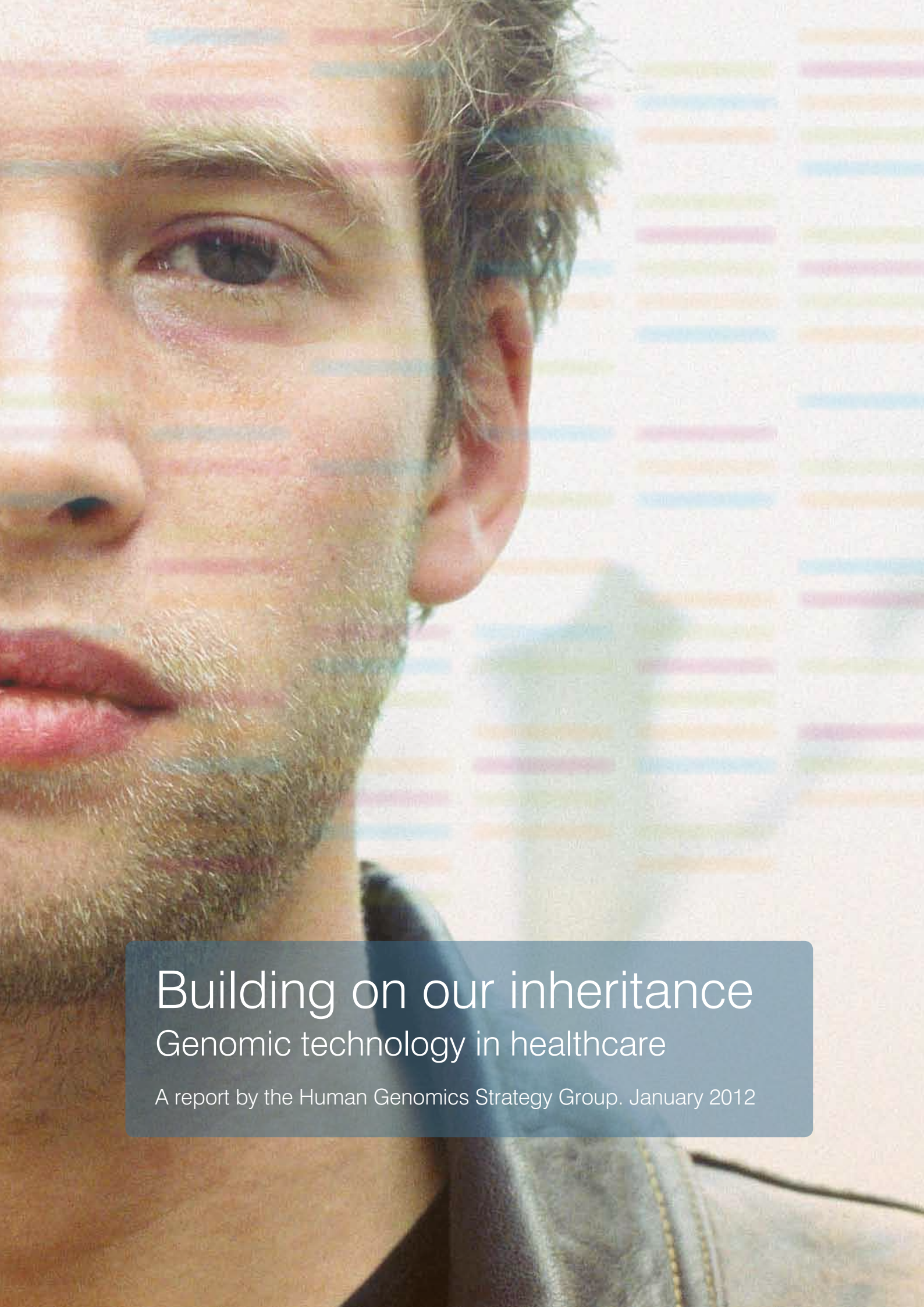

Building on our inheritance

Genomic technology in healthcare

A report by the Human Genomics Strategy Group. January 2012

Foreword

The Human Genomics Strategy Group (HGSG) was established as part of the Government's response to the 2009 House of Lords Inquiry into genomic medicine. We were given the remit to:

- monitor advances in genetic and genomics research, both basic and translational, to evaluate their benefit to healthcare services in the NHS, and
- develop, in partnership with other stakeholders, a vision for genomics in the NHS.

Since its establishment in 2010, the HGSG has brought together many of the UK's key individuals and organisations in the field of genetic research and its application to medicine. We have worked together to share knowledge on emerging technologies and existing procedures, to identify the practical barriers that need to be overcome for the NHS to reap the significant potential benefits that genomic technologies can bring, and to suggest potential solutions.

The UK has successfully adopted *genetics*, and its associated specialty Clinical Genetics, into healthcare to the real benefit of patients and health services alike. We continue to lead the world in the advancement of Clinical Genetics, providing specific and proven expertise in understanding the importance of inheritance and the consequences of disease on whole families as well as individuals. This has been achieved through a clear, shared direction from policy to practice, as part of a systematic and coherent approach by the Clinical Genetics community to overcoming the issues and potential barriers to adoption that existed.

Genomics is the application of specific technologies to analyse wider sets of genetic information – information, in fact, about the entire genome. This can then be harnessed to provide a greater ability to determine disease risk and predisposition, to support more accurate diagnosis and prognosis, and to select and prioritise therapeutic options in a wider set of pathological disorders. It can be used in every branch of medicine, as well as to enhance the capabilities within the specialty of Clinical Genetics. Already, it is beginning to move 'from bench to bedside' and, as it does so, the potential for NHS-wide adoption and diffusion of genomic technology is becoming increasingly clear.

Genomic medicine covers a wide spectrum of disciplines and potential applications, all linked by their use of the same underlying technologies, which allow ever faster analysis and comparison of individual genetic and genomic data against 'known' patterns. It incorporates Clinical Genetics and molecular pathology, and is as valuable in frontline care as in public health. For this to flourish and deliver the best patient outcomes possible, all specialties and fields need to work together in a strategic way, and the input of the HGSG is designed to help to understand what that way should be.

The starting point for our strategy is a clear vision of what we wanted to achieve, which we describe in this report. Thereafter, we set out the fundamental steps that must be taken on the journey to realising that vision.

At present, we are in a position of strength. As the recent life sciences strategy highlighted, the UK is a recognised world

leader in biomedical sciences, and is home to many of the leading academic and commercial research centres spearheading the global development of genomic medicine and furthering the use of Clinical Genetics. This gives the UK an outstanding opportunity to exploit its scientific lead, via the NHS – a unique service delivery environment in which clinically validated genomic medicine will be able to thrive. The challenge is to make our vision a reality for the benefit of the NHS, for the benefit of the UK biomedical industry and, above all, for the benefit of patients and their families. It is also to move sufficiently rapidly that our leadership position is not undermined by other countries who have also recognised this opportunity and are now pursuing it.

I therefore have the pleasure to present this report for the consideration of Government, especially the Department of Health, the Department for Business, Innovation and Skills and the Technology Strategy Board.

I would like to thank all the members of the HGSG for their commitment and engagement in examining the challenges we face and helping to define our shared vision.

Professor Sir John Bell
Chair, Human Genomics Strategy Group

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Executive summary and recommendations

This report sets out a strategic vision for how the healthcare system in the UK – and particularly in the NHS – can benefit from the mainstream adoption of genomic technology. It also provides specific recommendations on the steps that need to be taken to realise this vision.

Genomic technologies have the potential to transform the delivery of healthcare in the UK, providing vital insights to support more accurate diagnosis of disease and inform therapeutic decisions – so that more patients get the right treatment at the right time. They can enhance preventive care and enrich our understanding of disease risk, as well as enabling outbreaks of infectious diseases to be controlled faster. Indeed, as the report shows, genomic technologies are already beginning to deliver these benefits within the NHS and UK public health.

Our report looks at how the achievements to date can be built upon, moving towards a world-class system for adopting innovation and spreading the application of genomic technologies within the NHS and through public health programmes, aiming to improve patient outcomes and overall population health. More importantly, it considers the challenges that need to be addressed if the UK is to realise these benefits. These include:

- ensuring the successful translation of laboratory and academic research into quality-assured care pathways
- developing a service delivery infrastructure that will enable equitable and affordable access to high quality genomic and genetic testing services, from commissioning the initial test through to counselling patients and their families
- putting in place the bioinformatics platform needed to underpin genomic and genetic testing and facilitate ongoing research
- training the NHS and public health workforce of today and tomorrow
- recognising the legal and ethical issues around the use of genomic data, and developing appropriate safeguards and processes to protect individuals, and
- raising public awareness of genomic technology and how it can be used to benefit the care of patients across the NHS and indeed the world.

Throughout our review and analysis of the current development and application of genomic technology and its role in healthcare delivery, it has been clearly evident that the NHS and UK academia and research and business communities have the ability to produce and adopt innovative genomic technology. To ensure that the UK remains at the forefront of this rapidly evolving field of science, and that patients and providers gain maximum benefit from it, action needs to be taken in the short, medium and long term, and investment will be needed at various levels and at different times.

This is already occurring. In December 2011, the Prime Minister set out, in his statement on investing in UK health and life sciences, the actions that will be taken to make the UK a world-leading place for life science investment. As part of this initiative, the Department of Health (DH) and the Department for Business, Innovation and Skills (BIS) described the substantial investment already being applied in this area – in stratified medicine, building better

bioinformatics capacity and developing the Academic Health Science Networks.[1]

The findings and recommendations contained in this report not only complement this strategy and other initiatives for life science investment and building the UK's life science economy, but they also show how genomic technology could be adopted and diffused in the NHS to ensure better patient care through a more informed and intelligent application of genomics and genetics. As the Chief Executive of the NHS in England, Sir David Nicholson, has already noted in his report on innovation in the NHS,[2] much has been achieved but we need to continue to advance the great progress we have made to date.

This will take a concerted effort from all key partners, from across the UK and beyond, matched with a political commitment to realise this vision. However, we must not lose sight of the need to remain engaged in discussion and debate with those who truly hold the key to the success of genomic medicine: the public.

[1] HM Government (2011) *Investing in UK Health and Life Sciences*; Department for Business, Innovation and Skills (2011) *Strategy for UK Life Sciences*

[2] Department of Health (2011) *Innovation, Health and Wealth: Accelerating adoption and diffusion in the NHS*

Recommendations

1. To realise the potential of genomic technologies within healthcare, and for the UK economy, a co-ordinated, strategic approach to the longer-term development of genomic technology is required. This would set out clear objectives and an agreed framework that will help to steer us towards achieving them. **We therefore recommend that the Government should produce a White Paper, or similar cross-cutting strategic document, which sets out overarching policy direction on genomic technology adoption in the NHS. To inform this work, we recommend commissioning health economics studies to quantify the costs and benefits of investing in genomic medicine.**

2. As technology advances and we gain ever more knowledge about the role of the genome in the development and treatment of disease, the greater is the need to analyse and archive data. To capitalise on the rapid development in sequencing technologies and to allow us to interpret genomic data accurately and in a clinically relevant way, the highest possible quality standards need to be in place around the management, storage and use of data from research through clinical usage. **DH in partnership with BIS and other relevant partners should develop proposals to establish a central repository for storing genomic and genetic data, and relevant phenotypic data from patients, with the capacity to provide biomedical informatics services and an open-data platform that small and medium-sized enterprises can build upon.**

3. Commissioning is central to the adoption and diffusion of innovation and new technology within the NHS. Commissioners need to understand how innovations will deliver improved care for the same or lower cost; they also need to be able to commission innovative services and technologies in the confidence that they meet required quality standards. Pilot work on stratified medicine in cancer has already shown that more needs to be done to ensure that the NHS has the capability to roll out molecular pathology to the necessary standards to meet all patient needs – not so much because current services are failing, but fundamentally because they are unable to keep up with the rapid pace of technological change. Given this, and the level of technological complexity involved, we believe that genetic and genomic services would, at this current time, be best delivered through national specialised commissioning via centres that can demonstrably meet quality, turnaround, cost and data standards. **We therefore believe that the NHS Commissioning Board (NHSCB) should take a lead in the commissioning of genetic and genomic services. This should include:**
   - **ensuring that genetics, genomics and genomic technology and their development in the NHS are a clear and unambiguous responsibility of a board member**
   - **bringing forward proposals for the establishment of a strategic network to deliver expert advice on the strategic development of genomic and genetic services**

- **developing national tariffs for genetics and special pathology tests, and ensuring that the cost of genetics diagnostics is included in the clinical specialty pathway**
- **developing, in collaboration with commissioners, the UK Genetic Testing Network and the National Institute for Health and Clinical Excellence (NICE), a robust process for the evaluation of clinical validity and utility of all genetic and genomic tests and markers and setting minimum national quality standards**
- **ensuring that NICE Diagnostics assess the validity, utility and quality of all new molecular tests, e.g. for cancer, with input from all relevant specialties including pathology, and**
- **putting in place agreements that require data from tests carried out by NHS-commissioned laboratories – in the NHS or private sector – to be made available to nationally designed research databases within a framework that ensures patient confidentiality and data protection.**

4. There has already been considerable work to improve service delivery, especially within pathology services. This should be applauded, as it is important that services are reviewed and modernised to ensure that they remain fit for purpose. The Human Genomics Strategy Group (HGSG) has given careful consideration to service development for genomic technology, building on the skill base and resources that already exist. **We would therefore recommend that DH and the NHSCB should work together to develop a service delivery model for genetic and genomic technologies with the objective of putting in place a network consisting of Genomic Technology Centres, Biomedical Diagnostic Hubs and Regional Genetics Centres.**

5. The current review of training and education for NHS healthcare professionals, including the establishment of Health Education England (HEE), provides an opportunity to refresh strategies for education and training in genomic technology. In the field of genetics, programmes started through initiatives such as the 2003 Genetics White Paper and Modernising Scientific Careers have already delivered impressive results. However, if health professionals more generally are going to embrace the potential of genomics, it is vitally important that work commences immediately on preparing them to respond to these challenges, given the length of time it takes to effect changes in education and training programmes. **We therefore recommend that urgent action is taken by DH, working with professional advisory structures, the NHS and the educational sector, to ensure that workforce developments do not lag behind service developments, and that an appropriately skilled workforce is available. In particular:**
   - **an immediate review of the existing provision of genomics training and education for each profession should be conducted (informed by the developments in education and training for healthcare scientists) and an action plan developed, focused on building the skills and knowledge of the current workforce and planning for the future**

- **as HEE is being established, education and training in genetics and genomics should form part of its overall function, with a requirement to develop core educational standards for genomics and to monitor outcomes**
- **the expertise of the National Genetics Education and Development Centre should be retained and it should become part of the National School for Healthcare Science, and, in conjunction with delivery partners, develop core quality standards for both the curriculum and the training needed for the current workforce, through a training needs assessment in each professional group**
- **the workforce planning needs of the specialist clinical genetics, bioinformatics and pathology workforce to support the new service models outlined in this report need to be urgently addressed, to ensure that skill gaps are minimised and continuity of supply is secured**
- **in conjunction with the higher education sector and other funding bodies, there should be further developments in masters, doctoral and postdoctoral training programmes in Clinical Genetics, epidemiology and bioinformatics to support clinical academic career development and research capacity and capability building for the future**
- **within the formation of HEE, consideration should be given to ensure that education and training curricula evolve to keep pace with the changing face of genetics and genomics, perhaps through wider arrangements for evolving training within and across healthcare science, and**
- **joint working between the NHS and the educational sector should ensure that educators are effectively trained and developed.**

6. The UK has greatly benefited from its proud history of robust and open debate on many areas of cutting-edge, human tissue and cell-based science. However, most individuals are concerned to retain control over their personal data and have the right to give consent to its use or otherwise. The HGSG believes that such consent is a basic right which should always be respected. We also believe that consent is more easily gained not only when individuals are presented with information on a specific, personal circumstance, but also when there is an understanding of the general needs and principles behind any request. **We would therefore recommend that the Government should ensure the continued provision of high quality public engagement on the ethical, legal and social issues associated with further integration of genomic technology into mainstream healthcare provision, and that a key aspect of this work should be the development of a national model for generic consent, through broad consultation with all relevant partners and stakeholders.**

1. A vision for genomics in healthcare

"Every so often, a scientific advance offers new opportunities for making real advances in medical care…we believe that the sequencing of the human genome, and the knowledge and technological advances that accompanied this landmark achievement, represent such an advance."

House of Lords Science and Technology Committee's report into Genomic Medicine (2009)[3]

We are currently on the cusp of a revolution in healthcare: genomic medicine – patient diagnosis and treatment based on information about a person's entire DNA sequence, or 'genome' – becoming part of mainstream healthcare practice. Increased knowledge and better use of genomic technologies and genetic data will form the basis for a reclassification of disease, with important implications both for predicting natural history and for identifying more effective therapies.

1.1 Genetics in the NHS

For some years now, we as a society have benefited from genetics in healthcare. The most obvious application of this is an increased ability to diagnose rare inherited diseases, caused by a mutation in a single gene, quickly and accurately. These conditions are collectively known as Mendelian disorders.

This has led to more accurate diagnosis of conditions such as cystic fibrosis, sickle cell anaemia and Huntington's disease, as well as hundreds more conditions. While these are individually rare – defined as affecting fewer than five in every 10,000 people – cumulatively they are surprisingly common. As the *2009 Annual Report of the Chief Medical Officer* for England noted, "There are more than 6,000 rare diseases, so in fact one person in every 17 has a rare disease – around 3 million people in England."[4]

The UK and the NHS have not been complacent in harnessing the potential of genetic testing. Considerable government investment over the past decade means that genetic tests for more than 1,000 diseases are now available via the NHS, which together have resulted in hundreds of thousands of patients and their families benefiting from a precise diagnosis. What's more, genetic testing enables diagnosis to be made earlier in a patient's life, often before the disease becomes more advanced, and so the patient can receive treatment sooner.

This is only right for a country that has played such a significant role in the advance of genetics. It was, famously, in Cambridge that the double helix structure of DNA was first discovered by Watson and Crick in 1953. In the 1970s, DNA sequencing was pioneered by Frederick Sanger, also in Cambridge, opening the door for the development of genetic testing, as well as wider research into whole genomes. Alec Jeffreys from Leicester and Edwin Southern from Oxford contributed two other key genomic technologies, DNA fingerprinting and DNA arrays. From the 1990s, UK scientists such as John Sulston played a key role in the Human Genome Project, which led in 2000 to the pivotal achievement of the first full sequence of the 3.3 billion base pairs of DNA that make up the human genome.

[3] House of Lords Science and Technology Committee (2009) *Genomic Medicine – Volume 1: Report.* 2nd Report of Session 2008–09
[4] Chief Medical Officer (2010) *2009 Annual Report of the Chief Medical Officer*

1.2 From single gene to whole genome: the advance of genomic technologies

Today, with genetic research continuing apace, many more conditions will be conclusively linked with a specific single gene mutation. But recent advances in medical science – in particular, the completion of the human genome – have opened up much greater possibilities, to understand the impact of genetic variation not just in a single gene but across multiple genes or even the whole genome. This is the basis for the field of genomics, which is the application of specific technologies to analyse wider sets of genetic information, and it is leading to transformational developments in our ability to determine disease risk and predisposition, to support more accurate diagnosis and prognosis, and to select and prioritise preventive or therapeutic options in a wider set of pathological disorders.

