



Human
Genetics
Commission

Profiling the newborn:

a prospective gene technology?

March 2005

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**A report from a Joint Working Group of the
Human Genetics Commission and the
UK National Screening Committee**

March 2005

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Foreword

In 2003, when Ministers published the White Paper on Genetics, they asked the Human Genetics Commission (HGC) to work with the UK National Screening Committee (NSC) to conduct an initial analysis of the ethical, social, scientific, economic and practical considerations of genetic profiling (the analysis of a person's entire genome in order to reveal their personal genetic information) at birth.

This work was taken forward by a Joint Working Group which included both HGC and NSC members. I would like to take this opportunity to thank all the members of the group and the Secretariats who have worked together to ensure that this subject received the thorough examination it deserved. This collaboration provided a wide range of experience and opinion, and the Joint Working Group has produced an excellent report.

One of the things I am most pleased about is the range of people who have contributed to this debate. In May 2004, we took part in a youth forum discussion in Bristol to hear the views of young people on the costs and benefits of genetically profiling babies at birth. We also spoke to researchers involved with the Avon Longitudinal Survey of Parents and Children. I would like to thank everyone who took part in these discussions. I would also like to thank the members of the HGC's consultative panel who provided contributions to the report. The panel is made up of over 100 people with direct experience of living with a genetic disorder, and the HGC created it to act as a sounding board for HGC reports and recommendations. The panel members' comments provide an important view from people who have personal experience of living with a genetic disorder. I am very grateful for their continued involvement in our work.

We have concluded that there are important ethical, legal and social barriers to the introduction of genetic profiling of babies at birth as a public health service. Apart from these, it is unlikely to be publicly affordable within the next 20 years, though commercial services are likely to be offered in this timeframe, potentially raising issues of regulation. It is important that research continues in order to establish how far profiling could be clinically useful, and it is critical that developments are kept under review. Specifically, we are recommending to government that the entire topic should be revisited in five years, when technologies will have moved on and the prospect of this becoming a reality is closer.

Baroness Helena Kennedy QC
Chair, Human Genetics Commission

March 2005



Introduction and recommendations

- 1** The Human Genetics Commission (HGC) and the UK National Screening Committee (NSC) were asked, as part of the Genetics White Paper *Our inheritance, our future – realising the potential of genetics in the NHS*, to provide an initial analysis of the case for and against genetic profiling of babies at birth. We take profiling to mean the analysis of a person's entire genome in order to reveal the majority of their genetic variations. From our review of the current state of scientific and medical knowledge, this is not likely to be affordable in the public health context in less than 20 years. It also raises a number of important ethical, legal and social issues which need to be addressed before any such scheme could be acceptable.
- 2** The HGC advises UK government on the ethical, legal, social and economic aspects of developments in human genetics as well as their effects on health and healthcare. The NSC advises government on whether or not a screening programme should be started, continued or stopped. This report is the work of a Joint Working Group established by HGC and NSC to examine the case for and against genetically profiling babies at birth. The terms of reference and membership of the Joint Working Group are at Annex A.
- 3** During our discussions, some strong objections were raised to genetically profiling babies at birth. Some of the concerns are that the information coming from the tests could be used to stigmatise individuals and that this might also lead to discrimination in areas such as insurance, employment and education; and that the information might be used by police for unwarranted purposes. We did agree that any move towards universal genetic profiling would strengthen the case made previously by HGC and others for the development of comprehensive safeguards around confidentiality and non-discrimination on the basis of a person's genetic makeup.
- 4** Throughout this report, we do not want to perpetuate a view of genetic determinism, ie that people's health, behaviour, intelligence and so on are determined chiefly by their genes. Many of the key causes of differences are social, economic and environmental factors. Genetic variation is just one of many factors affecting a person's health and needs to be considered together with other medical, lifestyle and family information.
- 5** In writing this report, we were concerned with striking a balance among a number of factors: possible clinical value in the face of limited scientific evidence; public health considerations; the rights of individuals to have, or not to have, information (including genetic information) about themselves; developments in the pharmaceutical industry and other sectors; and broader ethical, legal and social considerations. Many of these issues have been previously discussed in HGC's reports *Inside Information* (2002) and *Genes Direct* (2003). In *Inside Information*, we did indeed anticipate the future possibility of genetic profiling in healthcare.



Conclusions and recommendations

- **Genetic profiling is feasible and likely to become available commercially in less than 20 years (Chapter 3).**
- **Before the offer of universal genetic profiling could be considered at a population level, steps would need to be taken to preclude any misuse of information derived from it (Chapter 3).**
- **Genetic profiling is unlikely to be publicly affordable within 20 years (Chapter 4).**
- **For newborn genetic profiling, issues of consent and the welfare of the child are problematic (Chapter 5).**
- **Genetic profiling may in the future have clinical potential but its effectiveness cannot yet be judged (Chapter 6).**
- **There is a pressing need to develop a programme of research to define the full costs and potential benefits of genetic profiling for the health of children and adults (Chapter 7).**
- **Genetic profiling cannot be applied as an NHS screening programme in the near future. The topic should be kept under review and be revisited in five years.**

1. Background and remit

1.1 The Genetics White Paper *Our inheritance, our future – realising the potential of genetics in the NHS* was published on 24 June 2003. It set out the Government’s strategic vision for genetics and healthcare and gave a plan of action and investment aimed at making the NHS a world leader in genetics-based healthcare. It included significant new initiatives aimed at:

- strengthening specialised services;
- building genetics into mainstream services;
- spreading knowledge across the NHS;
- generating new knowledge and applications; and
- ensuring public confidence.

1.2 The White Paper was particularly concerned to foster new initiatives aimed at strengthening the role of genetics in general health services and in providing screening programmes for a number of genetic disorders. In considering these activities, the suggestion was made that it might be possible:

‘... to screen babies at birth... and to produce a comprehensive map of their key genetic markers, or even their entire genome.’ [White Paper 3.36]

It went on to suggest that:

‘the baby’s genetic information could then be securely stored on their electronic patient record for future use. It could then be used throughout their lifetime to tailor prevention and treatment regimes to their needs as further knowledge becomes available about how our genes affect our risk of disease and our response to medicines.’ [White Paper 3.36]

However, it was noted that a more thorough knowledge of the impact of genetic variation on health, together with public debate on many of the wider issues, would be needed before any such system could be considered.

1.3 The White Paper highlights the importance of starting to think through such possibilities now, including the social and ethical issues, so that we are best able to capitalise on any possible future health benefits. It goes on to suggest that before this, it would need to be widely agreed that any benefits would outweigh the risks and that any risks could be satisfactorily avoided. On this basis, Government made the recommendation that HGC work with NSC to provide an initial analysis of the ‘ethical, social, scientific, economic and practical considerations’ of genetically profiling babies at birth.



- 1.4** In compiling this report, we have taken note of a number of discussions and initiatives including:
- previous HGC discussions about consent and confidentiality of personal genetic information;
 - previous HGC consultations and reports including: the MORI survey on *Public attitudes to human genetic information* (March 2001); *Inside Information: Balancing interests in the use of personal genetic data* (May 2002); and *Genes Direct: Ensuring the effective oversight of genetic tests supplied directly to the public* (March 2003);
 - NSC’s discussions about newborn screening for medium chain acyl-coA dehydrogenase deficiency (MCADD). MCADD is a rare inherited disorder where the child may develop a low blood sugar and brain swelling, leading to either sudden death or brain damage, as an abnormal response to prolonged fasting, reduced food intake or infection;
 - the Department of Health’s guidelines for consent to examination or treatment;
 - the Department of Health’s initiatives on choice in the delivery of health and social care; and
 - the report *Genetic Testing – Which way forward? Report of a public dialogue held by the Royal Society’s Science in Society programme* summary at Annex C.
- 1.5** We have also considered a range of information and views. This includes an examination of the feasibility of genetically profiling newborns, the use of genetic profiles in clinical practice (including the potential for pharmacogenetics) and in research, and the ethical, social, legal and scientific considerations. We have also considered newborn screening in current practice and how genetic profiling might differ from this. We have only briefly touched on economic factors since at this point it is not possible to determine future costs or benefits in any definitive way. However, we did consider private markets, because developments here will have implications for the NHS.
- 1.6** Another important source of views for the Joint Working Group came from HGC’s Consultative Panel. The Consultative Panel was established by HGC to act as a sounding board for HGC reports and recommendations. They give insight into the issues and concerns facing people affected by a genetic disorder. The panel is made up of over 100 people with direct experience of living with a genetic disorder. A number of their comments have been included throughout the document as direct quotes. In addition, we spoke to a group of secondary school students in Bristol to ask them their views on the prospect of genetically profiling babies at birth, as well as to researchers from the Avon Longitudinal Study of Parents and Children (ALSPAC) (see Annex D). A broader general public consultation was not undertaken for this initial report. While this would be crucial in any later review, at this point we are necessarily limited to horizon scanning. In the meanwhile, we hope that this report will stimulate public debate.
- 1.7** The recommendations made here have come after a series of debates and discussions. Some of the points discussed have been contentious, not least the relationship between current screening programmes for specific conditions and the possibility of genetically profiling newborns in the future. There has been debate about the balance between clinical usefulness and ethical, legal and social factors. We have been mindful of the need to balance any potential technical developments with their broader implications.



