one percent of the sequence), but the updated regions would be disproportionately enriched for areas of interesting biology and likely disease-associated regions. The reference gene and biology resource were growing in stability and utility and were also making advances in non-protein coding genes, but the dynamic nature of these databases would necessitate a similarly dynamic structure for clinical genomic databases, capable of adapting to advancing knowledge. Dr Birney expressed the view that information infrastructure in genomics was at present well funded, though this needed constant investment from research councils and charities and was coordinated worldwide.

By contrast, it was not yet clear how patient information would be coordinated, assuming, for example, that we might have the capacity to sequence the entire population's genomes in five to ten years. This raised many questions: how should patient data be coordinated with the reference genome? How would raw genomic data be archived to allow for periodic recalling, for example if technology advances yielded new information? Should genomic information be part of SPINE (NHS care records system)? How would genomic information be delivered in a useful way to practising clinicians? Dr Birney suggested that useful answers might emerge from comparison and dialogue with pilot projects such as the informatics components of the 1,000 genomes project

Although resequencing projects have large storage requirements, Dr Birney did not believe that disc space would pose a problem for storage of genomic information compared to other high density medically important datasets. Dr Birney compared the disc space required for storing genomic information to that needed to store a complex X-Ray digitally, and far less space than that needed to store a CT scan. However, the challenge in storing genomic information about patients was that the software and the delivery would need to be custom made.

Finally, in resolving how to construct a usable "clinical knowledge base" Dr Birney pointed to a number of existing projects that could already provide partial or prototype solutions. These include dbGAP/EGA and the EU-funded Gen2Phen

projects which linked genotype to phenotype; the Online Mendelian Inheritance in Man database (OMIM) which provided clinician-friendly data on genes and mutations underlying Mendelian (single-gene) disorders; and a growing number of locus-specific and in-house databases.

Governance of genomic data (Professor Graeme Laurie)

Professor Laurie identified six challenges for optimal governance of genomic data: consent, confidentiality, public confidence, commercialisation, collaboration and counselling.

Discussions on governance and genetics had taken place over a long period. One of the first reports to be published was by the Nuffield Council in 1993 titled “Genetic Screening: Ethical Issues”. The Human Genetics Commission (HGC) also reported on a regular basis. We all share the same basic human genome although each of us had individual variations that distinguish us from other people. This highlighted our common interest in the fruits of medically-based genetics research and a common public good that could be achieved by optimum governance of genomic information. However, an underlying assumption was that genetic information was unique to an individual but that must not belie the fact that there is a range of private and public interests at stake.

Consent had become the dominant paradigm in governance of biomedical research, but there was a risk of over-dependency on consent. Professor Laurie expressed the view that consent was neither necessary nor sufficient to protect individual interests and over-reliance on consent may serve as an obstacle to important public interests.

There had been much recent discussion in the UK around confidentiality and privacy. Protection of privacy under the law in the UK was piecemeal. The Data Protection Act only protected an individual’s information when the individual could be identified: anonymised information was not protected. Common law covered certain aspects of privacy such as doctor-patient confidentiality, and the Human Rights Act consolidated these protections. However, an individual’s privacy was not an absolute right: there were exceptions when information could be processed to promote public interests. Professor Laurie raised the question whether there were sufficient flexibilities within existing law to promote such public interests while adequately protecting the public interest in individual privacy.

Security of genetic information was a serious public concern. There may be informatics solutions to providing security but these would not necessarily provide complete answers and did not address all of the public expectations with respect to their privacy. It was interesting to note how limited the current law was in protecting the interests of others, such as family members, especially when the genetic information of one individual may have direct consequences for other family members. Another important security issue was access to information: who had access, why, and, particularly, where?

Public confidence in governance and government was fundamental to progress in genomic medicine and genomic research. The UK Biobank Ethics & Governance Council was set up to oversee the legal and ethical implications of the UK Biobank project and to monitor and advise the funders of the project on these issues. The project had already recruited 100,000 participants of the projected 500,000 and broad consent was given by the participants based on robust confidentiality and a transparent ethics and governance framework. There were ongoing questions

about data access in the future and commercialisation of the data which were incompletely resolved at this stage. It is the role of the Ethics and Governance Council to advise on these and other future developments.

With regards to commercialisation, Professor Laurie highlighted the need for transparent access policies in today's world of private investment in order to achieve fair, just and equitable sharing. Open access may work for certain aspects of research but not for others such as development of new drugs, or other discoveries and inventions that may be commercially viable. It may also carry unacceptable risks to individual privacy.

The UK Biobank was seen as setting the gold standard in collaboration. Professor Laurie also referred to the Public Population Project in Genomics (P3G), an international collaboration which aimed to promote scientific interoperability between biobanks to ensure maximisation of scientific data generated, and to facilitate scientific interoperability and data sharing. The P3G project was also considering the governance regimes in different biobanks, asking whether harmonisation of heterogeneous governance and data protection regimes could facilitate progress and advance global interests in genomics.

Professor Laurie ended by stating that optimal governance was not yet with us. There were many examples of "self-help" good practice such as UK Biobank and Generation Scotland. He suggested that, in some cases, formal legal and ethical regimes were too rigid and perhaps did not strike the best balance of interests. There was an additional problem of a lack of regulatory "joined-up-ness" across the various elements of innovation trajectories, from initial conception through research, development, market and beyond.

Discussion

Discussion took place in which Committee members, speakers and other attendees participated.

One participant gave the view that discussions on clinical management run the risk of being hijacked by genetic enthusiasts who overemphasised the importance of genetic factors and genetic testing. Other conventional and possibly more important factors in disease aetiology and management, such as lifestyle, social factors and family history could therefore be disregarded. In relation to drug therapy and pharmacogenetics, the current trial and error approach to prescribing might be equally cost effective in predicting efficacy and side effects as genetic testing, which may only lead to relatively small advances in clinical practice. Some participants agreed that the science was ahead of clinical practice.

A commonly expressed view was that new genetic tests were potentially of value but required evaluation before being brought into mainstream clinical practice. The importance of assessing the utility of genetic tests was highlighted by several participants, though it was pointed out that it was not clear who would fund research into clinical utility, as NIHR (National Institute of Health Research) excluded funding of laboratory-based research projects.