For example, new genomic technologies enable rapid comparison of an individual's DNA against the common 'reference' genome, or selected parts of it, which in turn creates significant opportunities in clinical care and public health. This has enabled researchers to pinpoint common genetic variants that are present in those who have a specific disease but absent in those who do not – so giving a new level of insight into disease risk. From a patient perspective, it means that preventive treatment can be considered. Already, this ability has helped to identify the genetic abnormalities that cause around two-thirds of cases of sudden cardiac death. If an individual possesses some of these abnormalities, decisions can then be made about preventive treatment.

Similarly, researchers have been able to analyse and compare the DNA of patients who have responded best or worst to a particular treatment to see if there is a common genetic link between them. This kind of research has provided a growing body of evidence about how certain genetic mutations lead to a side effect from a certain drug or, equally, where possession of a mutation promises increased efficacy. Used in a clinical setting, this insight can ensure that the right therapies are prescribed sooner.

Genomic technologies are also enabling pathologists to identify precisely how one disease subtype differs from another at a molecular level – an insight that can be used to ensure that patients get the most appropriate treatment for their condition. Already, this ability is being widely used to inform decisions about therapies for certain cancers – reducing the need for chemotherapy, for instance, and instead allowing patients to be treated with highly targeted drugs. In public health, genomic technologies are being used to identify exact variants of pathogens such as MRSA, *Clostridium difficile* and *Mycobacterium tuberculosis* and then track their transmission – offering significant advantages in tackling the spread of the variant and enhancing infection control.

Furthermore, genomic technologies have shown that even in common diseases such as diabetes, cancer or neurodegenerative diseases, there are significant numbers of individuals with forms of disease that behave like Mendelian disorders: in other words, many individuals with common diseases actually have forms of disease akin to single-gene disorders.

However, these advances are just the tip of the iceberg. The amount of genomic data available is now expanding rapidly, meaning that links between a genetic variant and a certain disease can be more readily identified and assessed. DNA sequencing is becoming faster, cheaper and more accurate; a range of different technologies and approaches to sequencing now exist which are allowing a global genomic knowledge base to be developed and expanded at speed – providing a vital reference point for future testing and research.

These next generation sequencing technologies have already reduced the cost of sequencing 10,000 fold: at current rates of progress, it is not unrealistic to suggest that in a few years' time, we will be able to sequence a person's entire genome for the same cost, or less, than it currently costs to sequence a single gene.

1.3 The potential of genomic medicine for the NHS

The potential of this for the NHS is considerable. It already means that we are able to diagnose diseases and detect variants far more precisely and quickly, tailor treatments both to the exact variant and to reflect a person's wider genetic make-up, and better identify those at higher risk *genetically* of inherited disease and a range of common chronic conditions.

Crucially, such capabilities and information could be available not just to specialists dealing with rare diseases, but to GPs in everyday settings, to help them identify subtypes of disease and to inform treatment decisions. Ultimately, GPs may even be able to confirm, through a simple test conducted in the practice, whether a patient has a particular strain of virus or bacteria, so that they can give the right advice. Patients will be able to get more effective treatments sooner; NHS resources will be put to better use with highly specific therapeutic pathways, producing better patient outcomes. This is the ultimate destination of the journey that began with the discovery of the DNA double helix, and the UK has, via the NHS, the perfect environment in which to realise the potential of genomic medicine within clinical practice.

While medical science gives us the belief that such outcomes are possible, they are by no means guaranteed. There is, and has long been, a significant gap between the worlds of cutting-edge biomedical research and everyday healthcare, as the NHS innovation report, *Innovation, Health and Wealth* acknowledged.[5] For innovations to bridge that gap there must be an active process of translation, helping the research reach maturity, demonstrating clinical utility and cost-effectiveness and identifying how those innovations can best be used in healthcare. That includes understanding and putting in place the systems and structures to facilitate adoption and diffusion, integrating new practice into established patient pathways, and meeting the education and training requirements of those working in frontline healthcare. To quote the *Innovation, Health and Wealth* report, "Innovation is not just about the originating idea, but also the whole process of the successful development, implementation and spread of that idea into widespread use."

Genomic technologies are more than just another innovation: they present a major step-change in medical practice and public health. They offer tangible benefits across

[5] Department of Health (2011) *Innovation, Health and Wealth: Accelerating adoption and diffusion in the NHS*

the spectrum of patient care, including GP surgeries, mainstream clinical specialties and highly specialist units. They can provide far greater insights into disease risk, thus supporting preventive action, and can help to ensure that patients receive the most effective treatment sooner. They are the very essence of an innovation that can add value and reduce cost. And, with the pace of technological change at an unprecedented level, many uses of genomics are set to enter mainstream clinical practice within the next three to five years.

If we do not prepare for this now, and develop a clear strategic plan to enable widespread adoption on an equitable basis, the lead that the UK currently holds in this field – both in pure scientific terms and in terms of current practice – could be severely, and perhaps permanently, undermined. The consequences of this would not only be bad for healthcare services, but entrepreneurial opportunities across industry, research and academia may also be affected.

1.4 Our vision for genomics in healthcare

We believe that the UK is well placed to lead the global adoption of genomic technologies within mainstream clinical practice and to support public health. The foundations lie in our world-class research, our existing use of genetics and the increasing partnerships between the NHS, academia and industry, making it possible, with the right motivation, to embrace innovation at every level.

These enabling factors have all been considered in stating our vision for genomics in healthcare in England – incorporating both the NHS and public health.

By 2020, the NHS will be a world leader in the development and use of genomic technology in the areas of healthcare and public health. It will be seen as a first-choice partner for industry, academia and research, contributing substantially to the global genomics knowledge base by supporting and facilitating innovation and novel research.

Genomic information and clinical genetic testing will be used across the NHS, improving diagnosis and treatment decisions by identifying the right therapies to maximise efficacy and reducing adverse effects. Genomic technology will be accessible on an equitable basis, with cost-effective and quality-assured processes in place for requesting and conducting tests, together with specialist expertise and advice to aid interpretation and clinical decision-making.

Healthcare providers within the NHS will confidently use genomic information within their roles, supported by enhanced and responsive education and training in genetics and genomics. Clear and unambiguous consent procedures will provide assurance to patients, making the individual the sole gatekeeper of their personal genetic and genomic data.

Effective public engagement will increase awareness of the role of genomic information in healthcare; how it can inform health choices; and the need for consent to access, study and use genomic data for the greater good.

1.5 Realising the vision

We believe that this vision, though ambitious, is realistic and achievable. However, delivering it requires a number of pieces of the jigsaw to be put in place. These include:

- rigorous and standardised processes for establishing the clinical validity and utility of genomic tests – and for quality assurance of each particular test, test centre and technology (chapter 4)
- clear commissioning standards for genomics and clinical genetic testing within clinical pathways, providing a straightforward and universal process for healthcare professionals to request tests and receive results (chapter 5)
- a secure and robust bioinformatics infrastructure to enable rapid, low-cost testing of genomic individual information against known variants (chapter 6)
- a healthcare workforce with the skills and knowledge to make effective use of genomic technology. This includes a strong cadre of genomics and genetics specialists in all specialties of medicine to carry out testing, manage data and analyse results, as well as greater understanding and awareness of genomics and its role across the range of NHS workforce and public health professionals (chapter 7)
- development of the UK legal framework to address adequately the complex challenges that genomic medicine – and particularly the availability of genomic information – creates, thus providing protection against abuses of genomic data (chapter 8), and
- a co-ordinated and consistent approach to engaging with the UK public to promote understanding of genomics and what it means for healthcare (chapter 9).

These are the initial steps on the next stage of what, to date, has been an exciting and fruitful journey for genetics-based technology in the NHS. They are the fundamental building blocks that must be in place if we are serious about integrating innovation into mainstream medicine within the NHS.

The proposals in this report cannot be achieved by the NHS alone. They will require continuing involvement of the research community, academia and – vitally – industry, both large and small. The UK and the NHS should be seen as the natural home for cutting-edge research, development and innovation. We believe that this is achievable, but the work must begin now.

2. The potential impact of genomic technology in the NHS and clinical care

The increased use of genomic information in the diagnosis of disease and selection of therapeutic pathways will revolutionise the knowledge available to clinicians as part of the decision-making process.

First and foremost, genomic analysis will be the tool used to understand, in many cases for the first time, the biological pathways disturbed in disease. This will lead to a new taxonomy for many diseases, subdivided via pathological process, which will refine our ability to predict natural history. For example, research has shown that mutations in the *IDH1* and *IDH2* genes occur in many invasive gliomas (the most common type of brain tumour). Genomic analysis allows clinicians to test whether or not these mutations are present. This is important, because there are considerable differences in the natural history and potential outcomes of tumours depending on whether they contain *IDH* mutations, and it is likely that specific treatments for such tumours will emerge in the future.

Not only does genomics increase our knowledge of the pathology of a disease (stratification), but it can also offer vital insights into how individuals are likely to respond to any drug therapy available according to variation in drug metabolism pathways or susceptibility to drug toxicity (pharmacogenetics). For patients, this means receiving the right therapy, in the right dosage, at the right time. Those who we know will not respond can be referred for alternative treatment earlier and, most importantly, patients who will have an adverse reaction to some treatments will be identified.

From a clinical perspective, this is clearly highly desirable: targeting patients who will respond positively to established therapy while focusing research on the development of other drugs that offer more comprehensive benefits for well-defined patient populations. From the service perspective, it promises shorter diagnosis and treatment pathways and the delivery of savings through avoiding the application of ineffectual therapies.

This increased ability to better stratify population cohorts and provide more personalised medicine complements the five domains on the NHS Outcomes Framework:

	Outcome	**How genomic technologies will help**
Domain 1	Preventing people from dying prematurely	By enabling earlier, more accurate diagnosis and prognosis, helping clinicians to select treatments that are more likely to be effective

Domain 2	Enhancing quality of life for people with long-term conditions	By helping to identify those for whom established therapies will be less effective, thus enabling an alternative to be used
Domain 3	Helping people to recover from episodes of ill health or following injury	By understanding precisely the pathology of a disease so that the right treatment pathway is selected sooner
Domain 4	Ensuring that people have a positive experience of care	By reducing the need for invasive testing procedures, and above all by accelerating the process of diagnosis, treatment and recovery
Domain 5	Treating and caring for people in a safe environment; and protecting them from avoidable harm	By enabling clinicians to check whether a patient's genetic profile makes them more likely to suffer an adverse reaction to a certain drug – thus avoiding the use of that drug where appropriate

But to ensure that genomic technologies can make this significant contribution to the patient outcomes, the NHS will need to consider a number of changes to practice, service delivery and commissioning.

2.1 Transforming diagnosis and therapeutic decision-making: stratified medicine

Across the entire field of healthcare, there is an increased emphasis on stratified medicine – essentially selecting a highly specific treatment pathway based on a greater understanding of the exact pathology of disease. These principles are not new, and have in part been driven by advances in molecular biology and genetics, as well as by a growing body of evidence which shows that commonly prescribed drugs and treatments, while working well for many, do not deliver the desired or anticipated results in others. The goal of stratified medicine is essentially the goal of medicine *per se*: to find the optimum treatment for a given condition. However, the advance of genomic technologies increases our ability to stratify, something that is already being demonstrated in cancer treatment.

As a result of numerous multi-centre clinical trials, particularly in the field of haematological malignancy, breast cancer and most recently colorectal cancer, the feasibility of a network model for testing in a clinically relevant timeframe has been demonstrated. In leukaemia, the minimal residual disease network currently provides

molecular stratification to international standards for treatment of children with acute lymphoblastic leukaemia (ALL) across the whole of the UK, and in addition now also provides a service for adults with ALL.

The potential is therefore clear. However, it is still the case that cancer drug therapies are typically effective in less than 30 per cent of the patients who receive them.[6] Any further insights that can increase this effectiveness rate could be invaluable.

Building on existing research platforms, the Cancer Research UK Stratified Medicine Programme aims to test whether molecular characterisation of tumours can be carried out as a standardised, cost-effective, routine practice during the treatment of cancer patients in the NHS.

Phase One of the programme, which is now under way, involves 20 hospitals across seven Experimental Cancer Medicine Centres. The programme aims to include 9,000 patients across six tumour types: melanoma and cancers of the breast, bowel, lung, prostate and ovary.

During this phase, patients will be asked their permission for surplus tissue from their diagnostic tumour sample to be sent to one of three NHS genetic testing labs, where DNA will be extracted and analysed for a range of molecular faults linked to cancer. Test results will be sent back to the clinical team to demonstrate a service that could inform treatment decisions. Test results and clinical data will be stored at the hospital, and could potentially support decisions made around the care of the individual patient, but are also collected in the NHS Eastern Cancer Registration and Information Centre so that appropriately authorised researchers can compare genetic differences, treatments and patient responses. This will build a valuable knowledge base linking outcomes to genetic data. In parallel, the Technology Strategy Board (TSB) is funding companies to develop new, cost-effective gene panel tests that can deliver these results in a single assay, as well as new secure information technology to collect, anonymise, store and analyse the data.

[6] Spear BB et al (2001) Clinical application of pharmacogenetics. *Trends in Molecular Medicine* 7(5):201–4

Genomic technologies supporting stratification of cancer treatment

Already, insight into genetic mutations is influencing the choice of therapies for certain types of cancer.

- The Cancer Genome Project is under way and aims to search for all genes that stop working properly in human cancer cells.
- In childhood ALL, it is now seen as standard practice to determine the patient's ALL subtype via DNA testing, as some treatments work better for some subtypes than for others – thus reducing the amount of time patients spend in hospital, as well as reducing the overall cost of treatment.
- In chronic myeloid leukaemia, one of the first diseases to be linked to a genetic abnormality (the 'Philadelphia chromosome'), the highly targeted treatment imatinib is now the standard therapy. However, further research has shown that mutations in the ATP binding site of the causative *BCR/ABL* fusion gene, which triggers the cancer, result in resistance to imatinib – but allow use of more effective agents such as dasatinib.
- Similarly, for patients with gastrointestinal stromal tumours (GISTs), targeted drug therapy with imatinib is now recommended by the National Institute for Health and Clinical Excellence (NICE) as a preferred treatment.
- Mutations in the *B-RAF* gene are associated with over half of all melanomas. A number of different *B-RAF* mutations have now been discovered, making it possible to be highly selective in the use of therapies. Recent research has found that in patients with metastatic melanoma with the *BRAF V600E* mutation, response rates and patient outcomes were significantly better with the targeted drug vemurafenib when compared with the standard treatment dacarbazine.
- In approximately 33 per cent of bowel cancer patients, the *K-RAS* gene does not function normally, meaning they are unable to benefit from the advanced drugs cetuximab and panitumumab, and can even be harmed by them. Testing for faults in the *K-RAS* gene is now an important precursor to treatment selection in bowel cancer.

Phase Two, planned for the two years 2013–15, will then look at how the lessons learned can be actively translated into routine practice within the NHS. The DH Cancer Policy Team has committed to a review of the commissioning and funding of cancer gene tests in parallel to this programme.

The programme is being supported by DH, the NHS, the TSB and pharmaceutical companies Pfizer and AstraZeneca. It aims not only to ensure that cancer patients in the UK get equal access to high quality molecular diagnostics, but also to help research by providing a large-scale, real-life understanding of the interaction between

genes and treatments. This will create a repository of molecular profiling data obtained with full patient consent, which should help to ensure that the UK becomes recognised as ideally suited to targeted genetic research in cancer – something that benefits our researchers, our healthcare research industry and, ultimately, patients.

Case study: Cancer genetics enabling stratified medicine for lung cancer

A non-smoker, aged 49, is diagnosed with non-small cell lung cancer after investigations for weight loss and a persistent cough. Her oncologist requests a DNA test on her tumour sample to help him make a decision on the best treatment for her. The test is requested because research has shown that tumours with a mutation in the *EGFR* gene have a high chance of response to targeted tyrosine kinase inhibitor drugs such as gefitinib. Although these patients represent a small proportion of all non-small cell lung cancer patients, the potential for giving them treatment with a significantly higher likelihood of benefit justifies the test.

The test shows that the patient's lung cancer contains this mutation and so she is eligible for one of these new therapies, which can be taken as a tablet, and which – in the appropriate population – has better efficacy than other existing therapies.

Genomic research is also beginning to indicate differences between variants in many conditions. An interesting example here is schizophrenia, where a recent study has highlighted small but important genetic differences in patients, suggesting there may in fact be multiple genetic variants of the disorder.

2.2 Pharmacogenetics: understanding how genetic background influences drug response

Other work is also being undertaken as part of stratified medicine innovation. The 2003 Genetics White Paper[7] established the position of NHS Chair in Pharmacogenetics (the study of the variability in drug response because of a person's genetic make-up), which was awarded to the University of Liverpool in September 2007. To date, the Chair's work has focused on both research and policy issues, as part of the plan for integrating genetics into mainstream practice, and provides funding for pharmacogenetics research projects. Projects have included randomised controlled trials of the drug warfarin, to test the clinical utility of genotype-guided prescribing compared with current clinical care. Such studies will help to build the evidence base for integrating pharmacogenetics into routine prescribing practice. In addition, the UK Pharmacogenetics and Stratified Medicine Network has been set up to engender collaboration, share best practice, and enhance interaction between different stakeholders (academia, clinicians, industry, regulators), all of whom will be playing a role in determining the pace of development in pharmacogenetics and stratified medicine.

[7] Department of Health (2003) *Our Inheritance, Our Future: Realising the potential of genetics in the NHS*, www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4019239.pdf

Pharmacogenetics research elsewhere is also beginning to yield data which is likely to have a clinical impact on the NHS by helping to avoid adverse drug reactions, which are estimated to cause approximately 6.5 per cent of all admissions to UK hospitals. Genomic analysis has been able to identify specific gene variants that make such reactions more likely.

For example, carbamazepine is an anticonvulsant and mood-stabilising drug used widely in the treatment of epilepsy and bipolar disorder, but around 1 in 10 patients experience significant adverse reactions to it. Recent studies have identified that possession of a specific gene variant (*HLA-A*3101*) is a predisposing factor for hypersensitivity reactions to carbamazepine – which could potentially lead to testing patients for this variant before prescribing the drug.

Pre-treatment testing for possession of gene variant *HLA-B*5701* is now routine in HIV clinics in the UK. This is because abacavir, an anti-HIV medicine that is available on the NHS, is also associated with a range of hypersensitivity reactions which in some cases can be fatal. Analysis has shown that these reactions are strongly associated with the presence of the variant, which also accounts for the rare acute liver failure seen in people prescribed the common antibiotic flucloxacillin.

Although important in their own right, these examples also indicate just how much additional knowledge around therapies could be gained from increased use of genomic technologies: the knowledge we possess today is just the tip of the iceberg.

2.3 Challenges to commissioning

While the ability to use genetic information to differentiate between tumours, or different variants of disease, can bring great benefit to patients, it presents a real challenge to commissioning. Quality assurance, equity of access and knowledge of the use of tests being developed and the management of new and/or increasing test costs will all prove significant practical issues on the road to mainstream adoption.

There is already some support for commissioners: the UK Genetic Testing Network (UKGTN) offers quality assurance on more than 600 simple genetic tests currently on offer to the NHS, and makes recommendations to commissioners. However, with genomics, the scale changes: there could be tests to identify many thousands of potential variants, and the clinical value of identifying these variants will differ considerably.