2. Genetic profiling and medical services

- 2.1** Human beings carry very similar but not identical sets of genes. The exact DNA sequence of each of these genes will vary from person to person (except in 'identical' twins). While many gene variations lead to non-medical differences, such as eye colour or height, others can have an effect on disease risk and some are directly responsible for inherited disease. Specific genetic variations may be implicated in the development of conditions such as cancer and heart disease, but the genetic variations are not directly responsible for the disease. These diseases arise as a result of the interaction between the genetic variants and environmental or lifestyle factors.
- 2.2** Genetic profiling is the analysis of a person's entire genome in order to reveal the majority of their genetic variations. This information is called their personal genetic information. Profiling differs from other genetic tests in not being focused on a particular variant or on the diagnosing or predicting of a specific disease. It provides information about a broad range of variations and associated health outcomes.

Genetic profiling

Genetic profiling is the analysis of a person's entire genome in order to reveal their personal genetic information. About 99.8% of our genetic information, which is coded in DNA, is identical in all people. Therefore profiling focuses on the 0.2% that is variable. Variations in the DNA, or variants, can also be referred to as mutations.

Genetic test

A genetic test describes a test that reveals information about a person's genetic makeup. Sometimes the genes themselves are tested to determine the presence or absence of a change in gene structure. For example in some cystic fibrosis screening programmes the baby's genes are tested. Sometimes tests aren't actually carried out on the genes but will reveal genetic information. In haemoglobinopathy screening, blood tests can indicate that someone is a carrier of a sickle gene (even though the gene itself is not examined).

UK Newborn Screening Programme Centre

- 2.3** The National Screening Committee defines population screening as:

'public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by, a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications'. (www.nsc.nhs.uk)



The aim is to identify people within a population who could be offered more specific tests with the hope of identifying and reducing the risk of disease or its associated complications. For example all women over 50 are offered breast screening every three years, the aim being to identify the risk of disease and to limit its associated complications.

- 2.4** In clinical genetic services, specific tests may be offered to those who are at risk of developing, or who have, a specific disease. For example they might be offered these tests on the basis of their family history (ie they might have an inherited condition) or because of symptoms suggesting a disease. The introduction of genetic profiling would mark a radical shift in that it would identify the majority of genetic variants as opposed to variants related to a specific disease. If genetic profiling were to be used as part of a screening programme, this would have additional implications. Screening is distinguished from other clinical services in that it is offered to an entire population, for example all newborns, women in a specific age group or people with high blood pressure, rather than to an individual who comes to medical services already anxious about or suspecting a problem.

Why profile?

- 2.5** The notion at the heart of genetically profiling babies at birth is to determine most of the variations that may be important in healthcare for that person throughout their life. The results could then be stored in some form and re-examined in the future as genetic knowledge expands. Each person could potentially be empowered to play an active part in maintaining or bettering their health in light of their own genetic makeup. For example some people might be more at risk than others of heart disease because of the interaction between their genetic variants and their lifestyle. On this basis, health professionals might suggest particular diets or drug regimes to reduce that person's risk of developing a heart condition.
- 2.6** Genetic profiling, in conjunction with other health, lifestyle and environmental information, brings the promise of a more accurate assessment of disease status, disease risk and an individual's susceptibility to various environmental exposures. Potentially, genetic profiling could tell people how they might interact with and respond to environmental pollutants, foods and infectious agents. It could allow disease risk to be assessed and provide a template against which people might be able to alter their lifestyle in order to reduce or at least delay the onset of disease. However, the evidence is not yet clear of the links between most genetic variants and disease.
- 2.7** It may also lead to a more widespread use of genetic information in prescribing medicines and have a far reaching impact in particular therapeutic areas. We do know that people respond differently to drugs and that part of the reason is genetic. For example certain drugs used in treating breast cancer are more effective in the treatment of some people than others because of genetic variation. Pharmacogenetics is the study of people's response to medicines based on their genome. It could in the future be used more extensively to help health practitioners to tailor drug treatments in order to improve their effectiveness, and to identify those people who might experience adverse drug reactions.
- 2.8** The use of genetic profiling is believed by many experts to be realisable at some stage in the future. It is seen as having the potential to be used in medical practice to predict and prevent disease, in addition to aiding in diagnosis and treatment. Disagreements have centred on timescales, pace of development and delivery of clinical value. Some experts suggest that such



scenarios will be a practical possibility within the next 10 to 15 years, while others predict that it will be many decades before such changes become a reality for clinical practice in the NHS.

The case against profiling

2.9 Beyond these clinical uncertainties, the idea that genetic profiling might be adopted extensively raises significant moral questions. Some feel that we may become more medicalised, seeing ourselves for instance as genetically determined in terms of health and behaviour. There are also concerns about confidentiality and how this information might be misused by insurers, employers, schools or even the government. Some of the information may be unwanted by the individual; furthermore the genetic information, once collected and stored, will require periodic re-evaluation in the light of developing knowledge in genetics, imposing new burdens on all concerned. Others have raised concerns about whether or not it would be possible for there to be fully informed consent.

I am concerned not so much about people having the information, but with what they might do with it with the current level of understanding and the current social stigma attached to disability and medical conditions in general. Consultative Panel Member

2.10 An additional problem is that testing healthy populations is less satisfactory than targeting specific groups of people, such as those with a family history of a disease. The reason is that healthy people are less likely to have the specific variations that lead to the disease, so the demands on the predictive power of the test are much greater (see Chapter 6).

2.11 Concerns have been raised as to whether the information would ever be comprehensible. Much more research is needed before a genetic profile is of value, even to experts, and interpretation for medical purposes will always be a complex task. Information from profiling would be very different from the type we might get now from a specific genetic test.

2.12 Before any genetic profiling of babies could be considered at a population level, a rigorous economic analysis of costs and benefits would need to be conducted. If there is no evidence that such a programme will result in significant gains in population health, then resources would be better spent on other aspects of healthcare, for example by improving people's lifestyles and their environments. We expect, however, that profiling will become available privately to those who can afford it. Indeed it is already on offer, but there are few takers because it is very expensive, not cost effective and the results are not clearly interpretable. As the price falls and research continues (see Chapter 4), we anticipate that private uptake will grow, with consequent impacts on the NHS (see Chapter 3).

Why at birth?

2.13 The proposal in the White Paper suggests that genetic profiling might be carried out at birth and that the genetic information might be stored for future use. The rationale for taking a sample at birth is that it would be relatively convenient to collect, and that the linkage of such data to a person's medical record and care might confer a clinical advantage. This could lead to improved healthcare in childhood in a way that could also improve adult health. However, before any introduction of genetically profiling babies at birth, a number of serious ethical, legal and social concerns would need to be addressed. Some of these concerns are highlighted in the following chapters.