The issue of the practical end of implementation was raised. Up until the present, almost all genetic testing had been carried out in Regional Genetics Centres, and most genetic tests have been for single-gene disorders. Now that genetic tests were being introduced for more common diseases, the Regional Genetics Centres would not have the capacity to carry out all new tests. However, carrying out the test represented perhaps only half the cost of the test, the remainder including genetic counselling. Another participant concurred with the need for genetic testing to

expand beyond Regional Genetics laboratories, but pointed out that there had been years of discussion about setting up molecular pathology laboratories, but this was prevented by “silo budgeting” to individual specialty laboratories. Data on new tests needed to be evaluated in a timely manner, and to achieve this, a new structure would be required to implement “health genomics”.

The NHS was not set up to take on board the changes that were associated with the move of genetic testing into the mainstream medical specialties. At present, introduction of genetic testing into mainstream specialties was piecemeal and reliant on presentation of data on new tests to local funders who did not have the necessary expertise or knowledge to make informed decisions on these matters. A particular concern was the lack of genetics expertise in Public Health, which was largely focussed on environmental, rather than genetic issues.

It was pointed out that new, rolling funds would be required to pay for updates to genetic testing equipment funded under the White Paper “Our inheritance, our future” of 2003, as such equipment only had a lifespan of four to five years. The need to fund translational research for evaluating new tests and bringing them into service was also highlighted. The funding model that was in place in Wales for these activities was commended.

The procedure for bringing new genetic tests for single-gene disorders into NHS use was described. The UKGTN had already approved 173 such tests. A similar mechanism needed to be introduced for generating data on the utility of new genetic tests such as single nucleotide polymorphisms associated with common diseases and pharmacogenetic tests of drug utility and responsiveness. No solution was currently in place to meet this need. Attention was also drawn to the need for education of healthcare professionals on genetic testing and commented that the National Genetics Education and Development Centre had focussed to date on surveying attitudes of health professionals and on learning outcomes. However undergraduates needed to develop a concept map of where genetics fitted into healthcare so that they were prepared with appropriate knowledge when they started to practice.

With regards to IT, more money needed to be invested in informatics and more IT experts would be required to set up and manage genomics information systems if genomics was to be useful in healthcare.

On the question on the desirability of “genomicising” medicine arose, it was regarded as inevitable that much of the medical profession would not like to move towards genomics in healthcare, and the pressure for this change may need to come from the science. Patients should also be at the centre of any changes and should participate fully in these discussions. There was resistance to change, and a significant fraction of the £2.5 billion spend on pathology services could be saved if sovereignty of individual specialties were to be given up.

It was asked whether epigenetics could be applied to modifying disease processes. Epigenetic contributions to disease processes cannot at present be quantified as accurately as genetic contributions but it was felt that dialogue between geneticists and epigeneticists should be encouraged, though this might be outside the remit of the Inquiry.

APPENDIX 5: VISIT TO WASHINGTON DC, UNITED STATES

Members visiting: Lord Patel (Chairman), Lord Colwyn, Baroness Perry of Southwark and Lord Warner. In attendance: Mrs Elisa Rubio (Clerk) and Professor Tim Aitman (Specialist Adviser).

The trip was hosted by the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health (NIH), and meetings were held at Lawton Chiles International House on the NIH campus over the three days of our visit.

The NHGRI, one of 27 institutes and centres that made up the NIH, and was a major contributor to the Human Genome Project, which had as its primary goal the sequencing of the human genome. The NHGRI's mission encompassed a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease and supported studies on the ethical, legal and social implications of genome research. It also funded the training of investigators and the dissemination of genome information to the public and to health professionals. The NHGRI received its funding through annual Congressional appropriation. Its 2007 budget was \$486 million.

Wednesday 4 June

Session 1: State of Science in Genomics

Presentations by Dr Francis Collins, Director of the NHGRI; Dr Teri Manolio, Director of the Office of Population Genomics, NHGRI; Dr Stephen Chanock, Chief, Laboratory of Translational Genomics; and Dr Jeff Schloss, Programme Director for Technology Development Coordination, Division of Extramural Research, NHGRI.

Dr Collins summarised developments in genome science, from the delivery of the double helix structure of DNA in 1953 to the sequence of the human genome in 2003. Technology advances, particularly dramatic reductions in sequencing and genotyping costs, had led to an exhilarating pace of discovery in the past two to three years about the genetic basis of common diseases such as multiple sclerosis, rheumatoid arthritis and Crohn's disease. He described parallel discoveries for genomic testing of drug efficacy and highlighted new opportunities for disease treatment that had arisen from this new knowledge, for example new drug development and gene therapy.

Dr Manolio emphasised that the new genome-wide association studies (GWAS), in which the Wellcome Trust had played a key role, had a requirement for very large sample sizes and for sophisticated IT. Fifty five GWAS had now been published. There had been few, if any, similar bursts of discovery in biomedical research previously. The studies had yielded many insights into the genetic basis of individual common diseases, and had also revealed a shared genetic basis, previously unsuspected, for a range of apparently diverse disorders. Dr Manolio also highlighted the potential for errors in such large studies, and that these initial studies, whilst very positive, were only skimming the surface in our understanding of the causes and potential treatments of common disease.

Dr Chanock talked about the advances in understanding the genetic basis of cancer since the start of GWAS in 2006. For example in prostate cancer, the

number of known genes had risen from one to 16. However these tools did not allow measurement of environmental contributions and it was also not known how these genetic factors interacted with one another. Therefore the completion of many GWAS should be seen as just the start in the long road to understanding the genetic basis of diseases such as cancer.

Dr Schloss described the extraordinary advances in sequencing technology that had taken place over the past few years. Alongside a massive increase in sequence output, there had been a 100-fold reduction in sequencing costs over the last ten years. Cost reduction by a further 10,000-fold was a current aim which would permit the sequencing of a human genome for just \$1000. The NIH had so far awarded grants totalling \$99 million to help achieve this goal. Dr Schloss also described many new technologies that were currently being supported in pursuit of the more immediate goal of the \$100,000 genome, which should be achieved by late 2008 or early 2009.

Discussion

The newly discovered genes for common diseases could lead to advances in diagnostics and therapeutics over the following five years. Insights into the genetic basis of breast cancer and colon cancer, for example, were already leading to changes in screening programmes for these disorders. Within five years, it would be possible to prove that new interventions were clinically useful on an individual basis. Therapeutic advances would take place by using the newly discovered genes as therapeutic targets but clinical trials of new drugs acting on these targets would take longer, perhaps 10–15 years.