A further issue exists around quality. Many of these tests currently use Sanger sequencing, which was one of the first established methods of sequencing. Recent studies have shown that there is a need for rigorous quality assurance standards with such sequencing as there is a significant risk of high error rates, which then create the possibility of false diagnoses. This has been particularly demonstrated in tests for mutations in the *KRAS* and *EGFR* genes, which are used to help decide on treatment pathways for certain cancers: the method used risks failing to identify mutations in tissue samples where cancer tissue and normal tissue are mixed.

Given this risk, there is a clear need to improve and extend the quality assurance

process both for individual tests and for the centres or laboratories that conduct them. Consideration could be given to an expanded role for the UKGTN, in collaboration with NICE, to meet this requirement.

2.4 Changing the R&D model

The pharmaceutical industry has a clear interest in the development of stratified medicine. Traditionally, business models based on the discovery of 'blockbuster' drugs given to a very large number of patients managed to provide sufficient returns to cover the extremely high costs of research and development (R&D). This model appears to be increasingly unsustainable as stratification increases, and reduces the number of patients for whom each drug will be effective. In addition, the productivity of the drug development pipeline is at an all-time low as development costs increase.

This is an accepted reality and work has already begun to look at alternative, genetically based solutions. For example, the work cited above that is being taken forward on cancer is part of a much wider programme to bring forward innovative stratified medicine technology. This programme, called the Stratified Medicine Innovation Platform, is led by the TSB along with partners the Medical Research Council (MRC), Cancer Research UK, NICE, Arthritis Research UK, DH and the Scottish Government Health Directorates. The aim of the platform is to make the UK the best place to develop stratified medicine and to adopt it, with a particular focus on enabling commercial translation to support economic growth.

The work of the platform includes collaboration between the TSB and the MRC to take forward four projects in the area of inflammatory biomarkers for more effective drugs. These involve developing the use of biomarkers to predict how groups of patients will respond to inflammation and immunology therapies, and would then mean only relevant patient subgroups will receive specific therapies, leading to better results in alleviating symptoms and side effects.

A further three projects are developing business models and value systems to determine the best ways to co-develop drugs and companion diagnostics, and the ways in which subsequent reimbursement can be distributed across the value chain. This should increase the number of stratified treatments that are developed, the speed of their development and their adoption by healthcare providers.

This work is very much industry-driven: all seven projects are being led by a commercial partner. The projects aim to improve the business model for developing drugs by using genetic information. For example, by using genetic information to better understand the underlying biology of the disease and the treatment, areas of research that are more likely to fail can be avoided. By identifying which genetic mechanism the drug acts on, trials can be targeted on more homogeneous groups of patients who have that genetic mechanism, making trials smaller and more likely to show a clear impact.

Another example of innovation is the research that, using genome-wide association, has identified a biomarker

Intellectual property

Another important issue around R&D of genomic technologies is intellectual property (IP). In its report on IP and DNA diagnostics,[8] the Human Genetics Commission identified a profound tension between the diagnostic industry's desire to exploit the financial value of biomarker patents and the frequent routine infringement of such IP in NHS laboratories. The Commission concluded that support should be given to senior NHS management at a national level to help develop the capacity to manage biomarker IP issues. We agree that this conclusion is worthy of further consideration.

Further, we also agree with the conclusion of the recent NHS innovation report *Innovation, Health and Wealth* which states: "We need to develop a strategy that rewards the innovator whilst allowing others in the NHS to have access to their ideas."[9] The report states that the existing NHS IP strategy will be reviewed: this review should consider the IP challenges that arise around genomic technologies, and in particular the use of biomarkers, to create a governance system that encourages innovation and adoption, but rewards and recognises the underlying research.

that accurately predicts whether or not asthma patients will benefit from inhaled glucocorticoids – the most widely prescribed therapy. It is already recognised that as many as one in three patients may not benefit from this treatment, but it has not been possible to predict which these may be. The research found that possession of a variant in the glucocorticoid-induced transcript 1 gene (*GLCCI1*), which is likely to exist in around 16 per cent of the population, will reduce the effectiveness of inhaled glucocorticoids, providing the basis for highly targeted development of a new treatment.

2.5 Patients and their families

As already stated, genetic testing via the NHS is among the most advanced in the world, both in terms of the range of tests available, and the pathways and processes around genetic testing. When a patient presents with a rare genetic condition, testing is made available through regional genetics services to other family members who may be at risk. This not only informs treatment of those who are already showing symptoms but, as importantly, can also help some to avoid ill health, or provide them with reassurance that they will not be affected by the same condition.

[8] Human Genetics Commission (2010) *Intellectual Property and DNA Diagnostics*
[9] NHS Chief Excutive Innovation Review (2011) *Innovation, Health and Wealth: Accelerating adoption and diffusion in the NHS*

Case study: Specialist genetics enabling familial diagnosis

When an apparently healthy 31-year-old woman died suddenly in her sleep, a full autopsy was ordered by the local coroner. Toxicology and evaluation of the heart by a cardiac specialist found no apparent cause, leading to a verdict of sudden arrhythmic death syndrome (SADS).

However, recent advances in genetics have linked SADS to a wide range of genetic cardiac conditions, so her three children all underwent cardiac evaluation at a specialist centre: in two of the three, ECGs showed mild QT interval prolongation, an indicator of long QT syndrome (anomaly in the heartbeat) which can cause palpitations, fainting and sudden death. Genetic testing for long QT syndrome was then carried out on samples from the two children, which revealed a mutation in the *KCNH2* gene – and the same mutation was found in a small frozen tissue sample retained from the autopsy. The children could then receive specific therapy for the disease to try to avoid its effects.

The dead woman's sisters, and their children, were also tested and the mutation was detected in several of them, who could also be treated. Some of the other members of the family were also found to carry the mutation, even though their ECG tests were normal – meaning they were similarly at risk of SADS.

This process delivered a number of important outcomes for the family:

- It explained fully the cause of death of the 31-year-old woman.
- It identified others with the same abnormality and therefore increased risk, and so allowed them to be treated.
- It identified carriers of the abnormality, who can now receive appropriate information about the risks of passing it on.
- It identified those who are unaffected.

The health economic benefits of genetic test cascading – i.e. testing the family – compared with clinical cascading have been proven in several studies, including a study funded by DH.[10]

[10] Wordsworth S and Leal J (2005–08) Genetic testing for sudden cardiac death. University of Oxford Health Economics Research Centre, www.herc.ox.ac.uk/research/suddencardiacdeath

Although the benefits of this approach are clear, it is already a significant practical challenge, with tests available via the NHS for hundreds of diseases. Also, as genomics advances our knowledge of the role and significance of genetic mutation in the cause and effect of disease, demand for testing will increase even further. This in turn creates a potential demand not only for additional therapeutic support, but also for genetic counselling and other support services to be available to help people understand the condition they, or their family member, have acquired and what they can do about it. While the clinical benefit of testing may be clear, there will often be a significant personal impact on the individual concerned: some individuals may prefer not to know that they have a specific mutation, but others may want all the information possible about it.

While this will mean that more resources may be needed at the diagnosis stage, these may be balanced out by the benefits of being able to inform family members of the presence, or absence, of a specific condition, as the case study above shows.

Fetal health – how genomic technologies are transforming pre-natal care

Pre-natal screening is offered routinely in the NHS for Down's syndrome and selectively for pregnancies at high risk of other disorders, including sickle cell anaemia and thalassaemia. However, there are a number of issues with existing screening methods, which advances in genetic testing promise to eliminate.

For Down's syndrome, the initial screening is conducted by the combined test which comprises ultrasound and the measurement of biomarkers in maternal blood. This gives an indication of higher risk, but does not offer a diagnosis: this has to date required an invasive test, such as amniocentesis or chorionic villus sampling, both of which increase the risk of miscarriage.

Advances in genomics, including the advent of next generation sequencing, have led to the development of methods for non-invasive pre-natal diagnosis (NIPD) using cell-free fetal DNA (cffDNA) present in maternal blood. The approach is technically challenging but advances in genomic technologies are now making it a reality, with the obvious advantage of offering safe, reliable and non-invasive diagnosis requiring only a maternal blood sample rather than an invasive test, and thus improved patient outcomes.

In the USA, this method has recently been used to develop a non-invasive test for Down's syndrome, which in a clinically validated study demonstrated a sensitivity rate of 98.6 per cent in women with high risk pregnancies of 10–22 weeks' gestation, albeit with a small false negative rate. This test is now commercially available to women with pregnancies at increased risk of Down's syndrome through healthcare practitioners in the USA at a cost similar to invasive testing. It is possible that, following further evaluation and refinement of these approaches, analysis of cffDNA may be useful as

an alternative to current Down's syndrome screening. However, ultrasound will still be required and the approach to early pregnancy screening as a whole will require detailed evaluation prior to implementation in England, as current screening goes beyond screening for Down's syndrome.

In the UK, cffDNA has been used for determination of fetal *RHD* status in RhD negative mothers at high risk of haemolytic disease of the newborn. In this situation, if the mother is found to be carrying an *RHD*+ fetus in a second pregnancy, then she is at risk of a recurrence and requires close monitoring in a fetal medicine unit, whereas, if the fetus is predicted to be *RHD*–, further care can be delivered in her local unit as the fetus is not at risk. NICE recommended evaluation of this technology to spare RhD– women carrying a *RHD*– fetus from exposure to anti-D (a human blood product), with potential savings to the NHS. Recent studies have shown that such testing is accurate from 11 weeks' gestation using a high throughput methodology and, if implemented in the NHS in early pregnancy, will be associated with a reduction in anti-D administration of around 40 per cent. Further evidence suggests that this will be favourably received by mothers who are keen to avoid anti-D if possible.

Analysis of cffDNA is also used to determine fetal sex in pregnancies at high risk of sex-linked genetic disorders. In women at risk of serious X-linked disorders, such as Duchenne muscular dystrophy, where definitive diagnosis informs decisions regarding pregnancy continuation, invasive diagnosis was reduced to 41 per cent: the majority of female-bearing pregnancies were able to avoid invasive testing with the associated risks. Early knowledge of fetal sex in pregnancies at risk of congenital adrenal hyperplasia reduced the invasive testing rate to 13 per cent in male-bearing pregnancies and reduced the requirement for dexamethasone administration.

A detailed health economic analysis of the three-year pilot programme, involving two NHS laboratories, showed that compared with invasive diagnostic testing, NIPD was cost-neutral for fetal sex determination in these two situations. Following evaluation by the UKGTN, NIPD for fetal sex determination using cffDNA was approved for clinical use in January 2011.

Stratified medicine also creates issues on the patient side, as evidenced by the Herceptin® debate. Media coverage highlighted the improved outcomes for breast cancer patients treated with Herceptin®, causing considerable demand for the drug and anger that it was not universally available. However, Herceptin® is only proven to be beneficial for breast cancer patients who are HER-2 positive – a clearly defined subgroup of all patients – and so would not provide universal benefit.

This example provides an important communications lesson. In a world where stratified medicine and pharmacogenetics are more commonplace, testing will increasingly enable differentiation between

therapies, and the selection of those that offer the greatest efficacy for certain subsets of patients. In patients who are not in these defined subgroups, great care will need to be taken when relaying medical decisions, especially to those who might not have an alternative therapeutic option.

2.6 Restating the benefits and recognising the costs

The issues outlined above serve to underline just how much of a change genomic medicine will make to routine clinical practice and the way in which the NHS operates. They are by no means the only challenges, nor are they insurmountable, but they demonstrate the wide range of factors that need to be addressed on the route to mainstream adoption. Yet as the case studies show, the potential benefits of genomic medicine to everyday practice are immense, empowering GPs, helping to identify at-risk patients and improving treatment success rates.

However, there is a vital aspect of this evolution of genomics into routine clinical practice that we have not yet considered: the economic challenge.

Even though increased use of genetics and genomics in healthcare has the potential to reduce misdiagnosis, eliminate ineffective treatments and help to discharge patients sooner – all of which could be of direct financial benefit to the NHS – mainstreaming will come at a cost. Staff will need to be trained, bioinformatics capabilities will need to be developed, testing quality assured and treatment pathways identified. All of this will require investment, both in the short and long term.

As a group, we are convinced that the potential of genomics merits such investment; we also strongly believe that the foundation on which this work can be built already exists in the NHS, and the UK's industry, research community and universities. However, any future investment decisions must be made on a sound evidence base – not just on the strength of research and industrial capacity, but also on an appropriate assessment of health economics, and within a broader strategic framework. This forms the basis for our primary recommendation:

The Government should produce a White Paper, or similar cross-cutting strategic document, which sets out overarching policy direction on genomic technology adoption in the NHS. To inform this work, we recommend commissioning health economics studies to quantify the costs and benefits of investing in genomic medicine.

A further factor in the cost/benefit equation is the fact that the UK Government has identified genomics, and biomedical sciences more broadly, as a vital growth opportunity for the UK economy. With an internationally renowned research base, a strong heritage in the field and a wealth of emerging companies alongside established ones, the UK can justifiably claim to be one of the world leaders in genomic innovation. Adopting genomics in mainstream clinical practice in the NHS would accelerate the commercial translation and development of those innovations, which is clearly crucial to fulfilling the economic potential of genomics for the UK.

3. The potential impact of genomics on public health

As the previous chapter demonstrates, the potential of genomic technologies to transform diagnosis and enable stratified medicine is immense. Yet there is a strong case that the greatest – and most economically significant – benefits of genomics will be seen in public health.

The Faculty of Public Health defines public health as "the science and art of promoting and protecting health and wellbeing, preventing ill health and prolonging life through the organised efforts of society". Genomic technologies are already contributing to this by:

- enabling highly targeted and less invasive screening for common conditions – including pre-natal screening
- improving our understanding of gene–environment interactions and the causes of common diseases – enabling people to change health behaviours to reduce their risks, and
- dramatically improving the speed and precision of analysis of infectious diseases – so enabling more effective treatments to be developed or prescribed earlier and reducing the impact of disease outbreaks.

In time, as the volume of available genomic information grows, there may also be an important opportunity to use it to gain new levels of insight about the mechanisms of disease for common complex diseases such as diabetes, cardiovascular disease and mental health. This will potentially allow more effective classification of patients into mechanistic disease categories, leading to earlier therapy to help prevent disease initiation or progression.

In short, genomic technologies can contribute to achieving all of the outcomes within the draft public health outcomes framework, as the table below shows:

	Outcome	**How genomic technologies will help**
Domain 1	Health protection and resilience: protecting people from major health emergencies and serious harm to health	By enabling precise molecular analysis of pathogens, so helping to identify new variants of highly contagious diseases and track outbreaks
Domain 2	Tackling the wider determinants of ill health: addressing factors that affect health and wellbeing	By building our understanding of gene–environment interactions so that we have a greater insight into increased susceptibility

Domain 3	Health improvement: positively promoting the adoption of 'healthy' lifestyles	By providing targeted information to those at higher risk of diseases, based on their genetic profile
Domain 4	Prevention of ill health: reducing the number of people living with preventable ill health	By enhancing the accuracy and range of screening programmes to allow earlier detection of common diseases
Domain 5	Healthy life expectancy and preventable mortality: preventing people from dying prematurely.	By enabling earlier, more accurate diagnosis and prognosis, and by helping clinicians to select treatments that a patient is more likely to respond to – as in the NHS outcomes framework.

With the setting up of a new public health service in England, we believe there is now a unique opportunity to plan for the role that genomic technologies can and should play in all of these areas.

3.1 Developing highly targeted and less invasive screening programmes

The NHS offers a range of screening programmes for different conditions and at different life stages. These include the cervical cancer screening and pre-natal screening programmes where advances in genomics are already providing highly targeted and, frequently, less invasive approaches for a similar or lower cost than existing non-genetic methods.

The cervical cancer screening programme offers women over 25 a three-yearly screening to check for early signs of cervical cancer. Women with abnormal test results are referred for more advanced testing and, if appropriate, treatment.

Current screening relies on the identification of abnormal cells in a cervical sample. However, it is has been shown that cervical cancer is linked to an infection with the human papillomavirus (HPV). Recent advances in genomic technologies mean that when changes are found in a cell sample, a DNA test can now flag up the presence of the oncogenic subtypes of HPV, and so confirm the need for, and prioritise access to, treatment. Where the test does not detect HPV, an unnecessary medical procedure is avoided. This is a good example of using genomic technologies to analyse a viral genome rather than a human one – an approach that will be used increasingly in both medicine and public health.

More refined DNA tests for high-risk HPV types and for other risk factors will identify women with the highest chance of developing abnormalities that may lead to cancer, giving them a fast track to diagnosis and treatment. The proof of this concept

has been researched in the USA as part of the Addressing the Need for Advanced HPV Diagnostics (ATHENA) trials.

The need to improve both the sensitivity and specificity of cervical cancer screening will lead to an ever greater role for HPV DNA testing, over time replacing cytology as the first-line primary screen. A negative result is highly accurate, safely allowing a longer period between screening recalls and saving NHS resources.

The screening programme is not compulsory and a number of women choose not to participate. It is hoped that the introduction of the HPV test will help these 'hard to reach' groups as it lends itself to at-home sampling, which for some groups may be a more acceptable alternative to a clinic visit.

The overall impact of HPV DNA testing will be to streamline the existing successful screening regime, form a safety net for the new vaccination programme and, by concentrating treatment on those women at highest risk, make best use of health resources.

This example, along with the use of cffDNA to support fetal testing discussed in chapter 2, illustrates the potential of genomic testing to enhance existing screening programmes; it is possible too that genomic technologies will offer the opportunity to develop new programmes for certain conditions.

For example, it has been shown that the highly penetrant *BRCA1* and *BRCA2* variants are present in 3 per cent of women with breast cancer and 10 per cent of women with ovarian cancer. However, the frequency is higher in patients with a family history of breast cancer and/or ovarian cancer. While all women from 50 years of age are invited to attend breast cancer screening, those with a known familial risk of carrying a *BRCA* mutation are now offered a genetic test to see if the variants are present: where they are found, this provides important information on disease prognosis and informs treatment options.

Clearly, any screening programme involves a number of public health concerns that go far beyond test performance and include such issues as health economics and the organisation and quality assurance of a major programme. Particular issues include informed choice regarding uptake and ongoing support for those with positive screening results, including false positives.

3.2 Improving our understanding of how gene–environment interactions can affect health

It is widely accepted that lifestyle and behaviour have an effect on people's life expectancy. Indeed, as the public health White Paper *Healthy Lives, Healthy People* indicated, there is strong evidence to show that a change in health behaviours could help to avoid a substantial proportion of cancers, vascular dementias and over 30 per cent of circulatory diseases.[11]

Central to this is ensuring that people understand the health consequences of their lifestyle and behaviour choices so that they can make informed decisions about their own and their family's health, wellbeing and care. Our growing understanding of gene–environment interactions, driven by genomic technology, can make a significant contribution to this.

[11] DH (2010) *Healthy Lives, Healthy People: Our strategy for public health in England*, White Paper

Gene–environment interactions refer to the fact that the same environmental exposures can have different effects on disease risk in people because of genetic differences. Our increased ability to study genomic variation is now making it possible to pinpoint the genetic factors that can lead to higher levels of risk. Raising awareness of these genetic factors – as part of public health programmes – will therefore help individuals make more informed decisions about health and wellbeing, although we recognise that it is by no means clear that knowledge will lead to lasting behaviour changes.