3. Ethical, legal and social implications

- 3.1** An examination of the ethical, legal and social implications of genetic profiling was our first priority. We also wanted to ensure that matters relating to personal choice and commercial considerations were taken into account, since some companies are already offering various forms of genetic testing direct to the public. We recognised that these matters, rather than the technical feasibility of genetic profiling, should determine our recommendations.
- 3.2** HGC's report *Inside Information: Balancing interests in the use of personal genetic data* highlighted a number of purposes other than medical treatment for which genetic information could be used, including medical research and parentage and relationship testing, and also raised a number of issues including consent and confidentiality. HGC's report *Genes Direct* stressed the right of individuals to have access to information about themselves but noted that these had to be balanced against the possibility of inappropriate exploitation and the causing of harm particularly to vulnerable people. We were content to accept the conclusions of these reports and did not go over ground covered in these documents.
- 3.3** We also noted the discussions of those involved with recommending and implementing current newborn screening programmes. We were particularly supportive of the view that screening programmes of whatever nature had to be undertaken on the basis of informed choice. It was, however, unclear how informed choice could be interpreted in the context of genetic profiling at birth. We also considered the available evidence regarding public attitudes towards genetic testing.
- 3.4** We worked on the assumption that any health intervention delivered by the NHS, whether preventive or therapeutic, should be supported by a strong evidence base, lead to measurable health improvement and take account of the potential social impact. Notwithstanding the new knowledge that will undoubtedly come from advances in genetic and molecular science, the prime determinants of ill-health in our population are still social and environmental factors. We noted that resources are finite and that in making any recommendations about health service interventions, priorities have to be set and choices have to be made between alternative uses of those resources.
- 3.5** At the same time, there may be very important benefits in using these technologies for research, and certainly people should be given choice. But there are possible tensions as individual choice and the drive for innovation are balanced against ethical, legal and social implications.
- 3.6** The paragraphs below set out the evidence from public surveys, the perspective of the commercial sector and people as consumers, specific ethical issues in genetic profiling, and the role of regulation.

Evidence from public surveys

- 3.7** In 2000, HGC commissioned a study on public attitudes to human genetic information. Almost 9 in 10 respondents felt that new genetic developments will bring cures for many diseases, and

almost three-quarters felt that new genetic developments will mean healthier children free from inherited disabilities. Respondents appeared wary, however, of genetic testing by employers and the use of personal genetic information by insurers.

- 3.8** This is generally supported in other recent surveys in the UK and other European countries, for example *Eurobarometer 58* (Autumn 2002), which shows that the public is generally positive about genetic testing for disease, regarding such use as ‘morally acceptable and to be encouraged’. Surveys such as the *British Social Attitudes Survey 2004* demonstrate that the majority of people are also in favour of having databases containing human genetic information if the purpose is to improve our understanding of disease.
- 3.9** In recent surveys, a dominant concern about genetic testing, especially in relation to population-based collections of genetic material, is that the information may be used for purposes unrelated to improving the individual’s health, such as job selection or setting insurance premiums. For example of the 71% sceptical about genetic testing in one survey, 34% feared such tests would be used for unacceptable purposes. The majority expect that over the next 25 years insurance companies and employers will use genetic data. As demonstrated in the *British Social Attitudes Survey 2004*, these concerns may reflect a lack of trust in the application of science and in the adequacy of the framework set up by government to protect the public from risks linked to genetic science: only 23% perceived such frameworks to be adequately protective and only 25% trusted those in charge of genetic science to act in society’s interests.
- 3.10** In *Eurobarometer 58*, concerns were also raised about the storage of genetic data, leading some to argue that, without socially sustainable legislation, genetic databases are undesirable. The pattern of attitudes that emerges is that population-based collections of genetic material, such as those that would result from profiling babies at birth, would be regarded ambivalently (positive about testing but negative about the potential abuse of such data and the ability of existing legislative and regulatory frameworks to protect against this) and may face resistance.
- 3.11** In *Inside Information*, HGC recommended that government consider in detail the need for separate UK legislation to prevent genetic discrimination.

Potential uses of genetic profiling in pharmacogenetics

- 3.12** In an attempt to understand the causes of disease and variability of drug response, several pharmaceutical and diagnostic companies are already exploring the impact of genetic variation in drug research, development and delivery. Government regulatory authorities worldwide are currently drafting guidelines that will detail how genetic information will be assessed and utilised in determining the overall risks or benefits of a medicine. Targeted drug therapies in cancer, such as trastuzumab (Herceptin) and imatinib (Glivec), which use genomic information prior to prescribing, have already been approved by the drug regulators in the United States and the European Union and are now available. It is likely that the application of genetic information to drug development and prescribing will be evolutionary and each application will require a case-by-case assessment in respect of healthcare improvement and performance of any associated genetic test. Predictions about the impact of genetic technologies on the commercial sector vary widely.
- 3.13** The idea that more medicines (and other health interventions) may in the future be developed and prescribed through the use of genetic testing is already an integral part of the strategic thinking of



many sectors in the pharmaceutical and diagnostic industry. This is not the right place to set out a detailed discussion of the potential for pharmacogenetics in future healthcare. Furthermore, for many purposes, measuring proteins or other substances in the body can be more informative than using results from a genetic test. However, we now know that an understanding of genetic variation in people may be used to predict the potential therapeutic value of drugs, or the propensity to develop adverse drug reactions. It may also be useful for indicating dosages of medication, as seen by the current use of such information in several treatments for cancer.

The commercial perspective and people as consumers

3.14 The fact that genetic analysis is carried out through the use of sequencing techniques or micro-arrays, and that companies (small and large) offer these services, is indicative of the technical potential of modern genomics. What is much less clear at the moment is the evidence regarding the causal relationship between many of the genetic variations that would be identified through profiling, and risk of subsequent ill health, let alone the effectiveness of any consequent strategies to avoid that state. This raises the question of how useful profiling might be in the clinical context. At the moment, genetic tests that identify specific genetic variations can be useful in identifying disease or the risk of disease. In relation to genetic profiling, the availability of sound evidence of clinical validity and utility is essential if the NHS or individual members of the public are to make informed judgements about whether or not to use such tests.

Clinical validity

The ability of the test to detect or predict the phenotype of interest.

Clinical utility

The likelihood that the test will lead to an improved clinical outcome, including assessment of the risk and benefits of genetic testing as well as economic evaluation.

Analytical validity

The ability of the test to accurately and reliably identify the genotype of interest.

3.15 There are already several commercial genetic testing services that claim to predict genetic susceptibility to disease. These companies advertise their tests on the internet or through alternative healthcare providers. Many people feel they have a right to use such tests if they want to. It was the view of HGC in *Genes Direct* that while the existing regulatory framework should be strengthened, there should not be a statutory prohibition of genetic tests. We are in general agreement with this view.

3.16 Genetic profiling differs from specific genetic tests, as all significant variations in the genome may be identified and the information obtained stored in computers to be used as and when required during the person's life. In the next section we consider whether or not genetic profiling raises any specific ethical issues over and above the generic issues of genetic testing and the use of genetic information, and whether the regulatory framework will need to be strengthened as a result.

3.17 The remit of this report is to provide recommendations for the NHS, but a relevant consideration is the expected appearance of a private market in genetic profiling. This is likely to develop during



the next two decades, raising questions about whether regulation is needed for testing offered outside the NHS context, as discussed in *Genes Direct*. In addition, the growth of private genetic profiling will have three important effects. One is that it will encourage research into the use and value of the technology. Another, perhaps less welcome, is that it may increase the number of the ‘worried well’ consulting NHS practitioners. Third, it may accentuate inequalities of access to medical testing and treatment.

Specific ethical issues in genetic profiling at birth

- 3.18** The following paragraphs reflect much controversy in the Joint Working Group. Some members argue that these sections express too much concern, and that, far from enhancing discrimination, universal profiling would lead to a levelling of attitudes. All of us carry some genetic variants that can be regarded in a negative light, and many more that can be regarded positively. Recognising the complex interactions of our genes with one another and with environmental factors, we could use profiling for medical benefit while avoiding simplistic classifications of people.
- 3.19** Others take a different view. They point to the tarnished history of genetics in the 20th century, to past evils in the name of eugenics, and to continued genetic discrimination in present-day society. Would some children be seen as less valuable than others, and would their genetic profiles have a destructive impact on a whole series of life choices? Even if simplistic over-interpretations were avoided in the clinical context, there will be no lack of offers in the market to cast an individual’s ‘genetic horoscope’. And the information could pose a greater threat to individuals in the future if the government of the day is less than benign.

I feel that genetic profiling should not be offered at birth as this may lead to discrimination from insurance companies and employers and that the information could be abused.

Consultative Panel Member

- 3.20** Despite these differences of opinion, the Joint Working Group is in complete agreement that there should be no contemplation of general genetic profiling without first greatly strengthening people’s entitlement to freedom from discrimination and to protection as consumers. The challenge will be to ensure that any concern about genetic profiling does not deter people from taking advantage of the clinical benefits of developments in genetics.
- 3.21** The idea that genetic profiling might be provided as a state-sponsored programme in which the entire population (or a subset of the population) is invited to undergo testing provides substantial challenges. Consent and its implications for minors who are legally unable to give such consent are dealt with at length in *Inside Information* and elsewhere in this report (see Chapters 5 and 6). In addition, genetic profiling raises some more general issues. The lack of data associating individual variations with disease is more of a problem with this technology than with more specific forms of genetic testing. Any test performed on an essentially healthy population may cause anxiety and provoke unnecessary and perhaps costly investigations, or may provide a false reassurance. On the other hand, many will find the knowledge, properly interpreted, both valuable and interesting. In either case, however, it may affect not just the person tested but other family members. It could force knowledge on people whose own consent had not been sought and might lead to unwanted revelations about paternity which would be better left untouched. Knowledge that a child might develop a disease in the future could have either a positive or a negative impact on family dynamics: many people are pleased to be forewarned of possible problems so that they can be caught early, but others feel concern, especially if there is nothing useful they can do.