It was difficult to disaggregate genetic and epigenetic effects, though epigenetic factors might be important in some diseases such as cancer. Some genomic tests might also reduce the need for animal testing, for example of drug toxicity.

The most important recommendations for further advances in this field were more support for research, more focus on disease prevention rather than treatment, and more thoughtful regulation and information on genetic testing.

Session 2: Translation to Clinical Care I

Presentations by Dr Mark Guyer, Director of Extramural Research, NHGRI; Dr Adam Felsenfeld, Programme Director of Large Scale Sequencing, NHGRI; Dr Leslie Biesecker, Chief and Senior Investigator, Genetic Disease Research Branch, NHGRI; and Dr Muin Khoury, Director, National Office of Public Health Genomics, Centres for Disease Control and Prevention.

Dr Guyer described the establishment of the National Human Genome Research Institute (NHGRI) as a change from a cottage industry to the efficient generation of a comprehensive catalogue of genomic information, with pre-publication release of data and very large-scale projects based on close international collaborations. Since completion of the human genome project in 2003, the NHGRI's mission had expanded and focussed on understanding the structure and function of the human genome and its role in health and disease. NHGRI had awarded substantial grants in genomics; one example that had yielded fruit was the cancer genome atlas, a partnership with the National Cancer Institute, funded at the level of \$100 million over three years. The project had already obtained significant results on the genetic basis of several cancers.

Dr Felsenfeld explained the design and progress of the 1000 Genomes Project, seen as a follow-up to the present range of GWAS. The 1000 Genomes Project was an international collaboration between the UK Sanger Institute and genome institutes in Beijing, Texas, Boston and Washington. The project would sequence the genomes of up to 500 people in each of three populations in Europe, Africa and East Asia. The advances brought about by this project would provide a complete catalogue of DNA sequence variation across several populations and a catalogue of much rarer types of variation than was hitherto possible. Data storage and transfer was a great challenge. It was anticipated that the 1000 Genomes Project and parallel projects in medical sequencing would identify many new sequence variations that underlie disease and would be medically relevant.

Dr Biesecker described the ClinSeq project and how major advances in DNA sequencing could provide benefits for individual patients in the clinic. Using examples such as the genetic diagnosis of patients with high cholesterol, he described how sequencing medically relevant genes could help medical research and treatment of patients.

Dr Khoury talked about the advances in genetics of common diseases in the context of four phases from transitional biomedical research to the clinic. Most discoveries became stuck at the second stage, the point at which evidence-based practice guidelines were developed. He emphasised the importance and strong evidence base of conventional public health, for example treatment with statins and aspirin for prevention of coronary disease, compared to the lack of evidence of clinical utility in the use of newly-discovered genes for common diseases for treating or preventing disease. He described several studies currently at an early stage which were designed to determine clinical utility of genomic testing. He cautioned against premature translation of genetic testing without an evidence base.

Discussion

It was recognised that it was easier to generate sequence data than to interpret that data and that whilst part of this was an informatics problem, the lack of prospective studies was also a major barrier to realising clinical utility. It was emphasised that conventional risk factors such as body mass index and cholesterol should lead to good advice about diet and exercise, while genetic testing in the context of newly discovered common disease genes might not add significantly to existing advice on disease prevention that was already given to patients. The major benefits of new disease gene discovery are likely to arise from the ability to develop new drugs based on novel targets. Genetics was a very fertile area of clinical research that could lead to clinically relevant advances, for example in increasing efficacy of drug prescribing. However many of the relevant clinical trials had not been carried out to date.

Session 3: Translation to Clinical Care II

Presentations by Dr Linda Avey, Co-Founder of 23andMe (via teleconference); Dr Dietrich Stephan, Co-founder of Navigenics and Director and Senior Investigator, Translational Genomics Research Institute (TGen); Dr Larry Brody, Senior Investigator, Genome Technology Branch, NIH; and Dr Amy Miller, Public Policy Director, Personalized Medicine Coalition.

Dr Avey described her role as co-founder of 23andMe in setting up genomic tests sold direct to the public. She described services such as “chromosome painting”, a

graphical tool to illustrate ancestry; “family tools”, a tool for graphically displaying information about inheritance across the genome; other tools for specific genes for attributes such as circadian rhythm and alcohol flush; and genomic profiling tests giving information on susceptibility to individual common diseases. For example, for type 2 diabetes, their tests indicated the relative risk of developing disease based on results from up to 30 low penetrance genes compared to the average risk of the population. The company provided an email counselling service which dealt mostly with technical or ancestry questions. They worked with national genetic counsellors rather than offering an individual genetic counselling service.

Dr Stephan, founder of Navigenics, talked about the activities of his company in providing genomic profiles direct to the public. The company provided a comprehensive service from customer acquisition of samples to generation and interpretation of test results via a personalised web portal, as well as ongoing update services for customers and academic partners. The company philosophy was that the private sector played a critical and necessary role in disseminating research findings, which was not at odds with responsible provision of a quality service. He expressed the view that these technologies could provide substantial savings, for example in prevention of Alzheimer’s disease and type 2 diabetes. The Navigenics laboratory had stringent quality control measures that were provided in the context of national accreditation schemes and education programmes for physicians and customers. The company worked with the Personalized Medicine Coalition in encouraging public and professional participation in the company’s activities. This included access to genetic counsellors within the Navigenics service and the desire to work within statutory and other regulations.

Dr Brody discussed whether the state of the science was ready for personalised medicine now or if it was too early. He included within his definition of personalised medicine the opportunity for individual diagnostics, pharmacogenetics risk assessment and modification, and development of new drugs. Genetic testing could be compared to other promising interventions such as early lung cancer detection by chest x-ray and treatment of back pain with early disc surgery. An important question was whether individual test results from research studies should be fed back to research study participants. As part of the Multiplex project, Dr Brody had studied 2000 participants tested for 15 genes in eight health conditions. Approximately half of those who took part in the study wished to receive their test results. The proportion taking part was lower in African Americans than white Americans. As with other healthcare interventions, reaching certain segments of the population would be difficult. To realise significant potential for healthcare impact at the population level it was important to learn from studies in practice.