One example of this is recent research into multiple sclerosis (MS). While the cause of MS is still unclear, it has long been believed that there is a link between MS and vitamin D deficiency. A new study has found a very clear link between a particular genetic variant, which causes reduced levels of vitamin D, and MS. When people inherit two copies of the variant in gene *CYP27B1*, they develop a genetic form of rickets – a disease caused by vitamin D deficiency. When they inherit just one copy, a particular enzyme is affected which leads to lower levels of vitamin D.

The link was identified following genomic sequencing of families where four or more members had MS, and was then tested in 3,000 families where a child has MS but parents do not. Researchers found 35 parents who carried one copy of this variant along with one normal copy. In every one of these 35 cases, the child with MS had inherited the mutated version of the gene rather than the other, normal gene. This provides strong evidence for the role of vitamin D in the development of MS, and builds a case for proactive public health measures to encourage increased vitamin D intake.

Other examples include:

- The discovery in Dundee of the central role of filaggrin in eczema, which focused attention on the importance of skin permeability to sensitising agents.
- Studies which have shown that there are strong links between certain genotypes and the likelihood of developing severe rheumatoid arthritis as a result of smoking.
- The retrospective conclusion that genetics had demonstrated the link between folic acid and neural tube defects before it was fully recognised epidemiologically.

As the quantity and quality of available genomic information increases, further such links will be identified and communicated, via different public health channels, to help people to make more informed lifestyle choices. Further into the future, when it becomes cost effective to routinely sequence whole genomes, the focus may shift to providing increasingly targeted lifestyle information and advice at different life stages.

3.3 Improving the speed and precision of analysis of infectious diseases

Using microbiology to understand the exact pathology of infectious diseases is vital not only for rapid diagnosis and treatment, but also for infection control. When a disease presents a wider threat, either because of its ability to spread or to resist standard treatment, microbiology assumes a public health role.

Traditionally, identification of an exact variant or resistant strain involved in an outbreak has required either growing the organism, or using chemical and

immunological methods. However, these methods take time, which in the context of an outbreak can be a significant issue.

Genomic analysis, and in particular whole genome sequencing, of pathogens has the potential to remove these limitations. It is a single method that will yield all of the information that can currently be provided by all traditional methods together, and promises to be possible in near real time. Sequencing will allow unprecedented levels of precision in the comparison of isolates in putative outbreaks and chains of transmission, locally, nationally and globally, as well as identification of antibiotic resistance and virulence markers. In short, once it is available at an affordable cost, whole genome sequencing will offer a universally applicable typing methodology that will replace the majority of systems currently used for clinical and public health investigation of infection.

At present, we are in a state of transition, where the application of genome sequencing to the investigation of infectious diseases is at the translational stage. The ease with which genomic sequencing can be applied to investigation of disease varies with the type of pathogen involved. For certain diseases, such as tuberculosis, where the genomes of the infecting organisms change slowly at a predictable rate, there is already evidence that whole genome sequencing could be applied as a standard typing method nationally (or even globally) in the near future in a way that would surpass information on outbreaks and transmission obtained via current methods (see case study). For other organisms whose genomes vary within the course of a single infection, or where there may be carriage of multiple genomic variants, interpretation of results is less simple.

However, whole genomic sequencing is already yielding results in the investigation of transmission of *Mycobacterium tuberculosis*, *Clostridium difficile* and *Staphylococcus aureus*. It has proved particularly powerful in tracking hospital acquired infections and providing guidance of managing episodes in hospital settings.

It is important to underline here that microbial genomes are many times smaller than the human genome and, given the current rate of decrease in sequencing costs, it is realistic to expect that within a few years the cost of sequencing a bacterial genome will approach that of current routine laboratory tests for identification. This suggests that sequencing should become the routine method for identification in hub microbiology laboratories in the fairly near future, and indeed translational research is under way, funded through the UK Clinical Research Collaboration (UKCRC), the National Institute for Health Research (NIHR) and the Wellcome Trust, that will make whole genome sequencing of microbes user-ready for the public health management of infectious diseases. This work is closely supported by the Health Protection Agency (HPA), which is set to become part of Public Health England (PHE).

It will be possible to use the results in-house for clinical management and infection control, while innovative approaches that combine genomic data with clinical data from hospital and primary healthcare record systems will allow public health practitioners to detect, track and respond to new strains of pathogens, upsurges in infection and outbreaks in near real time and at a local, national or international level.

Case study: Using genomic technology to investigate outbreaks of tuberculosis

Whole genome sequencing has now been used to investigate tuberculosis outbreaks in Canada and, as part of a UKCRC-funded programme (Modernising Medical Microbiology), in England. Tuberculosis is a particularly suitable infectious disease for developing whole genome sequencing approaches, because of both the large amount of existing epidemiological and microbiological data on previous outbreaks and the nature of the disease, which evolves slowly and predictably. The findings from sequencing results were compared with traditional epidemiological and microbiological methods, in particular variable number tandem repeat (VNTR) characterisation. Whole genome sequencing unambiguously showed that:

- cases from different towns, not suspected as being linked, were part of the same outbreak
- cases linked by social and geographical history represented more than a single outbreak
- the source or 'super spreader' in an outbreak could be inferred from genetic differences between isolates, and
- some cases had been incorrectly assigned by VNTR.

In other words, whole genome sequencing proved more sensitive and specific than currently used typing methods and offered unique insights into the epidemiology of tuberculosis. On the strength of current evidence, it seems that it will not be long before we see the implementation of whole genome sequencing as the standard method for investigating the transmission of tuberculosis.

3.4 Informing health planning and the new public health service

In addition to the specific uses of genomics to support health protection, there is reason to expect genomic information will play an increasingly important role in the strategic planning of public health services. The underlying goal in this is to provide effective, cost-effective, high quality, equitable service provision to an entire population.

As set out at the start of this chapter, these various potential – and current – uses of genomics add up to a compelling case for genomics to be high on the agenda as the new public health service in England develops. The Government has declared its intention to adopt an evidence-based approach to public health, and genomics will be a vital source of information within this.

Already it is clear that the new PHE will integrate and incorporate a number of current public health related bodies such as the HPA, the public health observatories and cancer registries. One of its responsibilities will be to provide specialist and reference microbiology functions, which have previously been the responsibility of the HPA. In reviewing how these functions are delivered, we would hope that PHE takes account of our

recommended service delivery structure for genetics and genomics, and in particular the role of the Biomedical Diagnostic Hubs.

The HPA in particular brings with it an expertise in the use of genomic technologies and analysis that will be an important foundation for the future of PHE and the public health community more generally. For example, over the past eight years, the HPA has developed a significant bioinformatics capacity with core staff, grant-funded staff and PhD students. This capability has not only supported the HPA's own genomic analysis (e.g. of viral outbreaks) but has also provided training in the field. It is one example of a specific and important function which will be inherited by PHE, which we can hope will be nurtured within the new organisational structure.

It has also been announced that PHE will be responsible for ensuring the provision of services for emergency preparedness and health protection, and that it will fund those services that contribute to health and wellbeing primarily by prevention rather than treatment aimed at cure. Clearly, there is a significant role here for genomics.

At the local level, public health will be driven by local authority-based Directors of Public Health. We believe it is essential that these directors understand the potential of genomic technology for public health – an issue we return to in chapter 7. Currently, genomics is rarely seen as a priority within local public health provision and planning, but, as illustrated above, there are many potential applications of genomic science to improve public health.

We believe that there needs to be a more comprehensive engagement with genomic technologies from within the public health profession. In particular, the Chief Medical Officer England and her colleagues in the devolved administrations should be asked to ensure UK-wide co-ordination and consistency for the role of genomic science in the public health practice of the 21st century.

It is also clear that the links between public health and NHS services must be protected, and that public health specialists are given the opportunity to provide input to and influence NHS commissioning and service planning at local level, reflecting the fact that public health will be part of the NHSCB's mandate.

The importance of this can be simply summarised by returning to the five domains of the proposed public health outcomes framework, shown at the start of this chapter. In all five, the potential of genomic technology is significant. It is therefore vital that genomics is 'built in' to the ongoing development of public health in England if its benefits are to be realised.

4. Translating genomic innovation to establish clinical validity and utility

With the development of automated DNA sequencing techniques in the 1990s, genomic research as we know it today became possible. The many millions of items of data that make up a genome sequence could be processed at ever increasing speed and accuracy, leading to the publication of the first complete human genome sequence in 2000, with the UK a leading contributor in this international effort.

4.1 The development of the reference genome

Since then, developments have followed at breakneck speed. Further genomes have been sequenced, at a lower cost each time, building up a more comprehensive picture of genomic variation. There are a growing number of international databases that hold this 'raw' genomic information, including the European Bioinformatics Institute (EBI) in the UK, the National Center for Biotechnology Information in the USA and the DNA Data Bank of Japan. The quantity of data held in these databases is currently doubling roughly every six months.

The scientific community has now embarked on the '1000 Genomes' project – an international collaborative project involving the Wellcome Trust Sanger Institute – which will feed into globally co-ordinated efforts to build a core of information, available to researchers across the world, on which to base genomic analysis.

Many different databases have been created to store genomic and genetic data. Initially these were often locus specific, but in recognition of the value to research of having a comprehensive database, a succession of projects have now begun to integrate data and move towards a shared repository of genotypic and phenotypic variation. The Human Variome Project (HVP) was launched in 2006 as an international attempt: it has now been endorsed by UNESCO and is negotiating to gain World Health Organization recognition. The Chinese Government has recently pledged $300 million to the HVP and wishes to support up to 5,000 gene-specific databases.

A similar initiative, MutaDATABASE, has been developed in Belgium with a plan to create an open source database and to develop an affordable reporting software tool, which will be available for purchase. Several major US commercial laboratories have begun to contribute diagnostic molecular data to MutaDATABASE.

The International Cancer Genome Consortium is mapping and collating data about cancer genomes from across the world. Cancer Research UK is leading on prostate and oesophageal cancers.

Work is under way, funded by the Collaborative Group on Genetics in Healthcare, to help integrate these efforts as well as other European initiatives such as Orphanet, an online summary of information about genetic diseases led from France; the European Union Committee of Experts on Rare Diseases; and the RareDiseasePlatform. As a proof of principle, active databases include the Cystic Fibrosis Mutation Database (CFTR1) and the InSiGHT (International Society for Gastrointestinal Hereditary Tumours) database, which now has an international committee evaluating variants of uncertain significance: both of these are recognised by the HVP and MutaDATABASE.

Understanding the gap between academic findings and clinical usage
Even with the work mentioned above, the compilation of such databases will not lead to a finite list of variants. As can be seen in recent findings from the University of Nijmegen, instead of being explained by traditional inheritance, many developmental disorders may be the result of spontaneous genetic mutations. The research suggests that some 60 per cent of severe learning disabilities can be explained by specific spontaneous genetic variants defined by whole genome sequencing.[12] Clearly, the potential significance of this is considerable, but much further research is needed before these findings can be used within clinical care. Research at Nijmegen, and elsewhere, is already under way on this process.

In the UK, the Human Gene Mutation Database developed at Cardiff University and operated by BIOBASE Ltd captures published variation. To support the diagnostic process in UK genetic testing laboratories and to improve the quality and consistency of diagnoses, NHS laboratories submit data on clinically significant mutations to the Diagnostic Mutation Database operated by the National Genetics Reference Laboratory in Manchester. In the future, it will be important that the NHS has access to a database containing clinically validated variant data.

It is clear that the international interest in the development of the reference genome is extremely high. Given this, it is beyond question that it is in the UK's interest to maintain its close working relationships with these initiatives to ensure that we get maximum benefit from their development.

4.2 From genotype to phenotype

A core reference genome provides the essential context for identifying genetic variation. But for information about variation to have medical value, the effects of each variation need to be understood too. This is known as phenotyping, and refers to the descriptive characteristics of a disease; that is, what the patient might suffer from in clinical terms. Such phenotyping might be simply the description of the disease, or might include radiological, physiological or pathological descriptions relevant to the patient. It also seeks to answer questions such as how does a specific gene variant 'behave'? Can the possession of a certain genetic pattern be clearly and repeatedly linked with increased susceptibility to a disease or reduced response to a therapy? Does a molecular difference between two variants of the same virus change the severity of symptoms, or make it resistant to a particular treatment?

This is a field where the volume of knowledge is set to grow exponentially. For every genetic variant, there may be many different clinically significant effects (or indeed, in some cases, there could be none at all), identified over a number of years and in many different studies.

Two approaches to creating a rich phenotyped database, alongside genetic information, are being pursued in the UK

[12] Vissers LE, de Ligt J, Gilissen C et al (2010) A de novo paradigm for mental retardation. *Nature Genetics* 42(12):1109–12

at present. UK Biobank holds data on a large population of individuals who have been phenotyped and are being followed for disease events. Their DNA is available for analysis and will create new insights into the relationship between genetic variants and phenotypes. Similarly, two established bioresources, the Oxford BioBank and the Cambridge BioResource, have collected DNA from large numbers of individuals, and these individuals are available to be selected for further phenotypic characterisation based on their genotypes. This allows detailed studies to be carried out to establish the links between genes and phenotypes.

This entire area needs close scrutiny. A link observed in one study may not be apparent in another. Even when a link appears to be clear between a certain genetic variation and a commonly observed effect, there is no guarantee that the variation is the cause of that effect.

4.3 Establishing clinical validity

The clinical validity of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical disease or predisposition. An important way of validating the link between a particular genetic variant and a disease is to find out whether other people with the same variant have the same disease. Furthermore, it is important to establish the prevalence and strength of the variant–disease association in a given population.

This is by no means a unique challenge for genomics: instead, it is a case of applying the same rigorous standards used in other areas of medicine to a new field. The challenge, however, is that unlike more established disciplines, the process for testing validity relies on technology and information that is itself evolving at speed.

Even with single-gene disorders, a number of different values will need to be determined to establish clinical validity. The evaluation will be more complex if the disease is linked to a number of different genes, as much more information needs to be analysed and many more secondary questions may emerge. The sequencing and testing technologies being developed today are better equipped to do this, but these ‘next generation sequencing’ technologies themselves are in development (see box on the next page). What’s more, there remains the practical challenge of having sufficient genomic data, of sufficient quality, to test against. Once a gene variant is seen in a certain number of cases, it becomes a valid thesis, but clinical validity – and the decision to invest in making the test widely available – will require much more evidence.

Next generation sequencing

Next generation sequencing is an umbrella term for a range of sequencing technologies that reduce the time and cost of DNA sequencing while increasing accuracy, compared with the original method known as Sanger sequencing. These new technologies are characterised by the ability to sequence huge numbers of fragments simultaneously. For example, the development of methodologies associated with massively parallel sequencing starts by immobilising template DNA molecules on a glass surface, rather than analysing DNA in a liquid state. This means that millions of target molecules can be sequenced in parallel (i.e. at the same time).

Currently there are three main next generation sequencing technologies: reversible termination, pyrosequencing and ligation. At present it is not clear which, if any, of these will ultimately be appropriate or effective for medical use, nor which will be the cheapest or most accurate for routine use. It may well be the case that more than one becomes widely used: if this happens, it will be essential that standards are put in place so that the sequence data that is generated can be read and used centrally, rather than having different databases for the data generated by each sequencing technology.

For a full description of how these different sequencing technologies work, along with a comparative analysis of their respective benefits, refer to the recent PHG Foundation report, *Next Steps in the Sequence*.[13] There is also a range of even newer approaches to sequencing, using nanotechnology for example, which are also detailed in the report.

4.4 Establishing clinical utility

Having established a valid relationship between the test for a variant, or other biomarker, and disease, it is also necessary to show that the test is clinically useful – that is, it will inform patient management and result in an improved clinical outcome.

In some cases, this will be relatively straightforward, as the test will confirm the precise diagnosis, thereby allowing for focused treatment and care. In other cases, however, the utility may be less certain: it may be just as effective or useful to diagnose without genetic confirmation, for example; or it may be that the diagnosis will not lead to any differences in treatment, if there is no particular therapeutic pathway available.

It is clear that a rigorous assessment of both clinical validity and utility is an important requirement for effective commissioning.

This work should be integrated with international efforts intended to develop international standard reference databases for clinically significant changes in all human genes.

[13] PHG Foundation (2011) *Next Steps in the Sequence*

4.5 Building on existing evaluation processes

Since 2002, the UKGTN – a collaborative group of genetic testing laboratories, clinicians and commissioners, and patient support groups – has been responsible for the evaluation of all new tests for single-gene disorders. The UKGTN aims to ensure the provision of high quality equitable genetic testing services across the UK. It evaluates the analytical validity and clinical validity and utility of tests through a standardised 'gene dossier' process, providing the necessary quality assurance around the testing process. Once a new test has been evaluated for use in the NHS, recommendations are made to NHS commissioners.

The gene dossier process has been used to provide a solid evidence base for the introduction of more than 600 tests for single-gene disorders into the NHS. These are now widely available across England, although local differences in provision of testing exist. These are a result of variation in the implementation and commissioning process, rather than the effectiveness of the evaluation system. The role that the UKGTN has played to date in advising the NHS is an example of a quality assurance framework that has delivered considerable benefit. For the future, the NHSCB should consider developing further the work of the UKGTN as a possible way to measure the clinical validity and utility of new markers and tests.

In March 2011, the UKGTN published its report, *Review of Commissioning Arrangements for Genetic Services and Strategic Recommendations*.[14] We see merit in the UKGTN's report and agree with many of its conclusions.

Another organisation with the potential to play a key role in the clinical evaluation of new tests is NICE, under its Diagnostics Assessment Programme (DAP). The DAP aims to support the NHS in adopting clinically and cost-effective technologies more rapidly and consistently. Now fully established, it is well positioned to evaluate new tests, and its role in providing a methodology for the evaluation of tests that are likely to have high *clinical* value, together with significant cost benefits for the NHS, should be considered by the NHSCB.

We welcome the actions outlined in *Innovation, Health and Wealth*[15] which focus on supporting prompt implementation of NICE guidance. This will be essential in ensuring that once tests are approved, they are made available equitably across the NHS.

However, the approaches historically used by NICE for the evaluation of therapeutics – in particular, the measurement of quality-adjusted life years (QALY) – may not be so appropriate to all of the potential applications of genomic technology. For example, testing parents and children in families where one child has a severe learning disability might reveal important information to inform and help reproductive decision-making; it might also save health services the time and resources that would be spent on non-genetic testing. Neither of these benefits can be measured in QALY terms. Many existing genetic tests deliver benefits 'downstream'; for example, diagnoses of single-gene diseases may

[14] UKGTN (2011) *Review of Commissioning Arrangements for Genetic Services and Strategic Recommendations*
[15] Department of Health (2011) *Innovation, Health and Wealth: Accelerating adoption and diffusion in the NHS*

help with initial treatment, but equally importantly they can influence future treatment decisions and potentially avoid the most severe symptoms developing: again, these are not necessarily measurable via QALY.

Similarly, professional bodies of specific clinical specialists, including the Royal Colleges but also smaller, more specialised organisations, should be involved in providing advice on defining the core evaluation process. Leading research bodies such as NIHR, the MRC, Cancer Research UK and the Wellcome Trust should also be consulted.