Do any of us have the right to know what is going to happen to us in the future? If we learnt that we were likely to have a heart attack in our middle years, or bowel cancer at 20 – is that really going to help us? Consultative Panel Member

- 3.22** Some would argue that the potential for discrimination will be enhanced if everyone is in possession of his or her genetic profile. The implications for insurance and employment of genetic test results were discussed in *Inside Information* and are being kept under review by the HGC. The potential for social stigma must certainly be taken seriously. The arguments that have been used with regard to specific genetic tests will be still more pertinent in the context of genetic profiling, where the volume of test abnormalities will be much greater and the interpretation of test results so much more complex.
- 3.23** Despite our reservations, we must not unnecessarily limit individual choice. The premise that people may, subject to the availability of a technology, choose to use these technologies at their own expense is one that must be accepted *prima facie* in a democratic society, even if that technology is not very informative. The significant question is whether, in relation to genetic profiling at birth, there are constraints that should be placed on the freedom of parents, and what those constraints might be.
- 3.24** Finally, if evidence of benefit is provided in the future, and if the technology is relatively expensive and only available to those with considerable resources, then, as with all healthcare innovation, issues of equity will need to be considered.

The role of regulation

- 3.25** The European In-Vitro Diagnostics Medical Devices Directive (IVD) does not require any greater degree of scrutiny for genetic tests on the market than other more conventional diagnostics. The Medicines and Healthcare Products Regulatory Agency (MHRA) has responsibility for the implementation of the IVD.
- 3.26** There was general agreement within the Joint Working Group that the proper evaluation of a genetic test should include the measurement of at least analytical validity, clinical validity and clinical utility and that it should also consider its ethical, legal and social implications. The IVD is a single market measure that regulates the safety, quality and performance of a device at the point of placing on or putting into service. Under present rules, the submission for approval of a procedure for genetic profiling will require the suppliers of the technology to show that the variations that it seeks to measure are actually measured and detected. There is no requirement for them to demonstrate that those variants have any clinical significance or utility.
- 3.27** In *Genes Direct*, HGC considered these issues in the context of over-the-counter genetic testing, and highlighted the need to achieve balance between personal freedom and public good. The report concluded that the IVD Directive, together with existing consumer legislation and voluntary codes of practice still evolving, would provide adequate protections for the consumer. In view of this and rapidly developing technology, HGC did not at that time (April 2003) recommend statutory legislation, but undertook to keep the situation under review. It did conclude, however, that the regulatory framework should ideally curb direct-to-consumer predictive tests and ensure that all tests meet stringent quality standards. This view finds support both here and in the United States. Recently, the Government has followed one of HGC's previous recommendations to introduce an offence of non-consensual testing of DNA for non-



medical purposes in the Human Tissue Act 2004. This addresses one of the primary concerns raised in the *Genes Direct* report about whether consent to a test would be valid if the sampling were done at home, since a testing company could not be sure that the sample related to the person requesting the test.

- 3.28** Many of the same issues apply to commercial genetic profiling services. Is it the responsibility of government to protect its citizens from ineffective, albeit harmless, information? Or is it up to the buyer to beware? These questions also raise the issue of how the concept of harm is to be understood in the context of the acquisition of individual genetic profiles. Clearly, simply acquiring the raw information cannot be physically injurious, but do we consider an interpretation of it that may result in unjustified anxiety, false reassurance or unwarranted expenditure harmful? We do not have scope here to address these issues fully, but further discussion is warranted.
- 3.29** Within the NHS there are structures in addition to statutory regulation that affect uptake. Not all products or services on the market are available on the NHS, since the National Institute of Clinical Excellence, professional guidelines and mechanisms that govern the commissioning of health services exert an additional layer of influence. Many believe that it is here that evidence of the clinical validity and utility of a product should be used to determine its place in the range of healthcare priorities. It is also possible to regard education strategies and mechanisms of clinical governance as a third layer of regulatory control. The argument here is that properly trained health professionals, with access to the evidence and the ability to assess it, will, in discussion with their patients, reach appropriate decisions. It is significant that the studies conducted for *Genes Direct* found that most people in the UK who wanted to be genetically tested would prefer this to be carried out via their own doctors.

Data protection issues

- 3.30** Along with the common law of consent and confidentiality, the Data Protection Act 1998 regulates the collection and processing of medical information including genetic information, and is administered by the Information Commissioner. The Data Protection Act 1998 covers the obtaining, storage, use and accessibility of the data – in this case a genetic profile relating to an individual. Briefly, under the Act, any processing must be according to a number of data protection principles. Genetic and medical information is ordinarily regarded as sensitive personal data and is subject to more stringent controls than other types of personal information. Although there are exceptions to the requirement for informed consent, in practice free, informed and specific consent of the person is normally required to perform any test that will yield data and for its processing thereafter. The Data Protection Act 1998 allows access to non-anonymised medical information for the purposes of medical research, provided that certain conditions have been met. The lack of clear purpose of profiling at present raises the issue of how to make sure that consent is properly informed. Consent is interpreted according to the usual meaning in medical practice (Chapter 5). The information required for treatment may well be different from that required for data processing, for example transfer abroad, to social services or for research. In each of these situations, questions arise as to how much information would need to be given to ensure transparency and ensure the consent is informed.
- 3.31** In *Inside Information*, HGC highlighted some potential shortcomings of the Data Protection Act 1998, for example in relation to the holding of and access to information about relatives. Since then guidance has been published on the interpretation of the Act in relation to medical information and there is an ongoing review of access both by patients and by their relatives.



There are recent moves at European Commission level to improve Data Protection Act 1998 enforcement procedures. However, as practice is evolving under the Act, and in view of some of the uncertainties in data processing terms, it would be necessary to liaise with the Information Commissioner when setting up any such profiling project.

- 3.32** Whatever the law and redress available, prevention of inadvertent release of personal information remains a priority and so technical security, as well as employment procedures and personnel training, remains key. We note that the National Programme for Information Technology is currently addressing these issues. However, personal genetic information may also be originated or transferred outside the NHS or outside the UK and security is equally important in these sectors.

Access to health data

- 3.33** Apart from access for medical research and medical treatment, the Data Protection Act 1998 allows access without consent for other purposes, including to the police for purposes of crime detection or statutory requirements such as a court order. Access without consent, except for purposes of public interest or under a court order, could be contrary to the common law of confidentiality and probably the Human Rights Act 1998.
- 3.34** However, concern has been expressed that, once available, any genetic information might be accessed without consent for other purposes, for example insurance or employment, and might lead to unfair genetic discrimination. This concern has in the past arisen because of the prospect of a central database originally gathered for specifically medical purposes being used for other purposes. The great volume of genetic data that would be produced by genetic profiling has again raised this issue. This matter should be kept under careful review.

Individual access

- 3.35** The Data Protection Act 1998 also gives rights of access by individuals to their own personal data. It specifies that this should be in an intelligible format. This would obviously raise issues of how to present the information relating to the data, and presenting it in a fashion that would not cause undue distress, bearing in mind that knowledge will be constantly changing, while at the same time respecting the growing trend for people to want to have greater access to information about their health. A specific exemption has been provided by statutory instrument for cases where disclosure of health-related data could be damaging. The Information Commissioner has produced guidance for individuals regarding the general rights of access in a medical context. Individuals may also require correction to records held about them.



HGC's Consultative Panel

One of the questions we asked the Consultative Panel for their views on was: If babies were to be genetically profiled at birth, who should have the right to ask for this information? Many felt that parents and doctors should have access to any possible information derived from genetic profiling:

... only they and their legal guardians that should have the information. Parents/legal guardians should perhaps be encouraged to share the information with GPs.

Parents should have a right to ask for the information, and that right should then pass to the individual when they come of age.

However, many also raised concerns about confidentiality, adding that safeguards would need to be put in place to ensure certain bodies would not have access, particularly employers and insurers:

The only people that would have any right to ask for the information would be the parents who have the babies' best interest at heart and would hopefully use the information in a positive way. No other group of people should have any right at all. The utmost safeguards should be taken to maintain confidentiality.