Dr Miller described the activities of the Personalized Medicine Coalition in educating policy makers and healthcare leaders about the opportunities for personalised medicine. With a wide membership from the commercial, academic and public sectors, the Coalition aimed to provide opinion leadership on public policy issues, to help educate public policy makers, government officials and the private sector about benefits of personalised medicine, and to serve as a forum for information and policy development. Areas of activity included the combined use of genetic testing with drug treatment, working with the FDA to change labels on pharmacogenetic tests, and discussions with international colleagues in the US, UK and elsewhere on optimum methods of regulation and development of diagnostic tests. She described tensions between the commercial diagnostic and pharmaceutical sectors, and anxieties of US pharmaceutical companies about

meeting recommendations of international bodies such as the UK National Institute for Health and Clinical Excellence (NICE).

Discussion

A major difference between genetic and conventional risk factors was that conventional, environmental risk factors could be modified whereas as genetic factors could not. The view was expressed that the use of currently known genetic variants as part of genetic testing to predict development of common diseases did not add substantially to risk prediction by using conventional risk factors. Public demand for genetic tests was acknowledged to be growing, but commercial products in this area had only been launched very recently. It was recognised that the benefits of early intervention in diseases such as Alzheimer's disease were based on assumptions rather than an objective evidence base.

Tour of NIH Chemical Genomics Centre

Presentation by Dr Christopher Austin, Director, NIH Chemical Genomics Centre.

Following a tour of the Chemical Genomics Center, Dr Austin gave a presentation in which he described how the Center had been founded in 2004 and now comprised 54 scientists including biologists, chemists, informaticians and engineers, who collaborated with more than 100 investigators world-wide and had the capacity to screen more than 250,000 compounds in their collection. The strategy was to bridge the gap between basic science discovery and commercial drug development in the pharmaceutical industry. Some discoveries had already reached commercial viability, for example a compound shown to be useful for the treatment of schistosomiasis. It was anticipated that the activities and strategy of the Center would reduce the cost, shorten the time, and improve the success rate in screening of lead compounds for drug development.

Session 4: Regulation and Policy I: General

Presentations by Dr M.K. Holohan, Health Policy Analyst, Office of Policy, Communications and Education, NGHRI; Dr Derek Scholes, Government Relations Manager, American Heart Association; Dr Louis Jacques, Director, Division of Items and Devices Coverage, Centers for Medicare and Medicaid Services; and John Bartrum, Associate Director for Budget, NIH.

Dr Holohan gave an overview of the Genetic Information Non-discrimination Act of 2008 (GINA), a federal law that prevented health insurers and employers from discrimination based on an individual's genetic information. GINA, which had been heralded as the first major new civil rights bill of the new century, prohibited health insurers from requiring genetic information or using it in decisions regarding coverage, premiums or pre-existing conditions. It also prohibited employers from requiring genetic information or using it for decisions regarding hiring, firing or any terms of employment. However, GINA did not apply to life, disability or long-term care insurance.

Dr Scholes classified genetic tests into four categories: tests for single-gene disorders such as cystic fibrosis, multi-gene tests for chronic diseases such as cancer, tests that aided disease management such as those carried out to ascertain

the correct dosage for blood thinners, and lifestyle type testing such as nutrigenomic tests and those for addictiveness to tobacco, etc. He highlighted three regulatory gaps in relation to genetic tests: (1) measurement of analytical validity (the extent to which a test was accurate and reliable) was not a requirement and was not assessed for all tests; (2) the majority of tests came to the market without FDA approval as they were developed in individual laboratories and therefore had exemption; and (3) scientists and administrators questioned the usefulness of many tests on the market.

The Laboratory Test Improvement Bill was currently being considered by Congress and the Senate although it was unlikely to be passed during 2008. The bill provided for FDA oversight of all laboratory developed tests, an FDA public registry of tests, and the submission of analytical and clinical validity data to the FDA.

Dr Jacques described the Medicare programme. It was a national programme with 54 million subscribers in the US, mostly over 65. The Social Security Act stated that payments should not be made for prevention and screening, only for curing. Therefore predictive or pre-symptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, were not covered under Medicare rules. Dr Jacques anticipated that Medicare was due to run out of money by 2019. The programme was administered region by region; therefore some services were available in one region and not in others. Ten percent of coverage decisions in Medicare were national and 90 percent were regional.

Mr Bartram explained the federal budget process of the NIH from its conception all the way to the President's signature. Different NIH departments had five year plans to identify trends. Most of the NIH budget was spent on the 10,000 grants given out each year with an average duration of three and a half years. The total programme budget was \$29.5 billion and it had been flat for the past three years. Mr Bartram highlighted two challenges in order to maintain the US as a pre-eminent force in biomedical research: the loss of purchasing power and ageing equipment and supplies.

Discussion

Physicians would be put in a difficult position if they were asked by patients not to include genetic test results in their medical records. Including life, disability and long-term care insurance under GINA would have been better for individuals, but it had taken 13 years for GINA to become law and if other types of insurance had been included it would have been almost impossible for it to have been passed.

Legislation of genetic tests had taken a long time to reach the statute book. Legislators preferred statutory protection as opposed to a code of practice, such as the UK insurance Moratorium, as the latter was not enforceable. New York State had prohibited direct-to-consumer tests and therefore an American company could not sell such products in that State.

Medicare did not see sufficient benefits for patients to justify payment for most genetic tests. If an individual were tested for the *BRCA1* and *BRCA2* mutations and then developed breast cancer, Medicare would pay for the treatment but not for the tests.

Session 5: Regulation and Policy II: Oversight of Genetic Testing

Presentations by Gail Javitt, Law and Policy Director, Genetics and Public Policy Center; Dr Phyllis Frosst, Senior Science Policy Analyst, NHGRI; Dr Steve Gutman, Director of the Office of In Vitro Diagnostic Device Evaluation and Safety, Food and Drug Administration (FDA); and Judy Yost, Director, Division of Laboratory Services, Centers for Medicare and Medicaid Services.

Ms Javitt talked about the Genetics and Public Policy Center at Johns Hopkins University. Certain goals were required in the oversight of genetic testing in order to achieve public confidence. These included ensuring that laboratory testing was of high quality, and that tests carried out were clinically valid and made truthful claims about tests' benefits and limitations. Oversight should encompass development of new tests to avoid delaying their translation into clinical practice. Continuing oversight of genetic tests would require new laws as current regulation did not fit the new context and technology continued to move rapidly.