A further crucial component in the process may be Genomic Technology Centres which, as we explain in chapter 5, we believe should be a key part of the infrastructure for enabling the NHS to make use of genomic medicine. These centres would bring together clinical, academic, scientific and bioinformatics specialists and so would be an obvious asset in evaluating both validity and utility; they would also be essential to the process of translational research – helping to define how genomic innovations are used and adopted in a clinical setting.

Together, these different organisations will all be able to contribute to the evaluation and demonstration of clinical validity and utility; however, rather than continuing to operate multiple different systems for evaluation, the goal must be to achieve a single, consistent and robust process.

4.6 Setting rigorous quality standards

Once a test or technology has demonstrated its clinical validity and utility and been approved by NICE, the UKGTN or another relevant authority, we would hope that it would be quickly made available across the NHS and that – in line with *Innovation, Health and Wealth*[16] – it would be quickly adopted.

However, it is imperative that rapid adoption does not come at the expense of quality. If tests are not conducted correctly, the risks of inaccuracy are high. This is hugely damaging not only to patients but also to public confidence in the entire field of genomics. To avoid these risks, we believe it is essential that the NHSCB puts in place rigorous quality standards that any potential provider of testing must meet. These standards should look at the way tests are conducted, DNA samples are managed and data is analysed, stored and shared.

4.7 Continuing to invest in and support research

Clearly, funding to enable research to develop the evidence to discover and implement pharmacogenetic biomarkers remains important. The recent initiatives led by the TSB and Cancer Research UK are a start, and we welcome the further £130 million funding for stratified medicine, announced in the Government's *Strategy for UK Life Sciences*,[17] building on current investments by the TSB and the MRC. However, more will be needed in order for the UK to retain its international lead in this area.

Many of the most significant developments in the use of genetics in the NHS came about as either direct or indirect results of government investment following the 2003 Genetics White Paper. Moreover, NIHR's Biomedical Research Centres and Biomedical Research Units are also leaders in scientific translation: the latter

[16] Department of Health (2011) *Innovation, Health and Wealth: Accelerating adoption and diffusion in the NHS*
[17] Department for Business, Innovation and Skills (2011) *Strategy for UK Life Sciences*

in particular have focused successfully on translating research in priority areas of high disease burden and clinical need that were historically under-represented, such as cardiovascular disease, dementia and gastrointestinal disease.

The process of translating leading-edge research and innovation into mainstream medicine will require adequate funding and a commitment to supporting research – for example, by reducing the bureaucracy involved in setting up research programmes. These, and other measures, will be essential in order to accelerate the transition and adoption of new technologies and testing methods.

5. Service delivery: commissioning and utilising genomic technology

Our vision for the use of genomics in the NHS makes it clear that cost-effective and straightforward processes need to be in place for requesting and conducting tests. As an integral part of our first year's work plan, we therefore created a Service Development Working Group, which was tasked with making recommendations about how genomic information and advanced clinical genetic testing could best be used, and the kinds of processes and structures that would be needed. This chapter focuses on those recommendations.

5.1 Guiding principles

In the chapters to date, we have made it clear that we believe genomic medicine will revolutionise the UK health system. However, in defining how we believe genomics should best be delivered, we are convinced that existing structures and processes should be used where possible: recapitalisation should not be the default option and we will not deliver an effective service by simply ensuring that everyone owns the most recent hi-tech 'kit'.

Instead, the primary challenge must be better identifying the most effective ways to incorporate genomic medicine into existing clinical pathways and programmes. This will allow services to be expanded quicker, and respond to the need for improved testing processes.

Any proposed infrastructure needs to be able to cope not only with genomics as it is today, but also with the future demands, as technology advances, the number of tests increases and ultimately techniques such as near-patient testing in primary care and outpatient settings become possible. The key assumption is that technology will be continuously developed and changed to improve accuracy, speed and cost, and that the science of genetics will provide a steady flow of new actionable information that will be used in all branches of medicine.

Finally and crucially, the infrastructure should be designed to deliver the desired outcomes – consistent and quality-assured clinical and molecular testing in the NHS with equity of access to services, where appropriate, to improve patient care – without putting unnecessary strain on the healthcare system.

5.2 The service delivery infrastructure

Currently, the majority of NHS genetics services are delivered by a network of Regional Genetics Centres that not only conduct testing – mostly for inherited diseases – but also offer genetic risk assessment, genetic diagnosis and counselling. They are multidisciplinary, with scientific and medical staff working alongside counsellors and data handling specialists, and typically serve a regional population of 2–5 million people. These services are mainly directed at supporting the specialty of Clinical Genetics, so will need reconfiguration if they are to provide services across a wide range of medical disciplines, such as cancer and microbiology.

In addition, some testing for inherited diseases takes place in other laboratories in pathology, such as biochemistry and haematology (haemoglobinopathies and thrombophilia). These laboratories generally offer both DNA and non-DNA based testing around a specific subject. They are also more likely than Regional Genetics Centres to provide testing for acquired genetic mutations (such as cancers).

While the majority of these services provide high quality services, concerns have been raised both inside government, highlighted in the House of Lords report,[18] and externally that testing services can vary considerably in quality. Some centres are still using outdated technology that does not produce the most informative data; some also lack access to technology development and evaluation, as provided by strong academic and translational groups. The expected expansion of genomics in medicine is likely to exacerbate these issues, and to underline the fact that current structures may not have the capability to meet new needs.

It is apparent that a transformation will be required in the relationship between specialist clinical and laboratory genetic services and the relevant clinical specialties. It is proposed that the former will move increasingly into a leadership and expert support role across many diseases and that the clinical specialties will take responsibility for diagnosing and managing specific inherited diseases. A recent report from the PHG Foundation, *Genetics and Mainstream Medicine*,[19] provides a more detailed consideration of how this might work. Moreover, as genetic testing increasingly forms part of routine medical practice, the development of capabilities in genomics (and the support that specialists in clinical and laboratory genetic services can provide) will be increasingly important.

Pathology services are also in need of organisational change. The Carter Report[20] proposed significant improvements in cost-effectiveness and quality through consolidation, and the advent of genomics – with its requirement for specialised equipment – makes this case even stronger. There is now an increasing need for highly specialised centres to undertake more sophisticated testing supported by expertise in immunohistochemistry, genomic testing and classical histopathology. It is clear that the centres most capable of achieving specialised testing are ones with both pathology and genomics capabilities, linked to technology development and translational research capabilities funded by NIHR.

In devising a service delivery infrastructure, we have sought to address these different issues so that genetics and genomics services can be made available equitably and at speed. **As per our recommendation 4, we believe that the most effective way forward will be to develop current service delivery models into a network consisting of Genomic Technology Centres, Biomedical Diagnostic Hubs and Regional Genetics Centres.** A small number of specialist Genomic Technology Centres would translate research knowledge into service protocols that the NHS can adopt. Biomedical Diagnostic Hubs would deliver the diagnostics services, at a scale that allows high quality and affordable testing. Regional Genetics Centres would then provide the link to patients with familial disease, initially directly diagnosing and managing patients but eventually supporting clinicians in the relevant specialty as outlined above.

This network model is similar to that now being implemented for pathology services within the NHS. It offers the vital benefits of consolidating both expertise and technology, to make services more efficient, productive and effective – essential given the anticipated surge in demand.

[18] House of Lords Science and Technology Committee (2009) *Genomic Medicine – Volume 1: Report* 2nd Report of Session 2008–09
[19] PHG Foundation (2011) *Genetics and Mainstream Medicine*: *Service development and integration*
[20] Lord Carter of Coles (Chair) (2006) *Report of the Review of NHS Pathology Services in England*

- **Genomic Technology Centres** would operate as specialist centres of excellence with a focus on the interface between translational research and service innovation in genomic services. They would bring together clinical, academic, scientific and bioinformatics specialists to translate cutting-edge research in a collaborative and inclusive manner to ensure the participation of specialist expertise and promote the adoption and spread of research and innovation. They would play a key role in evaluating new markers for cost and clinical effectiveness. They could specialise in specific disciplines, e.g. biomedical informatics, as part of their centre of excellence remit, operating as a knowledge development and dissemination service for the Biomedical Diagnostic Hubs and Regional Genetics Centres. A key requirement is that these organisations are designated as Genomic Technology Centres through open competition against a specification, and commissioning would be through the NHSCB.
- **Biomedical Diagnostic Hubs** with a strong integrated molecular capability should be developed to incorporate *all* current laboratory-based diagnostic services in pathology and genetics (inherited and acquired diseases). They are likely to be regional/network hubs of significant scale, and are emerging from the national Pathology Transformation Programme. A possible model for them can be seen in Cancer Research UK's Stratified Medicine Programme, which has defined the role of the hub as delivering a rapid, comprehensive, high quality screen of tumour biomarkers to inform management of all newly diagnosed cancer patients. These hubs would operate as the essential interface between the clinician and the pathologist for rapid and appropriate testing, particularly where co-ordination of sample processing and analysis is crucial. The exact number of such laboratories and the scope of testing to be undertaken requires further development but is likely to include high throughput analysis, frequently requested biomarkers and, for example, molecular tests for microbiology, virology and haematology.
- **Regional Genetics Centres** will continue to have an important role in the diagnosis of inherited disorders and the management of familial aspects of disease. They will continue to provide a key interface with patients with genetic disease. Clinical Genetics services will have an expanded role, in partnership with specialist clinicians, to provide genetic expertise as genetic services are expanded and embedded in clinical pathways. As clinicians in other specialties become more proficient and the number and range of specialties involved continues to expand, it is envisaged that the relationship between Regional Genetics Centres and other specialties will evolve to one which provides leadership, expert support and mentoring, and management of particular family issues such as reproductive counselling. Although these centres are unlikely to be responsible for all forms of expensive genome-wide testing, they will need at all times to have access to the

sequence data and analysis on their patient populations. This would not necessarily require data stored locally: patient sequence data could be stored securely in a national database, making it accessible to the centres but also to the patient's physician or GP. Such evolution will be vital to ensure provision of equitable high quality specialist services for heritable disorders across the UK, including the provision of support for genetic testing.

The exact number of each of these organisations will depend on capacity, demand and function, and further analysis is required. However, we believe that it is unrealistic and uneconomic to argue that all the Regional Genetics Centre laboratories will be able to capitalise and re-capitalise with the new generation of genomic platforms. Although some may be designated as Genomic Technology Centres, it is suggested that those laboratories not designated are associated with Biomedical Diagnostic Hubs where possible, to maintain and make use of their expertise.

Service reconfiguration to support diagnostics and therapeutic decision-making is already happening in other comparable countries. France's Institut National du Cancer initiative, a national network of molecular genetics platforms, has been set up to provide analysis of molecular biomarkers. It now offers a free testing service to all cancer patients, regardless of referring institution (public or private). At the request of the patient's oncologist, the pathology sample and clinical notes are sent to regional 'platforms' for screening and analysis. A platform consists of a number of individual labs, so that patients can benefit from all available testing techniques for their pathology. The regional network and funding system avoids a postcode lottery, enables patient access to the tests, and gives more rapid results (within two weeks). In the case of rare markers, specimens may be sent to another regional platform for specific analysis. The initiative is now developing research data capture and quality assurance mechanisms.

5.3 Commissioning tests

A central element of the service delivery process is setting out how genomic and genetic tests will be commissioned. In chapter 4, we focused on the need for tests to reach required standards of clinical validity and utility. In this section, we look at the next stage: the 'approval' of clinically valid tests for use within the NHS, and how such tests are actually requested on a day-to-day basis.

In making recommendations about the future commissioning of genomic or genetic services there would appear to be, at its most basic, a choice between leaving it to the market or putting in place processes which will ensure a more controlled introduction of new services. Any recommendation on commissioning genetics services must conform to NHS commissioning structures.

As set out in our recommendation 3, we believe that **the NHSCB should take a lead in the commissioning of genetic and genomic services through NHS commissioning structures**, with the aim of ensuring that high quality, standardised genetic and genomic testing is available across the NHS. This should include oversight of devolved commissioning

structures, be they regional, sub-regional or local clinical commissioning groups; given the complexity and novelty of genomics, we believe that it will need to play a pivotal role, particularly in the next few years, in the translation of genomic medicine into routine practice.

Specifically, **we recommend that a member of the NHSCB should be charged with the overall responsibility for genetics and genomic services and the adoption of genomic technology in the NHS**. The role should be supported by appropriate expert advice (ideally an expert advisory board) to enable current services to be built upon and improved and to make recommendations on how innovation in research and technology can be adopted more quickly and spread more easily across the NHS.

Currently, a range of medical genetics services are contained within the Specialised Services National Definitions Set, and are the only specialised service commissioned by all four NHSCB commissioning clusters (formerly Specialised Commissioning Groups) in England. We believe that this should now become the responsibility of the NHSCB, and the services within the set should be expanded to include appropriate special pathology tests, including infectious diseases and cancer and new markers/tests when necessary. By doing this, it will be possible for these services to be commissioned against an agreed set of quality standards. This will also help with equity of delivery. This approach fits with changes in fast-growing somatic mutation testing technologies, for example in cancer molecular pathology, where stakeholder groups are recommending centralised commissioning to address the access and quality issues that have been identified.

However, when it comes to requesting an individual test, or panel of tests (as opposed to commissioning the service), different rules should apply:

- high volume tests and routine pathology tests should be requested locally, and
- specialist pathology tests should be requested through the NHSCB.

This approach will ensure that the NHSCB is not a bottleneck to accessing tests, and that clinicians can request a test quickly and easily to support diagnosis or inform therapeutic decisions. When it comes to more specialist tests, of which individual clinicians or local commissioners may have little knowledge, centralised commissioning will ensure that tests are used in the correct circumstances.

Decisions may also be required on what will merit a whole genome analysis. Some conditions will need this *de novo* each time, but in other situations, where only a handful of separate tests are being proposed, whole genome sequencing could still be the most valid option – not least because, once done, it provides a wealth of information that could inform care of that individual in the future.

The definition of what is ‘specialist’ and what is ‘routine’, and the split between local and national commissioning, will need further consideration. As the role and function of the NHSCB become finalised, a detailed analysis should be carried out, involving appropriate authorities and

stakeholders, to ensure that there is clarity over the respective responsibilities and that any possible barriers or silo working practices are addressed.

We would therefore recommend that, **as part of its lead role in the commissioning of genetic and genomic services, the NHSCB should:**

- **develop, in collaboration with commissioners, UKGTN and NICE a robust process for the evaluation of clinical validity and utility of all genetic and genomic tests and markers and set minimum national quality standards, and**
- **ensure that NICE Diagnostics assess the validity, utility and quality of all new molecular tests, e.g. for cancer, with input from all relevant specialties including pathology.**

5.4 Paying for tests

One vital question for the NHS as a whole is how the costs of tests should be met: should they be funded centrally, as part of a resource available to all, or should the cost be part of the diagnostic care pathway? Our view is that, given the potential volume of tests that could be requested, the limits on testing capacity and the need to avoid unnecessary testing, the **cost of genetics diagnostics should be included in the clinical specialty pathway** – irrespective of the clinical setting in which the patient or their family members are seen – and should include both the rare and common Mendelian disorders.

This will ensure that genetic testing is used where it offers advantages over other diagnostic methods, but not simply as a matter of course in all diagnoses. Care pathways that are already developed for common disorders may need to be updated to include genomic tests as appropriate. However, for this process to work effectively, it is essential that costs are transparent, so that commissioners can make appropriate decisions about the tests they use. This is why we recommend that **the NHSCB should develop national tariffs for genetics and specialised pathology testing**.

Having such tariffs will help to provide commissioners with assurance on value for money and clinical utility, and place genetic testing firmly in the mainstream 'shop window' for commissioning.

Work is already under way through UKGTN to develop a costing system that measures diagnostic activity to enable the application of an agreed pricing mechanism. Further consideration, through NICE and UKGTN, of how this could be adopted within future NHS commissioning structures should be made. Any system should align costs within the patient pathway, promote efficiency and quality, and support technological developments.

5.5 Testing services

The actual testing process is intrinsically straightforward: a DNA sample taken from a patient will be compared with existing data to identify pinpoint matches – the presence of a specific mutation or pattern. In the short term, this process will continue to rely on physically delivering the samples to established laboratories, which in our model will mostly be the Biomedical Diagnostic Hubs, as well as the increasing number of private sector providers. These laboratories have the sequencing equipment and

access to bioinformatics databases needed to test the samples. Results are reported back to the clinician or team that requested the test, to inform their clinical decision-making.

Although effective, under this current system the cost, inconvenience and delay in carrying out specific genetic tests can create a barrier to routinely taking genetic information into account in clinical decisions. Therefore we anticipate the process evolving in a number of different ways, reflecting advances in medical science and biomedical informatics technology.

It is predicted that the costs of whole genome sequencing could drop to the point at which full sequencing is as cheap as conducting any specific test. This could see more and more individuals having their genomic sequence mapped and the data stored in some central point. At this point, individual clinicians or healthcare professionals will be able to request that electronic tests be carried out automatically, by software algorithms, via clinical decision-support systems. Test results could be obtained at minimal cost, with no additional inconvenience to the patient or healthcare professional, and in real time.

It is this potential that may well lead to routine genomic sequencing, as once genomic information can be used in every clinical decision to which it has even a small relevance (i.e. in deciding between two treatment pathways where the difference in effectiveness is marginal), then over a lifetime the cumulative effect will be significant. Once the value of this extra information to healthcare outcomes for an average individual exceeds the cost of genome sequencing, it could be justifiable to routinely determine an individual's genome sequence.

It is in this kind of environment that the role of the specialist geneticists will change; as well as focusing on ongoing research and 'specialist' tests, their role will increasingly evolve into expert support. Even before routine whole genome sequencing, the increased demand for testing, and increasingly standardised processes, are likely to mean that more and more testing is carried out by laboratories at a distance from the genetics services. Clearly, such provision must be quality assured, and we would like to see the introduction of minimum national quality standards for genetic and genomic services under the auspices of the NHSCB.

Currently, laboratories providing genetic and pathology services are required to participate in External Quality Assurance Schemes (EQAS) and be registered with Clinical Pathology Accreditation (CPA), now part of the United Kingdom Accreditation Service. In addition, the Royal College of Pathologists (RCPath) has issued a list of key performance indicators for laboratory services.

These schemes would provide a good starting point, but service specifications for providers and commissioners should be reviewed and improved to include quality standards and key performance indicators. There should be continuous dialogue with CPA to ensure that accreditation criteria reflect the future transformation of services, and with EQAS to ensure that new schemes are introduced as new markers come into service. On the commissioning side, service commissioning specifications

should include, within their criteria, a requirement that all providers of genetic and genomic services should fully meet CPA accreditation requirements. This will then ensure compliance with the Care Quality Commission's minimum threshold standards for such diagnostic services.

All laboratory services should be required to provide regular performance data to evidence that services are meeting service specification and quality criteria. These quality outcomes will also provide benchmarking information to inform payment of best practice tariffs, inform commissioners of best practice and assure continuous quality improvement.

6. Biomedical informatics: underpinning genomics

The rapid progress in genomics over recent years is as much a reflection of developments in IT as it is of advances in medical science. The processing power of today's computer technology makes it possible to analyse the sequence of DNA at a speed (and cost) which makes it feasible to use genomics in mainstream healthcare, while developments in data storage mean that the genuinely huge quantities of information that genomics generates and uses can be stored and managed practically.