There were also other members of the panel who felt that no-one should have access to any information derived from genetic profiling, while another felt everyone should:

Nobody – the thought that you would be put into a certain box, according to your profile, at such a tender age is horrific ...

Everyone, because partial disclosure would arouse suspicions of those not told and legislation, preventing discriminatory use against those with a bad profile could be comprehensively passed ensuring as level a playing field as possible for all concerned.



4. The feasibility of genetic profiling

4.1 We investigated the scientific and economic feasibility of genetic profiling. Our conclusions are that genetic profiling is a technology that is feasible now, though prohibitively expensive for general use. It is unlikely to be publicly affordable within the next 20 years. There are, however, estimates that within this timeframe it may be possible to produce a full genetic profile of a person for £1,000 or even less. This amount would only be for the test itself and would not take into account add-on costs such as counselling. However, it will be technically feasible to acquire sufficient information from every person to cover the most important genetic variations and to store such information. Meanwhile, the field will not remain static. Genomic and information technology will continue to develop and provide the ability to extract, analyse and store genomic information with progressively greater efficiency.

Genetic profiling as a technology

4.2 About 99.8% of genetic information is identical in all people. The focus of profiling would thus be on analysing the 0.2% of our DNA where there are variations. Our genome consists of two copies of a 3,000 million letter code. One way of profiling is to read out, or ‘sequence’, the whole of the genome, which has the merit of simplicity and completeness. At present it would cost about £5 million to map an entire genome. However, more selective sequencing, targeting only the 5% or so of the genome that is thought to be important in medicine, could be done for £250,000. Continued development of the technology in use today might reduce that sum to £25,000.

4.3 This is still a long way from the £1,000 target that is predicted. To achieve this by sequencing will require new methods, though some approaches that are in an advanced stage of development in the UK and elsewhere show great promise. While it is unclear whether these approaches have the potential to be translated into a clinical context in the very near future, it is likely that within 20 years this target will be achieved.

4.4 An entirely different approach is to look only at the variable letters that are now being catalogued through a project known as HapMap. The aim of this project is to develop a public resource to help researchers find genes associated with human disease and responses to pharmaceuticals. If the possible variations are known in advance, a specific test can be devised for each one and then applied in an automated way. If we assume that 1,000,000 letters must be analysed, then the entire genotype of relevance for an individual could soon be produced for £10,000. Further cost reductions are likely in this rapidly changing field. However, this approach is less powerful than sequencing in that new variants would be missed, so it would not provide a full profile on its own.

4.5 Whether sequencing or other genotyping technologies will win out remains to be seen. As more variants are catalogued, sequencing may become increasingly attractive. Developments in the next 20 years are also likely to result in techniques that are not yet thought of. But for the purposes of this discussion, the point is that even conservative extrapolation of what we know now suggests



that in 20 years it will be feasible to acquire sufficient sequence information from every baby to cover the most important genetic variations.

Genetic profiling as a technology – data storage

- 4.6** The amount of data required to represent an individual's entire genome sequence is not that large. It is already feasible for this information to be stored at a relatively low cost. In the longer term there will be few barriers to making such information available, even in the primary care setting. Most of an individual's sequence is the same as the reference sequence, so an efficient way of storage would be to represent only the differences. Even if we collect the entire set of differences we expect no more than 6,000,000 differences in each genome (fewer if we only store the medically important ones). If 100 bytes are used to represent the location and characteristics of each variation and other associated information, 600Mb (the capacity of a CD-ROM) would be sufficient for each genome.
- 4.7** A CD-ROM costs about 50p to create, and could be kept as part of the person's patient record and accessed when necessary during consultation using a standard modern desktop personal computer (PC) equipped with the appropriate software. The complexity is no greater than managing other data associated with the patient, for example the electronic storage requirement is lower than that needed for a set of radiological images. If a GP practice wanted the relevant data to be available on-line in a database, rather than on disks, the requirement for a 5,000-person practice would be of the order of a few terabytes, which is feasible now, though not negligibly cheap. However, disk costs per unit of storage are dropping by a factor of approximately two per year, so this should be completely reasonable by the time the requirement arises.
- 4.8** If someone required access to their data away from home, for example when seeing a consultant or a doctor elsewhere, the bandwidth required to access specific information relevant to a health query would be quite small and within the capacity of current broadband protocols. The challenge for remote network use will be to develop a standard protocol for such access, and manage authentication in a secure fashion. It is also now quite feasible to manage complex complete human genome data sets on a laptop computer. Within a few years, it will be completely within the capacity of any PC to run software that can make use of someone's complete (or partial) genotype in the context of other genetic knowledge.
- 4.9** The purpose of this scenario is to document the feasibility of storage, even using present-day equipment. Methods will advance rapidly, so that by the time genetic profiling becomes affordable, the physical means of handling the information may be quite different. But whatever the methodology, the genetic record will have to be closely integrated with other aspects of the individual's medical record in order to be useful.

Quality control

- 4.10** As the volume of sequence information rises, increasingly demanding issues of quality control must be addressed. Accreditation for a sequencing or genotyping laboratory might best be done to International Organization of Standardization (ISO) standards in the same way as DNA fingerprinting laboratories. The ISO is a federation of national standards bodies concerned with consistent rules or guidelines of technical specifications. Participation in external quality assessment in some form would be essential, but whether or not this would be the same as for



clinical laboratories would depend on whether they themselves were interpreting the data and producing reports to be used in clinical decision making.

Data protection

4.11 These are not the only costs involved. In addition, there will be a need for secure networks and to transfer information between clinics, to control access and to allow individuals to have erroneous records corrected. However, the means to do this will be put in place by the current build-up of NHS information technology (required for many purposes), and so should not be viewed as a charge to profiling per se.

Data interpretation and use

4.12 Further substantial effort will be needed in interpretation and use of the information by doctors. Counselling will include an ongoing duty of care to the patient by the clinic, to regularly check the profile against developing knowledge of health-related risks and to advise accordingly. While we note the trend towards people taking more responsibility for their health, we nevertheless consider that these services may cost at least as much as the profile itself and may require human resources not readily available.

5. Genetic profiling as a screening technology

5.1 The prime characteristic of genetic profiling is that it is not directed at or focused on any particular genetic variant, or on the diagnosis or prediction of any specific disease or risk of disease. In addition, the interpretation of specific bits of sequence may change over time as further research is done. These features contrast with most other forms of predictive or diagnostic technologies, whether used in clinical practice or as a screening test. This distinction is of crucial importance because of the implications it has for the evaluation of effectiveness, for levels of uptake, for consent and for the disclosure of unwanted information.

Criteria for appraising screening programmes

5.2 The NSC has set out criteria for appraising the viability, effectiveness and appropriateness of a screening programme. The criteria, which are set out in Annex B, are based on the World Health Organization (WHO) criteria. In brief, they are that:

- the condition should be an important health problem;
- the natural history and epidemiology should be understood;
- there should be a recognised pre-symptomatic or latent period;
- the test should be acceptable, safe and reliable;
- there should be an agreed policy on the further diagnostic investigation of people with a positive test result and on the choices available to them;
- effective and acceptable treatment or lifestyle advice should be available; and
- all other options for managing the condition should have been considered.

The NSC criteria take into account the rigorous standards of evidence required and concerns about the adverse effects of health interventions. It recommends that all the criteria should be addressed before screening is initiated.

5.3 An essential requirement for current screening programmes is that they are for particular conditions. The very nature of genetic profiling, in that no single disease or condition is defined to be the subject matter of its use, makes it problematic in the context of screening. The requirement that the test should be simple, safe, precise and validated also sets it at a disadvantage since clinical validity will be hard to determine in the absence of a reference standard against which to evaluate the test. The essence of genetic profiling, in that it seeks to detect variants in the genome without prior reference to specific disease, sets it apart from all known screening programmes.

It is very difficult to justify a screening programme which is unaccompanied by an effective cure or treatment. Consultative Panel Member



- 5.4** There are currently some screening or diagnostic tests where abnormalities may be identified that are incidental to the problem for which the programme was designed. For example, in relation to screening in pregnancy, an ultrasound scan may reveal unanticipated congenital abnormalities; or a karyotype analysis (ie an analysis of chromosomes), carried out to determine the presence or absence of Down's syndrome, may reveal unexpected chromosomal abnormalities. In terms of criteria for screening as outlined in Annex B, the identification of such abnormalities is a disadvantage and considered an adverse consequence rather than a desired outcome of the programme. Wherever possible, specific tests are employed that do not have these problems.
- 5.5** Some programmes or tests assess exposures such as smoking history or diet, or risk factors such as blood pressure, which can give useful information about several diseases at once. But the range of conditions to which the information applies is still relatively small, and in most cases the investigation is designed to focus on a particular condition, such as ischaemic heart disease. In contrast, the genetic variants that would be revealed by a genetic profile would not be specifically selected, nor does much evidence exist at present to link them to specific diseases.