The regulatory status of genetic tests depended on how the laboratory developed and performed the test. If the test was sold as a test kit or system then FDA had oversight of that test because it was classified as a medical device. By contrast, if a test were developed by a laboratory and carried out at the same laboratory FDA regulation was not required. At present most genetic tests were laboratory-developed and therefore clinical validation was not required.

Dr Frosst gave an overview of the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS). One of the activities of SACGHS was to identify gaps in the US system of oversight of genetic testing, and to make recommendations about how those gaps might be filled. Their report "US System of Oversight of Genetic Testing" was published in April 2008 and called for more oversight of genetic testing, citing "significant gaps" in validating the tests' usefulness, especially those sold direct to consumers. The SACGHS also recommended "to enhance the transparency of genetic testing and assist efforts in reviewing the clinical validity of laboratory tests", and that the Department of Health and Human Services should appoint and fund a lead agency to develop and maintain a mandatory, publicly available, web-based registry of laboratory testing. The SACGHS also called for the creation of a public-private partnership to evaluate clinical utility of genetic tests.

The Food and Drug Administration (FDA) was a government regulatory agency that helped ensure the safety and effectiveness of cosmetics, foods, drugs, and medical devices under the Federal Food, Drug, and Cosmetic Act. The Office of In Vitro Diagnostic Device Evaluation and Safety regulated all aspects of in-home and laboratory diagnostic tests (in vitro diagnostic devices (IVDs)). The standardised road map for evaluation assessed analytical performance, clinical performance and labelling. Although laboratory-developed tests were subject to CLIA (Clinical Laboratory Improvement Amendments, administered as part of Medicare), only some are considered medical devices by the FDA. Therefore the majority of laboratory developed tests were not required to carry out clinical validation or pre-market review and there were no post-market reporting requirements. Laboratory-developed tests, the most common path for genetic tests, had a less burdensome path to market and this could be the source of inadvertent or deliberate abuse, including in the development and marketing of direct-to-consumer tests.

The objective of the CLIA program was to ensure accurate, reliable and timely laboratory testing. The requirements were minimal and were based on test

complexity. Most genetic tests were categorised as high complexity. The programme was funded entirely by user fees, not government, and covered all testing on human specimens for health assessment within the 200,000 enrolled laboratories. Under CLIA, no specific evaluation for genetic tests existed because genetic testing was considered such a dynamic area that prescriptive standards would be quickly outdated and would lock laboratories into outmoded compliance. CLIA did not cover clinical validity, utility, or claims made by direct-to-consumer tests.

Discussion

The definition of what tests needed FDA approval was clear and was not necessarily determined by whether a test was viewed as genetic or non-genetic. Some direct-to-consumer testing companies claimed that they only provided genetic information and not medical information.

The number of genetic tests sold directly to the consumer was currently around 30, but this number was increasing weekly. There were around 24 companies that provided direct-to-consumer tests over the Internet.

Professional bodies were traditional in their approach and broadly opposed to regulation. There was no equivalent of the UK Genetic Testing Network (UKGTN) in the US and the FDA or CLIA had no contact with UKGTN.

Session 6: Bioinformatics

Presentations by Samuel Aronson, Executive Director of Information Technology, Harvard Medical School; Dr Peter Good, Program Director, Division of Extramural Research, NHGRI; Dr Jonathan Pevsner, Director, Bioinformatics Facility, Kennedy Krieger Institute; and Elizabeth Humphreys, Deputy Director, US National Library of Medicine.

Dr Aronson described the goal of the Harvard Medical School Partners Healthcare Center as providing an information infrastructure that improved patient care by enabling clinicians to use the increasing amounts of genetic and genomic data that were relevant to healthcare. Clinical decision-making by the physician was based on ordering genetic tests in a consultation lasting on average 14.7 minutes. The goal was to make widespread data sources including personal medical and genomic information available in a clinically readable format. The cost of DNA sequencing had dropped dramatically in recent years with the \$1,000 genome expected to be reached in 2015. At that time, it would be possible to apply a genotyping model to clinical practice, using a broad spectrum test for general use including sequence data of hundreds of thousands to millions of variations for each patient, which would be stored in a repository and routinely accessed to understand the implications of a patient's genome. When this model came to clinical practice the need for bioinformaticians would be enormous.

The NHGRI spent 13.5 percent of extramural funds in informatics, which amounted to \$53 million in 2007. There were two strands of spending: resource projects, such as model organism databases, data standard and protein/pathway databases; and technology development (research), or how to extract information from genome datasets. The NIH roadmap identified bioinformatics and computational biology as a key area. However there were many challenges ahead: the production of increasingly large amounts of data; new technologies, and new

data analysis methods; funding for resources; lack of recognition of computational biologists; and training.

Dr Pevsner defined bioinformatics as the interface of biology and computers, essentially the analysis of proteins, genes and genomes using computer algorithms and databases. Genomics was the analysis of genomes, including the nature of genetic elements on chromosomes. Bioinformatic tools were used to make sense of the billions of base pairs of DNA that were sequenced by genomics projects. There were great challenges when creating a disease database such as the difficulty in organising the data by genes or by disease; the complexity of disease mechanisms which were not readily captured; the often obscure connection between a gene and a disease; and the difficulty in estimating false positive and false negative error rates. A major ongoing challenge was to find ways of joining disease databases and DNA databases, and how to ensure that specialists from different disciplines such as computer programmers, biologists, clinicians and biostatisticians could use their combined expertise to extract the required information from databases containing different types of information.

The National Library of Medicine (NLM) had a budget of \$329 million and employed 1,330 staff and contractors, half of whom worked in bioinformatics. Their goals included seamless, uninterrupted access to expanding collections of biomedical data, medical knowledge and health information, and integrated biomedical clinical and public health information systems that promoted scientific discovery and speeded transition of research into practice. Ms Humphreys gave examples of databases that the NLM sponsored or collaborated with.

Discussion

The best health care computer systems had evolved over time and had included bioinformaticians from the beginning. The major challenge was for the public to trust the data being centrally held rather than stored in local doctors' surgeries and hospitals. Due to the health care system in the US there was little appetite for a centralised record centre. However, natural disasters such as hurricane Katrina had prompted people to start thinking about a centralised system. The Committee was told how when Katrina struck, people's medical records were lost and those individuals in the middle of, for example, cancer treatment found great difficulties in continuing their treatment.