This essential link between IT and genomic medicine is why bioinformatics is such a fundamental aspect of delivering genomic services, a fact recognised in both the House of Lords report[21] and the Government's response.[22] The HGSG was specifically asked by the Government to examine the bioinformatics requirements for the use of genomics in the NHS, in particular the House of Lords recommendation to set up a dedicated Institute of Biomedical Informatics. A working group of experts from within the HGSG was given the remit to focus on these issues. Their recommendations form the core of this chapter.

6.1 The changing data demand

To date, the recording and interpretation of clinical genetic variants has largely been carried out using the many locus-specific databases (LSDBs), most of which focus on an individual gene or a few gene loci. These databases are generally maintained by clinical research groups with a specific interest in particular diseases or loci, and while they provide a valuable resource in terms of genetic testing for those diseases, they vary widely in terms of software interface, stability of support, data accessibly and data quality.

Establishing an Institute of Biomedical Informatics

As noted above, the House of Lords report called for the establishment of an Institute of Biomedical Informatics. The HGSG subgroup on bioinformatics also came to the conclusion, summarised in section 6.5 below, that the principle of an institute was a valid one, albeit that the form it should take – either virtual, making use of distributed computing systems and efficient networking, or a 'bricks and mortar' institute – was something that needed further discussion.

As we have made clear, the HGSG supports the establishment of centralised, national genomic databases and biomedical informatics services that provide the translation, interpretation and archiving of raw genomic data to support the development of clinical tools. We recognise that considerable cost could be associated with such an initiative. One way to address this issue could be to deliver the Institute of Biomedical Informatics function through innovative use of existing provision as part of future initiatives. However, successful delivery through such an approach will be dependent on the full compatibility of the technology used, particularly if service components are fragmented.

[21] House of Lords Science and Technology Committee (2009) *Genomic Medicine – Volume 1: Report* 2nd Report of Session 2008–09

[22] HM Government (2009) *Government Response to the House of Lords Science and Technology Committee Inquiry into Genomic Medicine*, London: The Stationery Office

It is clear that LSDBs will not be suitable to support genomic medicine for three fundamental reasons:

- The sheer volume of data involved. Instead of focusing on a few genes or a specific disease, genomics necessarily involves whole genome data, which will mean a huge increase in storage requirements. Many labs will have neither the space nor the desire to manage this much data.
- The need for data to be integrated to derive the benefits of genomic analysis. Whether for research or diagnosis, it would be neither practical nor desirable to have to reference multiple separate databases. This is why a great deal of effort is already under way globally to create a database infrastructure to store and organise all publicly available human genome sequence data to create the representation of the structure and variation of the human population, and a separate but linked database infrastructure to integrate data from LSDBs and other validated sources about the link between genetics and disease (genotype and phenotype).
- The lack of mature tools to analyse whole genome sequence data in a clinical setting. This data is 'noisy' and requires sets of appropriate filters to make sense of it, making it currently hard to process swiftly in a clinical environment. Identification of causal mutants depends on identifying genes with variants associated with the pathways involved in disease, and ideally recognising if and when that variant has been seen in the context of a similar disease phenotype in another patient. There will continue to be a need to link the database with knowledge and input from clinicians and scientists who understand disease, as it is here that the link between genetic variant and phenotype is likely to be identified. This information will grow rapidly and the power of genetics will depend on the ability to access as many genotype/phenotype relationships as possible.

6.2 The foundations of a biomedical informatics infrastructure

As was explained in chapter 4, initiatives are under way globally to create raw data repositories and it will be important to manage the rapid growth in data deposits. In the UK, the Government has committed to support this expansion with funding through the Biotechnology and Biological Sciences Research Council (BBSRC) for the European Life Sciences Infrastructure for Biological Information (ELIXIR) project led by EBI. ELIXIR is one of the European Strategy Forum Research Infrastructures proposals. Additional work will be needed at EBI to create improved database structures to represent sequence variation extracted from the underlying raw sequence data.

Although EBI is also extensively involved in building genotype/phenotype databases, in particular via Ensembl, a joint project with the Sanger Institute, this does not contain significant amounts of patient-related clinical data. It is also clear that the publicly available stored data from literature and LSDBs is still incomplete and additional resources are required to log genotype/phenotype relationships.

These basic research databases are essential global resources, which is why it is vital that they remain open access and benefit from global investment – and from a commitment at all levels to add to them continually – contributing data as well as drawing on the information available. In this way, the databases can capture and organise all available evidence for likely relationships between genotype and phenotype, including effects of variation on disease. We believe it is essential that the UK continues to support these research genetic databases through funding agencies and initiatives such as ELIXIR.

Many of those involved in generating data from clinical samples believe that, in order to ensure optimal access for clinicians to genomic data, there will be a requirement to utilise centralised or distributed computing and networking solutions. This is being piloted by Illumina Inc. at present but provides the opportunity for patient data to be accessible continuously to all those involved in patient care, as well as to those involved in the analysis of the data, whether centrally or, more likely, in a distributed fashion.

Proposals for an international infrastructure

The US National Academy of Science recently convened a workshop to outline possible pathways to the future of genomic medicine. The workshop's output, a report called *Toward Precision Medicine*,[23] was released in November 2011 and calls for the creation of an international infrastructure for storage and analysis of genomic and molecular information that is flexible and responsive, serving the needs of discovery scientists, bioinformaticists and clinicians to more precisely define the mechanisms of human diseases.

6.3 From core data to clinical analysis

However, while the role of these databases is pivotal, the output from them cannot be used directly in the clinic. Therefore the vital next component of the infrastructure is a layer of clinical annotation to sequence variants – essentially explaining the clinically validated consequences of such a variant. This is currently done in LSDBs, but again needs to be centralised both for quality control purposes and to facilitate access. This activity goes beyond the remit of the basic research organisations that provide the underlying databases, and seems a natural core role for the proposed centre for biomedical informatics services which we believe should be established.

The centre would exist to bridge the gap between research genetics databases and health service clinical decision support systems. In particular, it should be responsible for the creation and cataloguing of an open-access database of clinical variants that builds on and interoperates with existing research database infrastructure components for storing, organising and annotating genomic DNA and patterns of variation at EBI and Sanger. We discuss its potential role, purpose and form in further detail in section 6.5 below.

With this centre in place, the next necessary aspect of a biomedical informatics infrastructure is a means of querying an

[23] www.nap.edu/catalog.php?record_id=13284#description

individual's genome sequence, against the database of clinically significant variants, to provide a usable report to healthcare professionals. Following our recommended delivery structure (see chapter 5), this is likely to take place, initially at least, via the Biomedical Diagnostic Hubs which will have the necessary ICT infrastructure to support large numbers of queries in near real time, as well as potentially via commercial providers which meet the necessary quality standards.

Querying this data will also require the development of algorithms to compare and combine data, such as from multiple variants. These will largely be developed in academia as part of the research and evaluation process, but here too some commercial providers are already developing their own proprietary systems. In the longer term, such algorithmic systems are likely to go beyond basic analysis of an individual's genetic variants and be based on a more complex computational model combining other information collected for that individual. It is the objective of large-scale research consortia, such as the IT Future of Medicine project (www.itfom.eu), to develop such approaches.

A primary concern for implementing this sort of scheme has been the scale of storage requirements for human genome sequence data. However, this may not prove to be such a major barrier: ultimately, once the reference genome is sufficiently stable, the only data that needs to be stored for each individual is variants, compared with that reference sequence.

Once an individual's data has been sequenced, it should then be possible to process it to create a personal variant file, which – using data compression – would be no larger than existing X-ray images. This means that files would be small enough to be attached to electronic patient records, and so would need to be determined only once during a patient's lifetime. An exception is cancer, where tests may need to be rerun in case the tumour has evolved, although the data from each cancer genome can be similarly processed, reduced in size and attached to a patient's record.

This approach obviously relies on the cost of sequencing an individual genome dropping sufficiently to make it viable as a routine practice, but, as discussed in chapter 5, it is conceivable that this will be the case within just a few years. In the interim, genomic data can be sequenced as needed, and the same principle of storing only the variants applied.

For this to happen, informatics tools will need to be developed which can process raw genome sequence data from an individual into a standardised compressed variant file, small enough to attach to a patient's electronic health record (EHR) in existing GP systems, and which can then compare a variant file with the global database of clinical variants, to deliver a computational genetic test result into decision support systems used by healthcare professionals.

Technology in practice
The Deciphering Developmental Disorders (DDD) study[24] in the UK provides an interesting model for data sharing and use. It has united all 23 Regional Genetics Centres in the search for the genetic causes of childhood malformation syndromes, using combined resources, including the latest microarray and sequencing methods, and expertise to accelerate sequencing and analysis of results. The aim is to provide specific diagnosis to those children and improve diagnosis of specific development disorders in the future.

6.4 Biomedical informatics and research

As well as supporting clinical decision-making, the other vital role of a biomedical informatics infrastructure is to support ongoing research into genomic medicine. This is part of both the initial research – looking for patterns in patient records to help identify potential links between genetic profiles and disease – and the clinical validation process, and should support both academic and commercial research. The infrastructure outlined here provides the basis for such research, but there are a few issues that need to be resolved.

Firstly, it is already recognised that there is substantial value in being able to look for patterns across the EHRs of the population and this has led to the creation of the Research Capability Programme in NHS England and similar programmes in both Scotland and Wales. An 'honest broker' system is planned to enable research using EHRs aggregated from GP practices in an environment that ensures the data privacy of individuals, and when variant files are attached to EHRs, these could be similarly aggregated. Research using EHR personal variation files will allow the discovery of new genotype/phenotype correlations that will feed into both basic variation databases and the clinical annotation databases of the biomedical informatics centres. We therefore believe it is essential that the honest broker system is formally extended to allow this.

Secondly, there is a clear benefit for research purposes both in the UK and elsewhere of being able to use international databases of information. Clearly, the infrastructure costs of storing, organising and cataloguing what will be phenomenal amounts of raw data are considerable, so we believe that this needs to be supported by a global public endeavour to ensure open access not to the data itself but to summary outputs, allowing federation with equivalent databases at a national and an international level. Outputs of these components being public resources could also facilitate competition and significant economic activity in developing tools and interfaces, reducing barriers to new entrants.

The corollary to this is that data generated in the UK within or for the NHS (i.e. a public service) must be added to the core databases for common good. This must apply not only to NHS genetics services, but also to any laboratories that are commissioned by the NHS to analyse genetic information. That is why, as part of our recommendation 3, we believe that

[24] See www.ddduk.org for more details

the NHSCB should be responsible for putting in place agreements that require data from tests carried out by NHS-commissioned laboratories – in the NHS or private sector – be made available to nationally designed research databases.

6.5 Creating a national Institute of Biomedical Informatics

The HGSG established a biomedical informatics subgroup to focus on developments in this area. Their conclusion was that, as stated in our recommendation 2, **given the rapid development in sequencing technologies and the need to interpret genomic data in a clinically relevant way, DH in partnership with BIS and other relevant partners should develop further the proposals to establish a centre to provide biomedical informatics services**.

Such an institute would and should play a vital role in developing and embedding genomics as an integral part of the diagnostic and treatment pathway, and would have four key responsibilities:

- developing and providing biomedical data and informatics services (focused on genetics and genomics data) that are fit for purpose for use in the NHS, including advising on an appropriate database for clinically validated variants
- performing investigator-led world-class research in biomedical informatics to enable translational medicine
- providing training in biomedical informatics for researchers and NHS staff, and
- providing an interface to industry, including technology transfer.

Its core function, clearly, would be to provide biomedical data and informatics services. This would include establishing, maintaining and managing genetic variant databases, assuring the security of the data but also allowing open access to that data, in line with data protection requirements.

A key part of managing that information and providing quality assurance will be through setting rigorous standards for data entry and referencing. Such standards should aim to be global, so would need to be developed in collaboration with all relevant partners and stakeholders. Likewise, the institute should develop its own systems with the clear goal of guaranteed compatibility with current systems to ensure the effective, secure and efficient sharing of data.

A related function would focus on evaluation of new tests: drawing on its expertise in data analysis, the institute would be able to help develop an evaluation system to confirm the quality of data presented to support new tests. We would also envisage the institute working with NICE, the NHSCB and UKGTN to develop the core criteria for clinical implementation of new genomic diagnostic tests.

The institute would also be a centre for biomedical informatics research, including developing algorithms for analysing and interpreting biomedical data; improving interpretation of genetics and population data; standardising and interpreting EHRs (including text mining); data mining; exploring the effects of variation; phenotype/genotype correlations in humans; disease models; stratified medicine; and systems medicine. Such a

centre of excellence would pump-prime new discoveries, new tools and the longer-term emerging UK bio-economy.

In all of this, a national Institute of Biomedical Informatics would clearly play a vital role at the heart of UK genomics, acting as an interface between research, NHS services, commissioning and industry. It would necessarily have strong links with other research institutes.

6.6 Improving the wider NHS IT infrastructure

The discussion to date has focused on the core bioinformatics infrastructure that we believe will be needed. However, it is equally clear that, to allow equitable access to genomic information, there also need to be a number of more general improvements to NHS IT platforms.

For example, it will be necessary for healthcare providers to send variant files to hubs for testing against core databases. Even in the compressed format outlined above, files are likely to be several megabytes. There will need to be sufficient network capacity to allow large numbers of such files to be shared. This will also create new demands for storage of information locally.

Priority must be given to the development of infrastructure links between healthcare providers to allow the rapid and secure electronic transfer of large volumes of genomic data, and to improve data storage and handling capability within NHS organisations.

In addition, standards need to be adhered to with regard to what data is stored and how it is compressed; in particular, there should be a national agreement on the interpretation of the RCPath/Institute of Biomedical Science guidance on *The retention and storage of pathological records and specimens*.[25]

6.7 The skills challenge

Finally, as well as the technical side of bioinformatics, it is essential that the urgent skills challenge is addressed. Currently, there is a recognised dearth of bioinformaticians both in research centres and hospitals. Without sufficient analysts, researchers and database administrators, any investment in technology will be of limited value. Therefore, there needs to be an urgent focus on training around bioinformatics – which we consider in more detail in the next chapter.

[25] www.rcpath.org/resources/pdf/g031retentionstorageaugust09.pdf

7. Preparing the workforce

As this report makes clear, genomic technology is set to have a transformative effect on mainstream healthcare, offering the ability to improve and accelerate diagnosis, understand the predictive risk of developing disease, inform therapeutic decisions and support public health programmes. Unlike Clinical Genetics, which hitherto has essentially been a small specialist service focusing on genetic variants and single-gene disorders, genomic medicine is not a niche but rather an integral part of mainstream clinical practice.

This in turn means that it is essential that mainstream clinical professionals understand genomics and can use genomic technology and information effectively within their everyday working lives. Without such understanding, across the NHS as a whole, the potential benefits of genomics will not be fully realised.

Major changes are currently being introduced into the way in which healthcare and education and training in England are planned, co-ordinated and delivered. This report reflects these changes to the best of our knowledge.

7.1 Understanding the education and training need

Genomics is a relatively new field in medicine, and as such has not been part of standard medical or healthcare professional education and training, apart from for specific specialist groups working in Clinical Genetics. While this is changing, it fundamentally means that the majority of those working in healthcare in England have a limited knowledge of genomic technology – and even less practical experience of applying genomics within their role.

This is of major significance because, as our report has shown, genomics will touch on almost every role and every clinical field – from GPs using individual genetic information to select between treatment pathways, to specialists being able to understand the exact pathology of a disease, to nurses carrying out screening programmes. While clearly some of these tasks are role-specific, and will thus require specific procedural training, there is a broad requirement to build an awareness, knowledge and understanding of genomics across the whole of the NHS and public health clinical professionals, focusing on issues such as:

- what genomic technology and information can tell us and the ways it can currently be used
- what is involved in sequencing and testing, and why it is so important to add individual data back into the wider knowledge base, and
- data protection issues around the use, sharing and storage of genomic information.

It will also be important to embed a level of awareness, knowledge and understanding of genomics in the education, training and development of public health specialists (including consultants in communicable disease control and public health directors), commissioners, managers and healthcare leaders.

These developments would ensure that the significant investment in bioinformatics technology, in setting up Genomic Technology Centres and Biomedical

Diagnostic Hubs, and in basic and translational research and evaluation will deliver returns, in particular in terms of outcomes for patients and broader benefit to the population.

The mainstreaming of genomics into more widespread clinical practice will lead to a considerable increase in demand for genetic testing, interpretation and genomic data management.

To meet this demand, it will be essential to secure the ongoing supply and development of the specialist Clinical Genetics workforce – particularly healthcare scientists (including clinical scientists, genetic technologists and biomedical scientists), medical pathologists, toxicologists and microbiologists – with the skills to conduct and interpret such tests and to manage sequencing technologies. As the volume of genomic data generated and stored increases, more specialists in bioinformatics will be needed to curate it and ensure that it is correctly added to core databases and stored securely. In this latter field, there is already a recognised skills shortage.

This means that, as well as creating a new service delivery and IT infrastructure, there will need to be a concerted programme to recruit, educate and train the specialist Clinical Genetics staff who will work in the new Genomic Technology Centres, Biomedical Diagnostic Hubs and the national biomedical informatics service, as well as to retain and develop those already working in these areas.

Given these considerable skill requirements which must be met if genomics is to be successfully integrated into mainstream healthcare, we believe that there needs to be a systematic approach to education and training in genomics for the wider healthcare workforce and for specialist Clinical Genetics staff– and that this needs to be clearly recognised within commissioning and funding arrangements for the future.

We understand that, within the new health education system, the Secretary of State for Health will have an explicit duty to secure an effective system for education and training which will ensure that the health workforce is equipped to deliver the NHS and public health outcomes frameworks. We welcome this duty, and in particular its clear focus on setting and monitoring educational outcomes.

We believe that, as this report has shown, genomics has a clear potential to assist in delivering the outcomes frameworks for both the NHS and public health, which in turn justifies investment in education and training in genomics and in particular the use of genomic technology.
A co-ordinated national approach to genetics and genomics education within HEE once it is established, providing full oversight, would match the national approach proposed for the commissioning of specialist genetic services.

7.2 Incorporating genetics and genomics into medical and healthcare education

The core infrastructure for medical and healthcare education and training in England is generally well established, involving a network of medical schools, universities and further education colleges that deliver (often under NHS contract) the education and work closely with NHS

organisations to provide clinical training placements. A range of professional and specialist bodies advise and input on curricula.

In 2009, Medical Education England (MEE) was established to provide a national professional advisory role to the workforce planning, education and training for medicine, pharmacy, dentistry and healthcare science. At the same time, professional advisory boards were also established for nursing and midwifery and the Allied Health Professions.

Under the NHS reforms, HEE will be established as a Special Health Authority to provide national leadership and oversight to workforce planning, education and training for the NHS and public health workforces and, where appropriate, to have agreed responsibilities for small specialist professions. Local Education and Training Boards will be set up so that healthcare providers can take on the functions of Strategic Health Authorities.

At present, the inclusion of genetics and genomics within undergraduate and any postgraduate curricula across the different clinical professional groups is inconsistent and lacking in coherence. For example, a recent report from the Nursing and Midwifery Professional Advisory Board highlighted that genomics is inconsistently addressed in nursing curricula. It recommended that all nurses and midwives, at all levels of practice, should be able to use information about genes to determine disease risk, diagnosis and prognosis, and to select treatments – something that would require a change to many courses. We endorse the recommendations of this report.