Choice and consent

- 5.6** There has been a policy shift in the UK towards the inclusion of the concept of informed choice and consent as an essential component of any medical testing and any screening programme. The General Medical Council produces guidelines on consent to investigation and treatment. They suggest that, in order to obtain consent, there should be information on the condition as well as the likelihood of any test result and its meaning. Current screening programmes are designed to detect early disease and offer intervention. The purpose of genetic profiling would be to detect those at risk of disease and there are few data on whether this is something that would be desired or accepted by people, or whether effective interventions will be available.
- 5.7** At the moment, people are encouraged to make an informed choice as to whether or not to participate in a programme based on an understanding of its potential advantages and disadvantages. An informed choice requires them to receive full information on the condition, the likelihood of false-positive and false-negative results and their implications, and the consequences of being presented with a positive test result. This practice has been developed because not everyone may want to know about disease risks, so individuals are given the opportunity to decide for themselves. For those who are tested, it is recognised that a good understanding of the test reduces both anxiety and false reassurance, and can facilitate adherence to subsequent intervention. In the case of genetic profiling, it will not be possible to address all the issues that might be needed to fulfil the NSC requirements for consent, not least because it is currently difficult to show how the results are to be interpreted. It may be argued, however, that a broad understanding might be sufficient and that individuals may be prepared to take on themselves the uncertainties of not having such information available to them.

The use of genetic screening at birth

- 5.8** Even if the principle of profiling as a screening intervention were felt to be acceptable, distinct problems arise in relation to its use at birth. The most important of these concern consent for the testing of children and how the information derived from any such testing should be used.

- 5.9** Parents, or a person with parental responsibility, may generally consent on a newborn's behalf to testing and treatment. The Department of Health guidelines on consent advise that parents must receive adequate information about the proposed procedure to make the consent lawful. Children can consent for themselves over the age of 16. If under 16, children are considered to be competent to make decisions on their own behalf when they are capable of fully understanding what is proposed. It is unlikely that profiling would currently satisfy this, because of its complexities and unpredictable consequences. The taking and storage of the sample would be regulated by the common law duty of consent and the provisions of the Human Tissue Act 2004 (when it comes into force); the information and its subsequent use would be regulated mainly by the provisions of the Data Protection Act 1998 and accepted clinical practice.
- 5.10** Newborn genetic profiling is particularly difficult to justify when it reveals information about diseases that may develop in adulthood rather than childhood. Although it may be legal for parents to consent on their child's behalf for testing, even for adult onset conditions, whether it is ethical to do so when no preventative steps can be taken is another issue. In the Joint Working Group, we discussed the fact that when a child reaches an age where he or she is able to consent on their own behalf, the child's right not to have information about future ill-health will have been abrogated because their parents gave their consent. The present consensus within the genetics community is that children should not be tested for adult onset disorders unless useful screening tests or medical interventions can be offered that will alter the course of the disease. In our discussion with students in Bristol, they largely felt the same way (see also Annex D). Some parents disagree with this view, considering that both they and the child have a right to know about probable outcomes for both psychological and practical reasons.

HGC's Consultative Panel

Another question we asked the Consultative Panel was whether or not parents had the right to know if their child might be at an increased risk of developing a condition later in life. The responses were mixed as the following comments demonstrate:

If a parent asks for their child to be genetically profiled, they should be given the option of being told whether or not their child is at increased risk of developing a condition.

Parents need information for decisions which they must take on the child's behalf before it can do so for itself, but should not be trying to organise their child's later life.

One respondent also felt that:

Parents have the right to choose to know but they also have the right to choose to not know.

Some concern was raised with respect to potential impacts this information might have on relationships and how children are raised:

I feel that if all the information was given to parents they would try and steer their children away from specific activities/professions. This could inhibit a child's development and therefore the parents could make decisions that the child should be allowed to make.



- 5.11** An approach that might be more acceptable would be to take and store the sample (or extracted DNA) but not analyse it until the person is able to give the appropriate consent. However, this would have significant financial, logistical and economic implications. There seems to be no real advantage to the individual in taking a sample at a time when the information it yields is not pertinent to that individual.

Genetic screening at birth using other technologies

- 5.12** Here we set out some of the advantages of childhood screening using other genetic technologies, and contrast the process of screening for single gene disorders with that of genetic profiling. Although many disorders are actually influenced by more than one gene, screening in those cases has mostly been used to investigate a single gene rather than to take account of variations in many genes at once.

- 5.13** One reason for attempting a genetic screening programme at birth is to identify those children at risk of a disease developing in childhood. Across the UK, babies are routinely tested for a number of conditions including phenylketonuria (PKU), a rare metabolic disorder which, if not treated soon after birth, can cause severe learning problems. The development of these learning problems can, however, largely be avoided by dietary treatment from infancy. PKU testing is a paradigm for the success of newborn screening in that the condition is serious, there is effective treatment and agreement on the screening test, and screening is the most effective way to identify and treat those who have the condition. By the time a child demonstrates sufficient symptoms to enable a diagnosis, irreversible damage will already have been sustained. Although PKU is a genetic disease, the large range of mutations responsible means that a direct biochemical test is more accurate in predicting the disease than a DNA based diagnosis.

- 5.14** Medium chain acyl-coA dehydrogenase deficiency (MCADD) is a condition currently being evaluated as a candidate for newborn blood-spot screening. This is a rare inherited disorder where the child may develop a low blood sugar and brain swelling, leading to either sudden death or brain damage, as an abnormal response to prolonged fasting, reduced food intake or infection. These critical illnesses do not arise in all children with the condition. There is indirect evidence that they may be prevented by avoidance of fasting and ensuring an adequate calorie supply during acute illnesses. The NSC has commissioned a pilot study to measure the clinical utility of this screening programme, since there is uncertainty as to its predictive value in relation to these adverse outcomes, and also to ascertain whether screening and early management does in fact result in a better clinical outcome. Screening for MCADD uses a technology (tandem mass spectrometry) that can, relatively easily, provide information about several other inherited disorders at one time. However, the meaning and value of that additional information for the child and their family is not yet clear. Hence the NSC emphasises the importance of basing policies for screening on specific conditions rather than specific technologies, and requires that there should be evidence addressing the benefits and potential harms on that basis to inform their policy decisions.

- 5.15** Another reason for testing is that the results may have reproductive implications for the family. The outcome of any such screening programme would be to offer reproductive choice. In reality, this situation would only apply to inherited conditions caused by high-risk genes that would be considered by the families to be serious. Screening at birth for a genetic disorder such as Duchenne Muscular Dystrophy (DMD) has little or no clinical benefit at present for the child who is screened. However, it may be of both practical and psychological benefit to the parents in



planning for family life and, if desired, in making decisions about future pregnancies. Newborn screening for DMD is currently not recommended by the NSC as a national programme.

- 5.16** In conclusion, genetic profiling of babies at birth would not fulfil NSC criteria for screening, because it would not be limited to identifying a condition for which we know the natural history and for which there is a useful intervention. There are also clear problems of consent.



6. The use of genetic profiling in the clinical context

- 6.1** We argued in the previous chapter that genetic profiling at birth should not be offered to the whole population for predicting disease. This leaves open the questions of whether genetic profiling may still have a place in a clinical context and of whether practice may change in the light of increased knowledge about human genetics. In particular, a person's genetic profile might some day have a more generalised use in healthcare delivery, for example in reducing disease risk through lifestyle choices or in the improvement of drug treatments through the optimisation of drug dosage.
- 6.2** If the condition warrants it, it is now relatively routine for individuals going to their doctor and health provider to be referred for a specific genetic test. In this chapter, we compare and contrast genetic profiling with specific genetic testing in the clinical setting.
- 6.3** Criteria that doctors and other health professionals may take into account in deciding with their patient whether or not a genetic test should take place include that:
- there should be a link between the genetic variants observed and disease or disease risk;
 - the individual, or, in the case of a child, the person with parental responsibility, gives consent;
 - the risk is modifiable based on some form of intervention, or some other change can bring benefit to the individual or family;
 - those identified as being at increased risk are likely to follow recommendations to reduce risks; and
 - the ethical, legal and social implications have been considered.