Session 7: Miscellaneous

Presentations by Dr Laura Rodriguez, Senior Advisor to the Director for Research Policy, NHGRI; Jean McEwen, Program Director, Ethical Legal and Social Implications, NHGRI; and Dr Raju Kucherlapati, Scientific Director, Harvard Medical School.

The Committee heard that the greatest public benefit would be realised if data from GWAS were made available, under terms and conditions consistent with the informed consent provided by individual participants, in a timely manner and to the largest possible number of investigators. Dr Rodriguez explored some of the ethical and policy questions during her presentation, for example, should individual results from basic GWAS be returned? How were the wishes of the individual participants respected? How could the public's trust be sustained? And what level of de-identification provided adequate confidentiality protection to participants without damaging the science? Immediate and unfettered access to all

qualified users provided maximum opportunity for scientific progress. Confidentiality of research participants should be protected and their consent provisions respected. Equally, the need of investigators for academic recognition should be recognised. There was consensus that GWAS data should be released to the public at the earliest stage and be available for use by all.

Dr McEwen gave the Committee an overview of the different approaches possible when returning results to participants in genetic research studies. She discussed three different approaches: to disclose (almost) nothing, to disclose (almost) everything and a balancing/contextual approach. It was key that this issue should be considered carefully from the outset of the research and communicated to the relevant ethics committee so that the appropriateness of the plans could be assessed. Such plans could be communicated to participants as part of the informed consent process. In the context of these areas of debate, there was a clear consensus that there was a need for more social/behavioural research in this area.

Dr Kucherlapati highlighted the view that personalised medicine would revolutionise the way medicine was going to be practiced. However, there was a need for a shift in emphasis towards prevention and better strategies for early detection. For existing drugs and treatments, it was necessary to show that incorporating genetics and genomics in clinical decision making resulted in better outcomes. Regulatory agencies would need to take bold steps for implementation of personalised medicine and a comprehensive training and education plan would be needed.

Discussion

Most new drugs were being developed in parallel with identification of biomarkers that predicted drug efficacy. These biomarkers could be developed into tests, the use of which might then become the norm. The cost of drug development should not increase because clinical trials that included a test of efficacy would be quicker and less expensive. Cohort size could therefore be smaller because efficacy and success rates would be higher. This approach could also bring into the market drugs that might otherwise have been shelved because of the low efficacy rate. The use of biomarkers in clinical trials may therefore increase efficacy to acceptable levels.

Genetic education would probably take place within individual specialties, because genetic counsellors currently mainly provided support for rare diseases and could not cope with the volume of counselling required for common diseases. Tools for online genetic education of healthcare professionals had been developed at Harvard and were potentially available worldwide.

Session 8: Training Needs in Genomics

Presentations by Joann Boughman, Executive Vice President, American Society of Human Genetics; Holly Peay, Associate Director, Genetic Counselling Training Program; Dr Jean Jenkins, Senior Clinical Advisor to the Director, NHGRI; and Professor Michael Rackover, Program Director and Associate Professor, Physician Assistant Program, Philadelphia University.

Dr Boughman described the different specialties and certifications available in the US, and the membership of the three main professional bodies that formed the genetics community: the American Society of Human Genetics; the American

College of Medical Genetics, formed of practitioners of genetics; and the American Board of Medical Genetics, with certified professionals amongst their membership. There were great challenges ahead when training professionals in genetics: the knowledge and technologies were fast moving; 30 percent of Board-certified Genetics posts were not filled; and the integration of genetics into health care was driven by both consumer/patient demand and cost considerations. Health professionals were the ultimate arbiters of how and when (and if) new technologies and practices were integrated into health care.

The mission of the National Coalition for Health Professional Education in Genetics (NCHPEG) was to promote health professional education and access to information about advances in human genetics to improve the health care of the nation. They also provided a central educational resource for all health professionals and developed tools to educate health professionals and incorporate genetics into clinical practice. Their educational resources covered general guidance, such as core competences and principles in genetics, as well as specific topics, for example genetics and psychiatric disorders. Their audience was wide-ranging, from nurses, family physicians and physician assistants to dietitians. Ms Peay highlighted crowded curricula, inadequate representation of genetics on certifying exams, misconceptions about genetics, and lack of knowledgeable faculty as barriers to genetics education for health professionals.

Ms Jenkins talked about the current genetic/genomic education priorities and progress in nursing. There were 2.9 million practicing nurses in the US in 2004 and of those only 26.6 percent were under 40 years of age. Most faculty and practicing nurses have had no genetics or genomics education or training and genetic and genomic content was inconsistently incorporated into entry level nursing programmes and licensing exams. Ms Jenkins described a number of initiatives designed to increase genetic/genomic knowledge in nurses such as the development of core competencies and agreeing education priorities with the main stakeholders.

Professor Rackover gave an overview of the Physician Assistant (PA) profession in the US and their training in genetics and genomics. PAs were licensed to practise medicine under the supervision of a physician. The United Kingdom did not have an equivalent profession. Through various programmes and initiatives the Physician Assistant Education Association achieved a substantial increase in genetics enhanced curricula in PA training.

Discussion

Public education was an area of the NIH that needed greater emphasis. A range of activities was taking place but public education programmes were not as robust as would have been ideal. Tools for educating the public about family history had been developed by the Surgeon General, the NIH and the Centers for Disease Control.

In certain areas the church could be a barrier to public education, in pre-natal testing for example. Some faiths such as Mormonism or Judaism had considerable emphasis on family history which was a rich source of medically relevant information. Some stand-alone training modules were described that were designed to train general physicians in analysing the medical significance of family history.

The scale of the training needs was huge because the number of healthcare professionals who were in contact with patients was very large and included

general practitioners, nurses, genetic counsellors, etc. The quickest way of introducing genetics into the curricula was through the assessment system, but progress was inhibited by curricula being set locally by each medical school. If more genetics content was placed in mandatory exams, students would be compelled more rapidly to study genetics, but it would require medical geneticists to take on this task.

Session 9: Miscellaneous

Presentations by Dr Lawrence Lesko, Director, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration (FDA); Sharon Terry, President and CEO, Genetic Alliance; Professor Christine Seidman, Departments of Medicine and Genetics, Harvard Medical School; and Dr Greg Downing, Program Director, Personalized Health Care Initiative, US Department of Health and Human Services.