However, for healthcare science – as part of the DH Modernising Scientific Careers programme – a co-ordinated approach has been taken. New education and training programmes have been developed, piloted and implemented across the UK which have provided enhanced specialist skills and expertise in genetic technologies and in combined clinical cytogenetics and molecular genetics. The programmes have also ensured specific training in applied molecular technology for all those working in the pathology specialisms, and more broader-based education for the whole healthcare science workforce on genomics and personalised medicine. Under these arrangements, the National Healthcare Science School of Genetics was established which is now integrated into the broader National School for Healthcare Science – hosted by NHS West Midlands Postgraduate Deanery.

We recognise and strongly support the approach that has been taken in healthcare science and endorse the value of the School in ensuring quality outcomes from training, which has been demonstrated by external evaluation. We would want to see this continue and be further developed in the future.

This work clearly provides a focus and direction for the necessary developments in education and training in other clinical professional groups, which could be facilitated by the MEE Healthcare Science Programme Board. This now must be built upon as a matter of urgency.

We therefore recommend that urgent action is taken by DH, working with professional advisory structures, the NHS and the educational sector, to ensure that workforce developments do not lag behind service developments, and that an appropriately skilled workforce is available. An immediate review of the existing provision of genomics training and education for each profession should be conducted (informed by the developments in education and training for healthcare scientists) and an action plan developed, focused on building the skills and knowledge of the current workforce and planning for the future.

Furthermore, as HEE is being established, education and training in genetics and genomics should form part of its overall function, with a requirement to develop core educational standards for genomics and to monitor outcomes.

7.3 Addressing the general healthcare workforce CPD challenge

Ensuring that genomics is an integral part of initial medical/health education and training will be an important step towards developing the workforce. But for the next 15 years at least, the majority of staff who will have to cope with the movement of genomics into mainstream clinical work will be those who are already trained and accredited. That is why the bigger educational challenge is to close the skills gap within the existing workforce, via continuing professional development (CPD) arrangements.

This is a challenge not simply based on the numbers involved but also the delivery structures. Ultimately, many decisions about CPD are made at the local level and reflect local development priorities and individual professional interests. But given the importance of training the current workforce in how genetics, genomics and stratified medicine could be relevant to practice, we do not believe that leaving it to local arrangements and local priority setting is enough. There needs to be a systematic and focused approach for the NHS and public health workforce, supported by central funding.

Initial awareness training needs to happen relatively swiftly; as demonstrated elsewhere in this report, genomic technology is already being used in a number of areas of clinical practice and the pace of change means that it will be used widely within the next few years.

We would propose that a training needs assessment is undertaken of the more general healthcare workforce (NHS and public health). This could establish which professional groups to prioritise for targeted CPD training, as part of a phased approach based on clinical relevance to practice over the next two to five years.

One major professional group that needs a level of awareness training are commissioners, so that they understand the potential of genomics more widely, can take an informed approach to commissioning of individual genetics/genomics services and recognise the importance of ensuring that their local workforce is trained in genomics.

The question of how such training should be delivered demands some consideration. The National Genetics Education and Development Centre (NGEDC) has taken a lead in providing training in genetics

and engaging the clinical community, with considerable success. While it could not deliver all the training needed, it has demonstrated considerable expertise in defining learning outcomes, working with healthcare professionals and their representative bodies, and in developing materials for wider use.

At present, the future of the NGEDC is not clear. It was established and is still funded in large part by a grant from DH; however, we believe that it – or its successor – will be key to the process of systematic awareness-raising, and to more specialist training of the NHS and public health workforce.

We therefore recommend that the expertise of the NGEDC should be retained and become a part of the National School for Healthcare Science, and, in conjunction with delivery partners, develop core quality standards for both the curriculum and the training needed for the current workforce, through a training needs assessment in each professional group.

The National School for Healthcare Science is a logical place for the NGEDC's expertise, as specialist clinical genetics expertise in education and training and monitoring outcomes will also reside there. This should happen immediately so that training of the current healthcare professional workforce can start following the training needs assessment in each professional group.

The Royal College of General Practitioners has worked with the NGEDC on providing exposure for GPs and this relationship should continue to be developed. For hospital and public health trainees, there is the possibility of rotations or secondments into specialist centres using these approaches.

A further future role for the NGEDC or its successor would be in providing quality assurance for education and training programmes, which in an increasingly diverse market will come from a wide range of providers.

7.4 Building and developing the specialist genetics and genomics profession

As highlighted above, in addition to raising awareness of genetics and genomics across the healthcare workforce, there is a pressing need for more specialised education and training to build a genetics workforce with sufficient capacity to meet the surge in demand and to provide specialist advice and guidance to the broader clinical team, as well as an ongoing need to ensure that this specialist workforce is continually developed to keep pace with change.

Crucially, the existing specialist workforce, including a large proportion of healthcare scientists working in clinical cytogenetics and molecular genetics (ideally working in a merged specialism of clinical genetic technology), must be maintained and further developed. The proposed service model involving Regional Genetics Centres, Biomedical Diagnostic Hubs and Genomics Technology Centres has the potential to enable this. Within this service model, there should also be a range of CPD opportunities for existing staff, with clear career pathways developed.

However, it is accepted that demand is likely to exceed supply, with more clinically

based geneticists with bioinformatics skills being required over the next few years. This demand might be considerable, with several hundred additional posts emerging from the developments in Clinical Genetics as whole genome sequencing technology begins to be used in the next three to five years. By itself, the rapid expansion in high-throughput sequencing of humans with different clinical conditions will require a pool of specialists with bioinformatic skills working collaboratively between the NHS and academia.

The relatively small numbers of professionals required with specialist skills in genetics warrant a workforce planning, education, and training and development programme co-ordinated at a national level to ensure not only continuity of supply of a multiprofessional specialist workforce including medical staff but also development of services in a rapidly evolving area. We believe that the needs of the more specialist workforce, including bioinformaticians, could be built into the planned national arrangements for healthcare scientists and into the National School for Healthcare Science, to ensure economies of scale in commissioning and monitoring of outcomes from training and to be aligned specifically to the programmes for scientists working in Clinical Genetics. This could work collaboratively with a postgraduate medical deanery which has a designated responsibility for developing the specialist Clinical Genetics medical workforce.

The provision of training for the specialist genetics workforce could be supplemented by specialist workshops/modules from informatics centres, such as EBI, the National Genetics Reference Laboratories and the proposed national biomedical informatics service. Such courses already exist, ranging in duration from one day to one week: for example, in the UK, EBI is active in providing short courses in bioinformatics.

Another profession where demand may well exceed supply is genetic counselling. Although a relatively new addition to the genetics workforce, genetic counsellors have already proved their worth in supporting families affected by inherited diseases. As the use of genomic technologies within routine care increases, many more patients and their families will need support to understand the implications of particular genetic findings, and potentially to help them make important decisions.

These various issues around the future workforce requirements lead us to recommend that:

- **the workforce planning needs of the specialist clinical genetics, bioinformatics and pathology workforce require national oversight and urgent action to support the new service models outlined in this report to ensure that skill gaps are minimised and continuity of supply is secured, and**
- **the ongoing CPD requirements of this highly specialist workforce need to be supported, given the pace of change in technologies and information and their critical role in supporting the broader healthcare workforce.**

While much of this chapter has focused on ensuring that clinical services have an appropriate specialist genetics and genomics workforce, we also believe

that formal clinical academic training for this workforce needs to evolve and be supported to help to nurture and promote research and innovation in this essential area of science.

We consider that this would be best developed by academic institutions with expertise in this area, working collaboratively with clinical genetics departments and the proposed new service delivery infrastructures outlined in this report as well as with regional academic health science centres and other specialist NHS research and innovation centres.

Research councils (MRC, BBSRC and Engineering and Physical Sciences Research Council (EPSRC)) have provided fees and maintenance support for some home students on Masters courses in genetics, epidemiology or bioinformatics, but the BBSRC is ending its support. These research councils and the Wellcome Trust are funding four-year PhD programmes which start with a Masters and proceed to a PhD, which will provide a major source of support for graduate training in more specialist areas of genomics. At the postdoctoral level, it is worth noting that the MRC provides a special training fellowship in biomedical informatics, which supports about three researchers each year in genetics, bioinformatics and systems biology.

The current structure of Masters, PhD and postdoctoral training outlined above, together with other academic programmes (for example, those supporting the education and training of healthcare scientists in clinical cytogenetics and molecular genetics), provide an effective mechanism for clinical academic training for the multiprofessional specialist team that needs to be further developed and enhanced.

Most of these programmes are based in active research centres and are regularly refreshed to maintain their training at the forefront of research. We believe that the best way forward would be to identify a network of university centres – many of which will have strong links to a Regional Genetics Centre, Biomedical Diagnostic Hub or Genomic Technology Centre – that are best equipped, based on current expertise, to deliver relevant Masters and doctoral programmes, whether as a route into further research or to help to build a highly skilled cadre of specialists within genomics and in particular the use of genomic technologies and bioinformatics.

We recommended that, in conjunction with the higher education sector, NIHR and other funding bodies, there should be further developments in Masters, doctoral and postdoctoral training programmes in clinical genetics, epidemiology and bioinformatics to support clinical academic career development and research capacity and capability building for the future.

7.5 Finding the educators

While this chapter has for the most part taken a long-term outlook, there is one urgent issue that must be addressed: a lack of educators within the field of genomics. The pool of those qualified to teach genomics is relatively small and those in this position may also have other

commitments such as service delivery and R&D.

At postgraduate level, healthcare scientists have started to address this issue through the DH Modernising Scientific Careers programme, in which genetics training has taken a lead and where NHS practice-based educators have been developed, with parallel developments in higher education teaching staff. Similarly, the work of the NGEDC cited above indicates that expertise in educating the workforce does exist.

However, **we recommend that joint working between the NHS and the educational sector is urgently required to ensure that educators are effectively trained and developed**. In particular, we believe that work should be done through the Medical Schools Council, the Council of Deans of Health and other strategic NHS and higher education groups to both expand the number of educators in genetics and genomics and enhance the ability of these staff to keep up with new developments in the field so they can teach these with confidence.

7.6 Keeping knowledge current

Finally and crucially, it must be underlined that we are still in the relatively early stages of the genomics revolution. Training at this stage will necessarily reflect existing technologies and validated clinical uses of genomics. But, within a few years, these may be superseded by more advanced approaches. One obvious shift will be when it becomes as cheap to map the entire genome as to conduct individual tests; at this point, the use of genomics within clinical practice will change dramatically.

It is therefore essential that genomics training is not seen as a one-off, nor that it is associated solely with a specific technology, test or disease. Instead, it must become part of an ongoing review of pre and post-registration curricula and a key element of the CPD landscape within the NHS and public health. Training must ensure that those involved in using genomic testing technology – whether in a specialist lab or in future near-patient testing – understand the need for flexibility as technology evolves. Equally importantly, they must understand their pivotal role in providing specialist advice and expertise to the wider workforce.

In order to achieve this, we recommend that, within the formation of HEE, consideration should be given to how it can be ensured that education and training curricula evolve to keep pace with the changing face of genetics and genomics, perhaps through wider arrangements for evolving training within and across healthcare science.

8. Developing the legal and ethical framework

As has been indicated throughout this report, the emergence of genomic technologies brings to the fore some important ethical and legal issues. These are not new: indeed, many of them have already been discussed in the context of advances in Clinical Genetics. However, as in so many other areas, genomics transforms the scale of the challenge: information from many large patient cohorts will be needed to fully exploit the potential that genomic technology has for transforming healthcare.

In order to realise our vision for the use of genomic technologies both within the NHS and in public health, it is essential to develop policy for genomic medicine within an ethical and legal framework which maximises potential health benefits while minimising potential harms such as information misuse, stigmatisation and discrimination.

In this chapter, we have not attempted to define what that framework should be. Instead, we have sought to summarise the issues that need to be considered when devising the framework, and set out the case for generic consent.

8.1 Securing the common good while respecting personal privacy

Genomic technologies are based on an ability to identify and study genetic variations from the 'norm' – and their impact on health, development, resistance to drugs, susceptibility to disease, etc. The more genetic data is available to define the norm, and to find out how common different variants are, the greater the potential benefit to society. As current and potential users of health services, it is in our common interest to ensure that as much genetic data as possible and practical is sequenced, and added to the global knowledge base.

This needs to be done in a way that respects personal privacy. An individual's genetic information is sensitive personal data, and a whole genome cannot be truly anonymised. This means that there is a risk of the information being misused. While few patients are likely to object to having a genetic test for diagnostic purposes and to inform their treatment, and most patients will consent to research use of their data if asked, it is essential that authorised and appropriate access to that information is safeguarded.

One of the principles that underpins both treatment and clinical research studies is that patient consent must be sought. However, the legal frameworks for consent were developed before the recent advances in our knowledge of the human genome and therefore the boundaries of consent are not clear when it comes to obtaining and using genetic information.

8.2 Specific issues around consent for use of genetic information

In general, consent is requested in relation to specific studies, after approval of the patient consent process by the National Research Ethics Service. This can be time consuming and resource intensive, as well as restricting the use of the sample to the particular study. Hospitals can have several different studies and consent information to deal with, and the consenting process involves research nurses having individual conversations with patients about the particular study. This is important in interventional studies, where the patient needs to understand the impact of the experimental course of treatment, but is over-burdensome for large-scale,

non-interventional, observational studies that pose limited risk to the patient – such as many genomic studies. Better understanding of disease and the development of new tests and treatments will require the routine collection and analysis of diagnostic samples from large patient cohorts.

Generic consent for non-interventional research use of genetic data offers an alternative approach. Under this model, patients give consent to their tissue or data being used in future research studies, the details of which may not be clear at the time the sample is taken. The approach is already used in some studies and tissue banks; however, wider adoption of this approach is necessary to maximise the benefit of genomic studies. As part of its Stratified Medicine Programme, Cancer Research UK reviewed how consent is obtained on NHS surgical consent forms; less than a quarter of the hospitals polled included an option allowing patients to give consent for use of their sample for research purposes. Yet, interestingly, feedback from consumer liaison groups suggests that patients would be supportive of this approach and, indeed, many were surprised that it was not happening already.

The nature of genomic research creates an additional challenge for generic consent – namely, what happens if the study reveals information that has a potential impact on the patient and/or their family. Many genetic research studies simply seek to use the genetic information contained within a sample and require no direct patient involvement, meaning that patients typically will not expect feedback on any individualised findings. However, if clinically relevant information, which is incidental to the research question, is discovered – in particular about a condition which is serious or preventable – the researchers and/or clinicians involved may believe that there is a duty to feed back to the patient. This may be the case even if patients have declined, when originally giving consent, the opportunity for individual feedback.

A number of organisations, including the Wellcome Trust and the Human Genetics Commission, are currently developing policy recommendations on these issues. The Wellcome Trust and the MRC are running a project to find out more about public attitudes to health-related findings in research. This was stimulated by discussions relating in particular to UK Biobank and other large population cohorts as to what should be done about incidental findings when using imaging for research and feedback of genetic information. The project will use qualitative information supply by lay focus groups and in-depth interviews with the general public, individuals with medical conditions and research participants to examine expert and public attitudes to the feedback of clinically relevant information arising in the course of research participation. The results of these will be discussed with an expert group of researchers, lawyers and ethicists with a view to the funders agreeing a final report and policy on feedback by early 2012.

The findings of this survey will need to be brought together with other studies to form the basis for consistent guidance.

Even if the patient has not requested feedback, the nature of genetic information means that researchers may discover information that affects family members. There is considerable anxiety among healthcare professionals about how to

communicate genetic information relating to increased risk, unless specific consent has been sought from the patient or their family. This anxiety can be allayed by developing generic consent processes and forms, as recommended by the Joint Committee on Medical Genetics,[26] that record patients' agreement to their records being accessed to enable the better care and advice of others.

If generic consent is sought in common terms for confidential clinical use and for research studies approved within the framework developed by the Health Research Agency, patients can balance their individual privacy interests with their shared interest in supporting a ealth system that can maximise the potential of genomic technology within medicine.

Selective feedback
The UK10K project has devised a consent model that allows information to be fed back to the patient only if it is pertinent to their disease or clinically relevant, i.e. if it could influence their current treatment or if there is a clinical treatment that could be used to mitigate the impact of the gene defect.

8.3 Relevant legal considerations

While the legal framework underpinning consent for genomic studies is still being developed, there are several key areas of law that can inform discussions. However, it must be underlined that the legal requirements of consent vary subtly depending on the specific area of law that applies. Any particular consent model may need to satisfy the requirements of more than one overlapping legal framework. The main relevant areas of law are:

- Taking bodily samples from living people requires sufficient justification to satisfy the law of 'trespass to the person' (assault and battery). This requires 'real' consent, which implies knowledge of the 'nature and purpose' for which a sample is taken – which, as we discuss further below, cannot always be confirmed specifically when it comes to genomics. We understand that the nature and purpose can be provided in very general terms, which suggests that use of a sample for future, as yet unknown, studies within a broadly defined category is not automatically precluded. This approach is already used in many biobank studies, including by UK Biobank, with a specifically devised ethics and governance framework. However, we are not aware of this having been tested in the courts.
- Storage and use of samples in England and Wales is governed by the Human Tissue Act 2004 (as is the taking of samples from people once they are deceased). The Act determines when consent to take a sample should be obtained and who is qualified to give it. It does not specify the format of consent, although there is some guidance in the codes of practice. *Code of Practice 9 – Research* advises that generic consent can be relied on provided that it is "valid".[27] *Code of Practice 1 – Consent* advises that information about "the nature of the intended activities and the reasons for them" should be tailored to circumstances, and leaves it to local

[26] Joint Committee on Medical Genetics (2011) *Consent and confidentiality in clinical genetic practice: Guidance on genetic testing and sharing genetic information*, London: Royal College of Physicians
[27] Human Tissue Authority (2009) *Code of Practice 9 – Research*, paragraph 47

trust policy to specify the minimum information that should be provided.[28]

- Any processing of sensitive personal information requires a justification under the Data Protection Act 1998. Consent is a primary justification under this legislation but not the only one; medical and research purposes are also recognised. A number of provisions exist to balance private and public interests in this area:
  - Section 251 of the National Health Service Act 2006 allows the common law duty of confidentiality to be set aside in specific circumstances where anonymised information is not sufficient and where patient consent is not practicable. Applications for approval to use section 251 are dealt with by the Ethics and Confidentiality Committee.
  - Under section 33 of the Data Protection Act 1998, researchers are allowed to utilise personal data for research without the consent of the individual, subject to certain conditions.[29]
  - The common law also recognises exceptions to the duty of confidentiality (where a breach would otherwise constitute unauthorised sharing of information that was thought to be given in confidence). Although not clearly defined for genomic research, they do include a public interest exception, where the public interest of disclosure must outweigh the public interest of maintaining confidentiality.
- The Human Rights Act 1998 requires public bodies to act in accordance with the European Convention on Human Rights (ECHR), in particular Article 8. This permits intrusions into a person's private and family life only if "necessary in a democratic society" and "proportional" to other defined "legitimate aims" which include the interests of public health and the rights and freedoms of others. Any challenge to a generic consent structure is likely to include reference to the ECHR.