Linking genetic variants and disease or disease risk

- 6.4** Demonstrating that a particular genetic variant leads to an increased risk of disease is a matter of some complexity. Concern has been expressed in the literature about the failure to replicate findings from studies looking at the association between genes and the onset and development of disease. It is a challenge to show that such links exist and are causal.
- 6.5** For example in haemochromatosis, a late onset treatable disorder of iron overload, a common mutation was identified in over 90% of patients with the disease who were of northern European origin. The mutation was within a gene that has a biological role in iron metabolism and it was thought that this particular mutation conferred a high risk of developing iron overload. However, further studies in other populations suggested that the risk for those with the mutation of developing clinically important iron overload was possibly as low as 1%. Thus the predictive value of this mutation for population screening is weak. The people in the original studies represented the severe end of the spectrum associated with the mutation, and it needs to be understood that other genetic and environmental factors can modify risk.



- 6.6** There are additional technical barriers in using genetic profiling for testing. Clinical experience tells us that the predictive power of any test is much less in healthy people because of the lower prevalence of disease in such a population. Tests of imperfect sensitivity and specificity have much poorer performance in these conditions. We therefore expect that genetic profiling will give more false-positives and false-negatives compared with specific genetic tests undertaken in a defined patient group.

False-negative result

A child with a false-negative screening result is one who really has the disorder even though the screening result was negative. For example a child who has a false-negative result for PKU is one who is told that they don't have the condition, and then it turns out that they do have PKU. Depending on the condition, this can be very serious. All screening tests are associated with a variable risk of false-negative and false-positive results.

False-positive result

A child with a false-positive screening result is one who is thought to have the disorder when in fact they do not. For example a child who has a false-positive result for PKU is a child who has been told they have the condition, and then it turns out that this is not the case. For parents, receiving a false-positive result can mean that they think that their child is sick, when actually their child is healthy. All screening tests are associated with a variable risk of false-negative and false-positive results.

Sensitivity of a screening test

The sensitivity of a screening test refers to the proportion of individuals who have the condition who are correctly identified by the screening test. A highly sensitive test may identify nearly all those affected, ie it has a sensitivity approaching 100%. The consequence of a test that lacks sensitivity is that individuals with a negative screening result may believe they do not have the disease when in fact they do. They have a false-negative screening result and are falsely reassured by the screen.

Specificity of a screening test

The specificity of a screening test refers to the proportion of individuals who do not have the disease who are correctly identified by the screen. A highly specific test means that all those who are not affected are correctly identified, ie the specificity approaches 100%. The consequence of a test that lacks specificity is that an individual may receive a false-positive result, indicating that they may have a condition when in fact they do not. Sensitivity and specificity are usually in a 'trade off', that is improvements in performance for one are usually associated with a worsening of performance in the other.

UK Newborn Screening Programme Centre

Consent

- 6.7** Genetic testing is currently used to identify a specific genetic variation. Consent is an important part of this process. Prior to testing, the person should be informed of the general nature of the information derived from the test and the potential implications of this information for them. Genetic profiling raises a different set of issues insofar as a great many genetic variations will be identified. Explaining what results might be expected and what this information means prior to



the test will be problematic given the number of variations being tested for and the scale of information derived from them. In addition, in the report *Inside Information*, HGC along with others argued that people have the entitlement not to know as well as to know genetic information about themselves. That is, even if people did consent to genetic profiling, information may come to light that the person tested did not want to know. If profiling were to be considered in the healthcare context, a form of generalised consent would be required to make the procedure practicable.

Disease risk modification and intervention

6.8 For there to be health benefits associated with the identification of someone at risk of a genetic disease, there needs to be some form of intervention. Currently there are few effective interventions for those identified as being at high genetic risk. For example women with BRCA1 and BRCA2 mutations, where these variations are associated with a higher risk of breast and ovarian cancer, are offered earlier breast screening than the general female population. However, the actual effectiveness of this strategy in reducing the incidence of breast cancer for this high-risk group is not known and has not been rigorously evaluated. On the other hand, the more drastic step of prophylactic mastectomy is of proven effectiveness. Another intervention is reproductive choice, where people might make a decision about whether or not to have children, have prenatal testing or use donated eggs, sperms or embryos, based on any risk of future children having an inherited genetic disorder. Some also argue that provision of the information to allow people to prepare for the onset of illness is sufficient justification. This is one of the arguments made in support of Duchenne Muscular Dystrophy newborn screening programme in Wales.

As parents (of children with a fatal genetic disease), we struggled to obtain a diagnosis and to have had some prior knowledge of what their life was to entail would have helped us the parents to make a number of decisions which would have improved their life and probably our lives, ie housing to accommodate wheelchair living, various other questions involving access and education etc. Consultative Panel Member

6.9 By far the most likely use of genetic profiling in the near future is for pharmacogenetic applications where the aim is to improve the likelihood of therapeutic benefit from drug use. Increasing the probability of selecting the most suitable drug at the best dosage, reducing trial and error and improving health outcome, is a worthwhile aim. However, whether the determination of pharmacogenetic data warrants a genome wide scan or just the analysis of key genetic markers has yet to be determined.

Taking up recommendations to reduce risks

6.10 Identification of those at risk is only the first step in reducing mortality and morbidity. The second step requires that people follow recommendations to reduce risks. This might involve taking prophylactic medication or reducing their risks by means such as stopping smoking and reducing the consumption of fatty foods. There are high expectations that informing people of an increased risk of developing disease will motivate behaviour to reduce these risks. However, from the few studies conducted to date there is little evidence to support this. Indeed, there is some evidence to suggest that responses to genetic risk are worse than to other sorts of risk, because of the commonly held view that less can be done about genetic factors than about other indicators of



disease. For example if a person is told they have a genetic variation that means they have a higher risk of developing heart disease, they may be less likely to act on this information to avoid disease onset than those without a genetic predisposition but who smoke, have high cholesterol and are overweight. On the other hand, there is also some concern that if someone is told they do not have a high genetic risk of developing a disease, then they will assume they have no risk.

- 6.11** From the few studies evaluating the impact of providing genetic risk information about children, responses of parents and children seem to show more variation than responses of such testing in adults, in some studies achieving more benefits and in others more harms than would be achieved in screening in adults. For example in one study of hypercholesterolaemia in children, a condition where the person has unusually high levels of cholesterol, there was an improved clinical outcome. In another, it resulted in some parents limiting their children's diets so much that growth restriction occurred.

Considering the ethical, legal and social implications

- 6.12** The ethical, legal and social implications of using genetic profiling as a screening tool have been discussed in Chapters 3 and 5. The question here is whether there are similar implications for the use of this technology in clinical practice. There is a broad consensus within the clinical genetics community that predictive testing for single gene disorders such as Huntington's disease, or testing in relation to reproductive choice, should only be carried out after due consideration of the consequences, both positive and negative, and after appropriate counselling. This is because the prediction is relatively clear. But whether similar caution needs to be taken with disorders influenced by multiple genes, where the predictive power is less, is a matter of debate. Genetic profiling would, of course, pick up both categories and so would need special consideration (for which ultrasound scanning provides a precedent).

Practical considerations

- 6.13** It is already practicable to screen many genes at the same time using gene chip technology. The progressive entry of these methods into clinical practice, both public and private, will provide a setting in which the merits or otherwise of a full genetic profile can be evaluated. It is likely that, given the emphasis on individual autonomy and choice and commercial realities, genetic profiling will reach the marketplace before a complete understanding of these criteria are achieved. Some people will want to use this technology even if we do not quite know what all the information means. In doing so, people may have to take on a certain degree of risk, especially since the significance of some of the information will change over time. Variations in genetic sequence may later be found to be more or less important than previously thought, and some variants may have both positive and negative associations.
- 6.14** We conclude that genetic profiling should not yet be used in NHS clinical practice, since the evidence base is currently insufficient to warrant its cost and important ethical, legal and social issues still need to be addressed. Genetic profiling will be available to people through companies and on the internet, though there will be few benefits in having such tests done. It remains the case that much more research is needed before the value of genetic profiling can be judged.