Dr Lesko described the activities of the FDA in giving approval to new drugs, and the opportunity for genomic knowledge and applications to be useful in new drug development and in improved use of previously approved drugs. He described the personalised healthcare initiative of the Department of Health and Human Services Secretary, Mike Leavitt, aimed at providing a conceptual foundation for policies in genomic medicine and pharmacogenomics. He drew attention to the fact that FDA approval for new drugs could be gained with only 30 percent efficacy and that genomic testing had the potential to increase these low efficacy rates. The FDA gave advice and instruction on labelling of drugs and Dr Lesko gave examples of recent changes in labels of drugs used in cancer therapy, lipid lowering and treatment of duodenal ulcer. Genomic tests were currently required for the prescription of six drugs, and recommended for a further six drugs.

Ms Terry described the founding of the non-for-profit organisation “Genetic Alliance” following the birth of her two children with the single-gene disorder pseudoxanthoma elasticum. She was listed as a co-discoverer of the gene for pseudoxanthoma elasticum and co-author of the *Nature Genetics* paper describing this discovery. The Genetic Alliance had patented the discovery of this gene and given all rights to the foundation in order to have stewardship of the discovery. The involvement of patients in biomedical research, and particularly the use of patient advocacy in drug trials was an important part of the Alliance’s mission.

Professor Seidman discussed the opportunities and barriers with regard to genetic testing and heart disease in the context of an increasing prevalence of heart failure within an ageing population. She pointed out that interventions such as use of implantable cardiac defibrillators were driven largely by the funding available from insurance companies, and that genetic testing could lead to much more efficient use of such devices. She described the ways in which genetic screening could be applied effectively, particularly since the introduction of GINA into statute which had significantly advanced the opportunities for use of genetic testing in research and clinical practice.

Dr Downing described the vision of the Health and Human Services Secretary Mike Leavitt in moving towards personalised healthcare. Policy had been established in three main areas: research and development in genomic and molecular medicine; adoption and networking of health information technology; and accelerated development and use of a genomic evidence base. A two year time-line for personalised healthcare had been developed that included improved

delivery, data integration, improved health information technology, and expansion of the science base. Policy actions already in place included an executive order in 2004 to establish a priority for electronic health records and the signing into law of GINA in 2008. GINA aimed to prevent discrimination in employment and health insurance coverage. Recommendations were also being drawn up to develop a plan for genetic screening of newborn infants and for use of pharmacogenetics tests.

Discussion

It was recognised that newborn screening by genetic tests was not a priority and that such tests could not be moved easily from the place of testing. Moving information across States was specifically prohibited. However screening for hearing disorders was currently complete in 84 percent of newborn infants. Currently screening was motivated by financial priorities but should be evidence-based as it was in the US academic health science centers. The small size of biobanks in the USA was noted compared to the very large biobanks in other countries. It was pointed out that work on systems for genetic testing was fragmented, with little coordination across the wide range of common diseases for which genetic testing was applicable.

APPENDIX 6: ACRONYMS AND GLOSSARY

Acronyms

ABI	Association of British Insurers
ABPI	Association of the British Pharmaceutical Industry
AMRC	Association of Medical Research Charities
AMS	Academy of Medical Sciences
ASA	Advertising Standards Authority
BERR	Department for Business, Enterprise and Regulatory Reform
BIA	Bioindustry Association
BIS	Department for Business, Innovation and Skills
BSHG	British Society for Human Genetics
CESAGEN	Collaborative Centre of the ESRC Genomics Network
DCTs	Direct to Consumer Tests
DoH	Department of Health
DIUS	Department for Innovation, Universities and Skills
DTI	Department of Trade and Industry
EBI	European Bioinformatics Institute
EHR	Electronic Health Record
ELIXIR	European Life-science Infrastructure for Biological Information
ESFRI	European Strategy Forum on Research Infrastructures
ESRC	Economic and Social Research Council
FDA	US Food and Drug Administration
GAIC	Genetics and Insurance Committee
GINA	Genetic Information Non-discrimination Act
GMC	General Medical Council
GWAS	Genome-wide association study
HGC	Human Genetics Commission
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
ICO	Information Commissioner's Office
IMG	Institute of Medical Genetics
IMI	Innovative Medicines Initiative
IP	Intellectual property
IPO	Intellectual property Office
JCMG	Joint Committee on Medical Genetics
LIMS	Laboratory Information Management System

MHRA	Medicines Healthcare products Regulatory Agency
MRC	Medical Research Council
MSC	Modernising Scientific Careers
NCBI	National Center for Biotechnology Information
NGEDC	National Genetics Education and Development Centre
NGRL	National Genetics Reference Laboratory
NHGRI	US National Human Genome Research Institute
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute of Health Research
OECD	Organisation for Economic Co-operation and Development
ON	Oxford Nanopore Technologies
OSCHR	Office for Strategic Co-ordination of Health Research
PCT	Primary Care Trust
PHGF	Public Health Genetics Foundation
PMETB	Postgraduate Medical Education and Training Board
PPRS	Pharmaceutical Price Regulation Scheme
RCGP	Royal College of General Practitioners
RCPath	Royal College of Pathologists
RCUK	Research Councils UK
SCG	Specialised Commissioning Group
SGPPH	Society for Genomics Policy and Population Health
SHA	Strategic Health Authority
SNP	Single Nucleotide Polymorphism
TSB	Technology Strategy Board
TUC	Trades Union Congress
UKGTN	UK Genetic Testing Network
WT	Wellcome Trust
WTSI	Wellcome Trust Sanger Institute