These laws refer specifically to research in the UK; different approaches exist across Europe – e.g. there are significant variations in the interpretation of the requirements of the data protection directive across Europe. The more conservative the interpretation, the more restricted genomic research will be. It is in the UK's interests, therefore, as it seeks to strengthen its reputation as a global leader in genomics and advanced research, to ensure that the legislative framework balances the need of the individual for privacy, the wishes of the individual to give consent for data to be used in research, and the common good.

8.4 The case for generic consent

The HGSG believes that introducing a national system for routinely requesting generic consent for the confidential use of the genetic and clinical data in patient records would significantly accelerate the development of new treatments and increase the attractiveness of the NHS as a place to do research, in a way that private or regional health systems cannot. It would also put the patient at the heart of the debate as their decision to consent or not would be made easier and simpler to enact.

[28] Human Tissue Authority (2009) *Code of Practice 1 – Consent*, paragraphs 97–99
[29] Administrative Data Liaison Service (ADLS), www.adls.ac.uk/

An initial review of the legislation in this broad arena suggested no insurmountable issues to generic consent, as long as a balance between individual protection and societal benefit can justify the necessary flexibility in interpreting these laws. However, it would require a co-ordinated, rational and cautious approach to protect the right of the individual to privacy while ensuring that minority interests do not hold back this area of significant shared benefit. A model for this was recently discussed in the *British Medical Journal*.[30]

We therefore recommend that, as a key aspect of the continued provision of high quality public engagement on the ethical, legal and social issues associated with further integration of genomic technology into mainstream healthcare provision, a national model for generic consent should be developed, through broad consultation with all relevant partners and stakeholders.

The HGSG is convinced that the existing genetic consent processes are onerous to deliver, run the risk of delay and are not optimised for national generic use. However, individual hospitals are now starting to include genetics in generic consent. We believe that a more effective route would be to integrate it into existing clinical practice.

Clearly, the success of routinely requesting generic consent is dependent on being able to assure members of the public that their genomic data is stored securely, and that its use will be carefully monitored and guarded. This is an issue that the Institute of Biomedical Informatics (proposed in chapter 6) would be placed to advise on, working to the guidance set by the Information Commissioner's Office on the use of personal and health data.

There will also be a training requirement for any healthcare professional managing a consent process to make sure that they provide patients with the correct information. In research programmes, this is typically done by specialised clinical or research nurses, but when moving to a model of generic consent, many more professionals may be involved. Similarly, there may be a training requirement for people dealing with issues of feeding back incidental or unanticipated findings.

[30] Kanellopoulou NK, Kaye J, Whitley EA et al (2011) Dynamic consent – a solution to a perennial problem? Rapid Response to Sheehan M (2011) Broad consent is informed consent [letter], *British Medical Journal* 343:d6900

9. Engaging the public and building awareness

Throughout this report, we have examined the systemic changes that we believe will be needed if mainstream healthcare is to reap the full benefits of advances in genomic technology, and referred to a series of building blocks that must be in place to realise our vision. But there is one important building block that we have not yet considered: engaging the public in developments in genetics and genomics.

This final chapter focuses on why public support is so important in this field, and what can be done to secure it.

9.1 Engagement to support shared decision-making

Regardless of the potential benefits of genetics and genomics, developments in this field are often viewed as controversial and have the potential to challenge society's values. More specifically, in a clinical context, genetic information can lead to conflicting priorities: information about a person's genome not only will inform their own care and treatment, but may also have implications for their relatives. In this context, traditional boundaries of confidentiality are challenged.

Evidence suggests that public awareness around genetics is generally low. The Wellcome Trust Monitor survey of 2009[31] found that while two in ten adults and 14–18-year-olds had seen or heard "a great deal" or "quite a lot" about genes and genetics in recent months, some five in ten reported that they had encountered "not very much" information or "none at all". When it came to understanding the ethical issues relating to genetic research, four in ten agreed that they had a good knowledge, but three in ten disagreed.

This gap in public awareness may not have had much impact at a time when Clinical Genetics was confined mainly to single-gene disorders and the treatment of families with inherited genetic conditions. However, as we move into an era when genetic testing and genomic technology will become more widely used in the NHS – from pre-natal testing to diagnosis of disease to whole genome sequencing – patients may feel that they do not understand or know enough about methods of diagnosis and treatment to agree to it, or be sufficiently empowered to take part in shared decision-making.

This not only will affect treatment decisions for common complex conditions, but also needs to be considered in the light of the predicted growth of direct-to-consumer genetic tests and the fact that more widespread use of whole genome sequencing increases the risk of discovering incidental clinically relevant findings when participating in research or receiving diagnostic treatment.

Greater awareness of the genetic basis of disease may also help to explain treatment decisions. The furore over access to Herceptin® is a case in point here; while access was undoubtedly inequitable, with variations in prescribing practice in different regions, the fact that the drug offers markedly better outcomes only for those with a specific genetic variant was largely ignored.

[31] Wellcome Trust (2010) *Wellcome Trust Monitor: Survey report,* www.wellcome.ac.uk/About-us/Publications/Reports/Public-engagement/WTX058859.htm

9.2 Engagement to support the common good

As well as contributing to the effective use of genomic technology within individual clinical care, public engagement in this field has another vital role: supporting the common good.

As we have discussed, genomics is fundamentally concerned with identifying and studying genetic variations from the norm. Hence, it is in the common interest to ensure that as much genetic data as possible and practical is sequenced. This requires, at the most basic level, a willingness among patients and the public to allow their genetic information to be part of the common knowledge base. Such willingness will depend on public trust in the application of technologies in diagnosis and treatment and, in particular, trust that information resulting from these technologies – in particular, personal information – is appropriately managed and safeguarded.

Responses to the Wellcome Trust Monitor survey showed that when asked about whom they would trust with responsibly using human genetic information held on medical databases, 82 per cent of adults and 83 per cent of young people aged 14–18 said they trusted their GP/family doctor and 61 per cent and 69 per cent respectively said they trusted the NHS. This apparent level of trust is a strong base on which to build.

While a discussion of policy measures to ensure genetic data protection and security is outside the scope of this report, it is clear that in order to facilitate the assembly of a common knowledge base, robust measures must be in place to maintain public confidence in how genetic information is being stored and used.

9.3 An integrated approach to public engagement

Public engagement is a complex issue covering the attitudes and involvement of both the general public and those patients, families and communities more directly affected by genetic conditions and by the potential applications of genomic medicine. Effective engagement will therefore require a co-ordinated strategic approach and organisation of effort across a wide range of areas and channels, from public health to science in general and, in particular, via education.

Young people will be growing up in a world where genomic science has advanced and has a significant influence on medicine and public health; by engaging with them today, we can prepare them to become informed citizens, patients and consumers and alert them to potential careers in this field.

Crucially, too, in developing a public engagement approach, attention must be paid to the specific needs of different audiences. For example, patients with a specific genetic condition and their relatives will require specific information. Some communities may need information tailored to health concerns in their community – for example, cousin marriage in certain Muslim and Jewish communities.

Given this broad range of audiences and issues, which go beyond pure healthcare into education and a range of social and cultural issues, we believe that there is a need for an integrated approach

to engaging the public. That is why we recommend that **the Government should ensure the continued provision of high quality public engagement on the ethical, legal and social issues associated with further integration of genomic technology into mainstream healthcare provision**.

The Government is best placed to ensure that the required integrated approach is taken. However, this does not and need not mean that engagement should only be conducted by the Government.

9.4 Consolidating existing engagement material

A wide range of organisations are already active in engaging the public in genetics and science in general, and any strategy for engagement could benefit from involving these organisations. Many have specific expertise and insight into a specific audience; many have also created engagement materials, including leaflets and other printed materials, websites, public events, online games and films for use in classroom teaching.

A useful starting point would therefore be to undertake a stakeholder mapping exercise to understand the landscape of potential partners and identify synergies and gaps, in order to build on existing work. It may be that the best course of action is to disseminate existing resources more widely but there may also be scope to create new resources where there are gaps. The Science for All[32] group, set up by BIS in 2009 to look at public engagement, developed a tool to help organisations think about the motivations for public engagement and provides a common framework to describe types and purposes.

Having gained an understanding of the wider landscape, it should be possible to help develop a more co-ordinated approach that avoids reinventing the wheel and makes best use of existing resources and partnerships.

[32] http://interactive.bis.gov.uk/scienceandsociety/site/all/2010/09/23/public-engagement-for-science-and-society-a-conversational-tool/

Appendix 1: Human Genomics Strategy Group Terms of Reference

1. The Human Genomics Strategy Group (HGSG) will be a cross-departmental group consisting of key individuals and organisations in the field of genetic research and its application to medicine. It will monitor advances in genetic and genomic research, both basic and translational, to evaluate their benefit to healthcare services in the NHS.

2. To enable this, the Group will:
   - monitor progress on the Government response to the 2009 Genomic Medicine inquiry
   - develop, in discussion with relevant partners, strategic options for genomics in the NHS informed by advances in research and technology in the field of genomics
   - oversee broader developments in relation to genetics in NHS services, and
   - provide, through an annual report, advice on potential benefits to NHS patients.

3. The Group will share its findings with other relevant committees, reporting on their impact on services and how they might be introduced into mainstream practice. This would include, for example, the Diagnostics Clinical Committee, the Ministerial Industry Strategy Group (MISG) and the Ministerial Medical Technology Strategy Group (MMTSG).

4. All members of the Group will be appointed for a period of two years (starting from the date of the first meeting). Members may be re-appointed for an additional two years upon notification by the secretariat.

5. The Group may commission other bodies or individuals to conduct research or provide papers to the HGSG for consideration and decision-making.

Appendix 2: Human Genomics Strategy Group membership

Professor Sir John Bell (Chair)
Dr Ian Barnes
Professor Gifford Batstone
Professor Sir John Burn
Dr Hilary Burton
Dr Trevor Cole
Val Davison
Professor Charles Easmon
Professor Peter Farndon
Professor Sue Hill
Dr Christine McCartney
Professor Gilean McVean
Professor Jonathan Montgomery
Mr James Peach
Professor Munir Pirmohamed
Mrs Jacquie Westwood

Department of Health

Dr Mark Bale
Dr Elaine Gadd
Ms Tarin Khanam
Mr Colin Pavelin
Dr Cathleen Schulte

Department for Business, Innovation and Skills

Dr Helen Bodmer

Technology Strategy Board

Dr Zahid Latif

Biotechnology and Biological Sciences Research Council

Dr Celia Caulcott

Medicines and Healthcare products Regulatory Agency

Dr Neil Ebenezer

Medical Research Council

Dr Declan Mulkeen

National Institute for Health and Clinical Excellence

Professor Adrian Newland

Welsh Assembly Government

Mrs Christine Morrell

Innovation Working Group

Professor Sir John Burn (Chair)	National Institute for Health Research Genetics Committee
Dr Jonathan Allis	GE Healthcare (to Feb 2011)
Dr Mark Bale	Department of Health
Professor Gifford Batstone	Department of Health
Dr David Baty	Clinical Molecular Genetics Society
Dr David Bentley	Illumina Inc
Dr Helen Bodmer	Department for Business, Innovation and Skills
Dr Laura Boothman	Academy of Medical Sciences (from Sept 2011)
Dr Gillian Borthwick	National Institute for Health Research
Dr Tony Bradshaw	BioIndustry Association (to Sept 2010)
Dr Celia Caulcott	Biotechnology and Biological Sciences Research Council
Dr Chris Chamberlain	AstraZeneca
Dr Trevor Cole	Joint Committee on Medical Genetics
Ms Jill Dhell	Department of Health
Dr Angela Douglas	Association for Clinical Cytogenetics
Dr Michael Dunn	Wellcome Trust
Dr Neil Ebenezer	Medicines and Healthcare products Regulatory Agency
Dr Robert Frost	Academy of Medical Sciences (to Sept 2011)
Dr David Griffiths-Johnson	Department for Business, Innovation and Skills
Dr Jim Houlihan	UK Intellectual Property Office (from May 2010 to Sept 2010)
	National Institute for Social Care and Health Research in the Welsh Government (NISCHR) (from May 2011)
Dr Sarah Jones	UK Intellectual Property Office (from Jan 2011)
Professor Jonathan Knowles	Oxford University
Dr Zahid Latif	Technology Strategy Board (from Feb 2011)
Dr Joe McNamara	Technology Strategy Board (to Feb 2011)
Professor Gilean McVean	Oxford University
Dr Declan Mulkeen	Medical Research Council
Professor Munir Pirmohamed	NHS Chair of Pharmacogenetics
Mr James Peach	Cancer Research UK
Dr Rachel Quinn	Academy of Medical Sciences
Dr Nathan Richardson	Medical Research Council (to Apr 2011)
Dr Gavin Roberts	Department of Health

Service Development Working Group

Dr Ian Barnes (Chair)	Department of Health
Professor Gifford Batstone	Department of Health
Dr Elijah Behr	St George's Hospital, London
Dr Hilary Burton	PHG Foundation
Dr Trevor Cole	Joint Committee on Medical Genetics
Professor Finbarr Cotter	Barts and The London School of Medicine
Dr Angela Douglas	Association for Clinical Cytogenetics
Dr Rob Elles	Central Manchester University Hospitals NHS Foundation Trust
Professor Frances Flinter	Guy's and St Thomas' NHS Foundation Trust
Professor Peter Furness	Royal College of Pathologists
Professor Andrew Hattersley	Peninsula College of Medicine and Dentistry, Exeter and Plymouth Universities
Professor Peter Johnson	Cancer Research UK
Ms Naz Khan	Manchester Regional Genetics Centre (to Apr 2011)
Dr Lynne Maher	NHS Institute Director of Innovation (to Jan 2011)
Professor Adrian Newland	National Institute for Health and Clinical Excellence
Dr Christine Patch	Guy's and St Thomas' NHS Foundation Trust
Mr Colin Pavelin	Department of Health
Mr James Peach	Cancer Research UK
Dr Imran Rafi	GP
Ms Radhika Sriskandarajah	Department for Business, Innovation and Skills
Professor Kieran Walshe	Manchester Business School
Mrs Jacquie Westwood	UK Genetic Testing Network

Education, Engagement and Training Working Group

Professor Charles Easmon (Chair)	Health Protection Agency
Dr Adrian Alsop	Economic and Social Research Council
Mr Paul Buckley	General Medical Council
Dr Trevor Cole	Joint Committee on Medical Genetics
Dr Aamra Darr	Bradford University
Val Davison	National Healthcare Science School of Genetics
Ms Jane Denton	Royal College of Nursing
Professor Peter Farndon	National Genetics Education and Development Centre
Mrs Karen Folkes	Department for Business, Innovation and Skills
Ms Georgina Hall	Central Manchester University Hospitals NHS Foundation Trust (from May 2011)
Dr Tim Hubbard	Wellcome Trust Sanger Institute
Mr Alastair Kent	Genetic Alliance UK
Ms Naz Khan	Manchester Regional Genetics Centre (to Apr 2011)
Professor Helen Langton	University of the West of England
Professor Jonathan Montgomery	Human Genetics Commission
Ms Sarah Norcross	Progress Educational Trust
Mr Colin Pavelin	Department of Health
Dr Imran Rafi	GP

Bioinformatics Focus Group

Professor Janet Thornton (Chair)	European Bioinformatics Institute
Professor Gifford Batstone	Department of Health
Val Davison	National Healthcare Science School of Genetics
Dr Helen Firth	Addenbrooke's Hospital
Dr Tim Hubbard	Wellcome Trust Sanger Institute
Professor Gilean McVean	Oxford University
Mr Colin Pavelin	Department of Health
Professor Michael J.E. Sternberg	Imperial College London
Professor Graham Taylor	Leeds University
Dr Michael Wright	Newcastle University

Appendix 3: Glossary

Glossary of acronyms

ALL	Acute lymphoblastic leukaemia
BBSRC	Biotechnology and Biological Sciences Research Council
BIS	Department for Business, Innovation and Skills
CPA	Clinical Pathology Accreditation
CPD	Continuing professional development
DAP	Diagnostics Assessment Programme
DDD	Deciphering Developmental Disorders
DH	Department of Health
EBI	European Bioinformatics Institute
ECHR	European Convention on Human Rights
EHR	Electronic health record
ELIXIR	European Life Sciences Infrastructure for Biological Information
EPSRC	Engineering and Physical Sciences Research Council
EQAS	External Quality Assurance Schemes
HEE	Health Education England
HGSG	Human Genomics Strategy Group
HPA	Health Protection Agency
HPV	Human papillomavirus
HVP	Human Variome Project
ICT	Information and communication technology
IP	Intellectual property
LSDB	Locus-specific databases
MEE	Medical Education England
MRC	Medical Research Council
MS	Multiple sclerosis
NGEDC	National Genetics Education and Development Centre
NHSCB	NHS National Commissioning Board
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NIPD	Non-invasive pre-natal diagnosis
PHE	Public Health England
QALY	Quality-adjusted life years
RCPath	Royal College of Pathologists
SADS	Sudden arrhythmic death syndrome
TSB	Technology Strategy Board
UKCRC	UK Clinical Research Collaboration
UKGTN	UK Genetic Testing Network
VNTR	Variable number tandem repeat

Glossary of genetic/scientific terms

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 biological processes, pathogenic processes, or pharmacological 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.
DNA	Deoxyribonucleic acid (DNA) contains the genetic instructions used in the development and functioning of all cellular organisms.
Gene	The basic unit of heredity found in chromosomes. A length of DNA that carries the genetic information necessary for production of a protein.
Genetics	The science of genes and heredity.
Genome	The entirety of an organism's hereditary information.
Genomic technologies	A range of tools that enable sequencing of the genome and analysis of genomic information against a reference point.
Genotype	Specific genetic constitution of an individual.
Massively parallel sequencing	A term used to describe the underlying technological approach used in next generation DNA sequencing technologies.
Mendelian disorders	Genetic disorders determined by the alteration or mutation in a single gene.
Microbial genomes	The genome of a bacterium. The ability to analyse microbial genomes is fundamental to the way in which genomic technologies will support infection control.
Molecular pathology	A discipline dealing with the origins and mechanisms of diseases at the level of macromolecules such as DNA, RNA and protein to provide precise diagnoses and possible avenues for treatment. It is interdisciplinary, including infectious diseases, cancer, inherited genetic disease and legal issues such as paternity or forensic identity testing.
MRSA	Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans.
Mutation	Relatively rare change in the sequence from the normal sequence.
Pathogen	A biological agent that causes disease or illness to its animal or plant host.
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.
Phenotype	The observable traits of an organism.
Pyrosequencing	Genetic analysis for sequencing/sequencing technology for accurate and quantitative analysis of DNA sequences.
Stratified medicine	The management of a group of patients with shared disease characteristics but different molecular characteristics by using molecular diagnostic testing to select the best therapy in order to achieve the best possible treatment outcome for that group.

Acknowledgements

The Human Genomics Strategy Group gratefully acknowledges contributions from Professor Lyn Chitty, Professor of Genetics and Fetal Medicine, UCL Institute of Child Health (chapter 2) and Professor Anneke Lucassen, Professor of Clinical Genetics, University of Southampton (chapter 8) in preparing this report.

407966 1p x100 Jan 12 (PF)
Produced by COI for the Department of Health