Glossary

Bioinformatics	The application of computers and computational expertise to analyse, visualise, catalogue and interpret large biological datasets in the context of the genome sequences of humans and other species.
Biomarker	A characteristic that can be objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
Biomedical informatics	The application of bioinformatics and computational expertise in support of the practice of medicine and the delivery of healthcare.
Biotechnology	The industrial application of biological processes, particularly DNA technology and genetic engineering.
Carrier	A person who has inherited a genetic trait or mutation but does not display the disease. Such a genetic trait can be passed on to successive generations.
Chromosome	A sub-cellular structure made up of tightly coiled DNA which contains many genes.
Clinical research	Studies performed in humans that are intended to increase knowledge about how well a diagnostic test or treatment works in a particular patient population.
Clinical trials	Research study conducted with patients, usually to evaluate a new treatment or drug.
Clinical utility	The risks and benefits resulting from using a test.
Clinical validity	The accuracy with which a test identifies or predicts a patient's clinical status.
Complex disease	A phenotype that results from the actions of multiple genes and their interaction with other factors such as lifestyle and the environment.
Copy number variation	The differing number of copies of a particular DNA sequence in the genomes of different individuals.
Cytogenetics	The study of the relationships between the structure and number of chromosomes and variation in genotype and phenotype.
Diagnostic test	A term used to describe particular tests that are able to identify a recognised condition.
DNA	(Deoxyribonucleic acid). The chemical that comprises the genetic material of all cellular organisms.
DNA sequencing	Determination of the order of bases in a DNA molecule.
Environmental factors	Factors in the environment that may have an effect on the development of disease, such as chemical or dietary factors.
Epigenetics	The study of changes in gene function that occur without a change in the DNA sequence.
Expression profile	A collection of genetic data, usually generated using microarrays, that describes the extent to which every gene

	in the genome is switched on or off in a particular tissue sample.
Gene	The basic unit of heredity found in chromosomes. A length of DNA that carries the genetic information necessary for production of a protein.
Gene expression	The process by which a gene is activated at a particular time and place so that its functional product, or protein, is produced.
Genetic counselling	Providing an assessment of heritable risk factors and information to patients and their relatives concerning the consequences of a disorder, the chance of developing or transmitting it, how to cope with it, and ways in which it can be prevented, treated, and managed.
Genetic epidemiology	Study of the correlations between phenotypic trends and genetic variation across population groups and the application of the results of such a study.
Genetic predisposition	Having some genetic factor(s) that may make an individual more likely to develop a particular condition than the general population.
Genetic screening	Testing a population group to identify a subset of individuals at high risk for having or transmitting a specific genetic disorder.
Genetic test	An analysis performed on human DNA, RNA, genes and/or chromosomes to detect heritable or acquired genotypes.
Genome	The unique genetic code or hereditary material of an organism, carried by a set of chromosomes in the nucleus of each cell.
Genomic medicine	The use of genetic information and genomic tools to determine disease risk and predisposition, diagnosis, prognosis, and the selection and prioritisation of therapeutic options.
Genomic profile	A collection of genetic information that records an individual's genotype at hundreds of thousands of locations in their genome
Genotype	The specific genetic makeup of an individual at a particular location in their genome. Sometimes used to indicate the collective genotype at all points in their genome. Although genotypes give rise to the phenotype of an individual, genotypes and phenotypes are not always directly correlated. For example, some genotypes are expressed only under specific environmental conditions.
In vitro	(Latin: within the glass) This term refers to experiments performed in an artificial environment like a test tube or culture media.
Locus (plural loci)	The specific site on a chromosome at which a particular gene or other DNA landmark is located.
Microarray	Sometimes called a gene chip or a DNA chip. A high throughput technology that enables the detection of gene

	expression levels or the detection of SNPs within the genome.
Mutation	A change to the nucleotide sequence of the genetic material of an organism.
Nucleotide	One of the building blocks of DNA or RNA. There are four nucleotides in DNA: Adenine (A), cytosine (C), guanine (G), and thymine (T). These are the “letters” or “bases” of the genetic code.
Penetrance	The likelihood that a person carrying a particular mutant gene will have an altered phenotype such as a genetic disorder.
Pharmacogenetics	The study of the way in which variation in individual genes affects drug metabolism and responsiveness, and the application of this information into clinical practice.
Pharmacogenomics	The study of the way in which genetic variation across the genome affects drug metabolism and responsiveness, and the application of this information into clinical practice.
Phenotype	The appearance of an organism based on a combination of genetic traits and environmental factors.
Polygenic trait	A trait affected by many genes, with no one gene having a large influence.
Prenatal test	Procedure done to determine the presence of disease or defect in a fetus.
Protein	A molecule composed of amino acids linked together in a particular order specified by a gene’s DNA sequence. Proteins perform a wide variety of functions including serving as enzymes, structural components or signalling molecules.
Protein expression	The measurement of the presence and abundance of one or more proteins in a particular cell or tissue.
Ribonucleic acid	A chemical that is copied from the DNA on an individual’s chromosomes, that carries the genetic information required to produce cellular proteins.
Sensitivity of a clinical test	The proportion of individuals with a disease phenotype who test positive.
Single nucleotide polymorphism (SNP)	A variation in a DNA sequence that occurs when a single nucleotide in a genome is altered in at least 1 per cent of the population. The human genome contains approximately 10 million SNPs.
Specificity of a clinical test	The proportion of individuals without a disease phenotype who test negative.
Stratified medicine	The targeting of healthcare interventions, particularly drug treatments, to well-defined subgroups of patients
Translational research	The process of using novel laboratory findings to develop clinical applications and practical advances in health care.

APPENDIX 7: RECENT REPORTS

Session 2005–06

- 1st Report Ageing: Scientific Aspects
- 2nd Report Energy Efficiency
- 3rd Report Renewable Energy: Practicalities and Energy Efficiency: Government Responses
- 4th Report Pandemic Influenza
- 5th Report Annual Report for 2005
- 6th Report Ageing: Scientific Aspects: Follow-up
- 7th Report Energy: Meeting with Malcolm Wicks MP
- 8th Report Water Management
- 9th Report Science and Heritage
- 10th Report Science Teaching in Schools

Session 2006–07

- 1st Report Ageing: Scientific Aspects—Second Follow-up
- 2nd Report Water Management: Follow-up
- 3rd Report Annual Report for 2006
- 4th Report Radioactive Waste Management: an Update
- 5th Report Personal Internet Security
- 6th Report Allergy
- 7th Report Science Teaching in Schools: Follow-up
- 8th Report Science and Heritage: an Update

Session 2007–08

- 1st Report Air Travel and Health: an Update
- 2nd Report Radioactive Waste Management Update: Government Response
- 3rd Report Air Travel and Health Update: Government Response
- 4th Report Personal Internet Security: Follow-up
- 5th Report Systematics and Taxonomy: Follow-up
- 6th Report Waste Reduction
- 7th Report Waste Reduction: Government Response

Session 2008–09

- 1st Report Systematics and Taxonomy Follow-up: Government Response