7. Research

- 7.1** The completion of the Human Genome Project provides unparalleled opportunities for research. It is now well understood that many diseases come about as an interaction between environmental and genetic factors. The balance varies, of course, but to a greater or lesser extent, both elements are implicated in most health conditions. The complexities of these processes mean it will be many years before we have a full understanding of the biological mechanisms. The development of infrastructures and technologies in order to enable such research to proceed is essential if society is to harness the healthcare benefits of advances such as the Human Genome Project.
- 7.2** Genetic profiling techniques are being developed as research tools. All branches of medicine will benefit from cheap techniques of DNA analysis, which will improve understanding of how cells work and how variations and mutations affect normal cell processes and may cause disease. A primary use of this approach will be investigation of which inherited genetic variations predispose to particular disease states.
- 7.3** The scientific and medical literature is filled with studies purporting to show the relationship or association between particular genetic variants and disease risk. These are usually of case-control design, that is they seek to compare the variation in the gene or genes of interest between a group of individuals with the disease and a control group without. For various technical reasons, such studies are insufficient for fully exploring interactions between genetics and the environment. The study of these interactions normally requires the use of groups of people whose history of environmental exposure is known and who are then followed for many years or decades. It is then possible to compare the incidence of disease in groups with certain exposures or with a particular genetic makeup with the incidence in those who are not exposed or who are genetically different.
- 7.4** Currently, there is a range of projects in place or under consideration in order to develop our understanding of the role of genetics in disease. Among others, these include studies such as UK Biobank, the Avon Longitudinal Study of Parents and Children (ALSPAC) and the European Prospective Investigation of Cancer (EPIC). The Joint Working Group held a useful meeting with researchers involved in the ALSPAC study, which served to demonstrate the need for carefully controlled studies of genetic and lifestyle factors relevant to child health and development. UK Biobank is a long-term national project that aims to follow the health of 500,000 individuals aged 45–69 for up to 30 years.
- 7.5** The prime requirement in these studies is that data are made available to allow correlations between environmental exposures, genetic variants and disease. It is not necessary for investigators to be aware of the identities of individual research participants, provided that arrangements (often coding strategies) are in place to link the genetic data with information about environmental factors and clinical outcome. Indeed there are some who believe that ethical and scientific requirements dictate that research participants should generally not be told that they have particular genotypes, as it is unclear whether these do in fact render them susceptible to disease, and that they should only participate on that understanding.



- 7.6** There is a particular need for research into the potential not only of genetic profiling, but also of specific genetic testing, in children. The lack of data in this area has hindered us from coming to firm conclusions about the value or otherwise of newborn profiling, and we consider that this field should be addressed urgently by the Research Councils. At the same time, much more research is needed into public attitudes.
- 7.7** We suggest that genetic profiling has much to offer as a research technique and that its use in both case-control and cohort studies should be supported and encouraged. If in future years genetic profiling is to be of clinical use, much more must be learnt about genetic variation and its link with disease, and the influence of environmental factors. The rejection of genetic profiling as a screening tool at present should not be taken as a rejection of its longer term potential.

HGC's Consultative Panel

Overall, the Consultative Panel were supportive of genetic research. Comments included 'I think research in this area is absolutely crucial' and 'I think that this is essential'.

Many felt, however, that additional protections for participants in research were needed.

What needs to be done is to have, over and above the Helsinki agreement, firm enforceable legal parameters to the outcomes of any research. These must be firmly embedded in a human rights framework ensuring the right of each and any individual to protection from violation of any of the rights.

And

Its use and access to it may need to be controlled.

HGC, in its report *Inside Information*, stressed the importance of research being conducted in an ethical manner and that regulatory frameworks need to be in place as they currently are in the UK context.



Annex A: Joint Working Group membership and terms of reference

Aim

To conduct an initial review relating to the ‘analysis of the ethical, social, scientific, economic and practical considerations of genetic profiling at birth’ as requested by the White Paper on Genetics.

Terms of reference

- To consider the feasibility or otherwise of the technical aspects of genetically profiling all babies at birth, particularly developments in laboratory technology, bioinformatics and decision-support systems.
- To review the evidence for medical benefits or disbenefits of information derived from genetic profiles of babies at birth. This will include clinical and research uses in the light of current and anticipated knowledge on genetics and the risk of common disease in children and adults.
- To consider any wider social and legal (including consent) implications of profiling all babies at birth, for example its possible implications for insurance, employment, forensic and use for wider identification purposes.
- To seek views from appropriate experts and interested groups on aspects of past, current and possible future developments in newborn screening programmes and birth cohort studies across the UK and overseas, in order to assess whether the introduction of such a programme would do more good than harm at a reasonable cost.
- To involve, as appropriate, wider public viewpoints, for example via open meetings and existing consultative mechanisms.
- To provide regular progress reports to the Human Genetics Commission and the UK National Screening Committee and provide an initial report to UK Health Ministers by the end of 2004.



Membership (joint with the UK National Screening Committee)

Sir John Sulston (HGC) (Chair)

Dr Bill Albert (HGC)

Professor Brenda Almond (HGC)

Professor Elizabeth Anionwu (HGC, to August 2004)

Dr Celia Brazell (HGC)

Professor John Burn (HGC)

Professor Carol Dezateux (NSC)

Dr David Elliman (NSC)

Dr Frances Flinter (co-opted HGC and NSC)

Professor Neva Haites (NSC)

Professor Peter Harper (HGC, to August 2004)

Dr Hilary Harris (HGC, to August 2004)

Professor John Harris (HGC)

Mr Michael Harrison (HGC) (from September 2004)

Professor Theresa Marteau (NSC)

Ms Hilary Newiss (HGC)

Dr Christine Patch (HGC)

Professor Martin Richards (HGC)

Mr Peter Sayers (HGC)

Dr Rosalind Skinner (HGC)

Professor Martin Whittle (NSC)

Dr Ron Zimmern (NSC)

Meetings

The Joint Working Group met in November 2003 to discuss the topic. It met a further six times between March 2004 and February 2005.

The Joint Working Group was disbanded in February 2005 on completion of this report.

Minutes of the meetings can be found on HGC's website: www.hgc.gov.uk



Annex B: The UK National Screening Committee criteria for appraising the viability, effectiveness and appropriateness of a screening programme

These NSC criteria are based on the World Health Organization (WHO) criteria developed in the 1960s (see *Principles and practices of screening for disease* by Wilson JMG and Junger G, Geneva, WHO, 1968) but take into account both the more rigorous standards of evidence required to improve effectiveness, and the greater concern about the adverse effects of screening.

These criteria are used to assess the suitability of screening for various conditions, and are part of the evidence used to create NSC screening policies.

Ideally, all the following criteria should be met before screening for a condition is initiated.

The condition

- 1 The condition should be an important health problem.
- 2 The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
- 3 All the cost-effective primary prevention interventions should have been implemented as far as practicable.
- 4 If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood, including the psychological implications.

The test

- 5 There should be a simple, safe, precise and validated screening test.
- 6 The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.



- 7 The test should be acceptable to the population.
- 8 There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
- 9 If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

The treatment

- 10 There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
- 11 There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
- 12 Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

The screening programme

- 13 There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (eg Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
- 14 There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
- 15 The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
- 16 The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie value for money).
- 17 There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
- 18 Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.
- 19 All other options for managing the condition should have been considered (eg improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
- 20 Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.



- 21 Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
- 22 If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

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Annex C: Summary from Sadler, W (2003). *Genetic testing – Which way forward? Report of a public dialogue held by the Royal Society’s Science in Society programme* *

The Second National Forum for Science, also styled the People’s Science Summit, provided an opportunity for general members of the public, scientists and representatives of other groups to discuss and make joint recommendations concerning government policy on genetic testing.

Genetic testing had been chosen because it was known that the government had plans to issue a major policy paper in this area and because it relates to a key concern expressed at the Society’s 2002 Forum, *Who controls science?* With 250 people taking part in a day long structured debate, this was consultation on a large scale and followed in the footsteps of a series of regional meetings.

The debate, most of which occurred in small groups, took into account outputs from the regional meetings and a scenario which stated that within 20 years all children could have their genome profiled at birth. Twenty ‘information providers’ representing advisory bodies, pressure groups, government, industry, consumer groups and others helped stimulate a balanced discussion. The principal recommendations which resulted from the day’s proceedings were:

1. That a regulatory body be set up to oversee legislative and other issues surrounding genetic testing
2. That the profiling of the genomes of children at birth should not proceed because as many people were against the idea as were in favour
3. That a strong effort be made to increase education about genetics for both the public and healthcare professionals
4. That the impact of environmental and lifestyle factors on health continues to be considered alongside genetic factors.

A commitment was made by the Royal Society to bring these recommendations to the attention of the Department of Health and the Human Genetics Commission.

*A full copy of the report can be downloaded at <http://www.royalsoc.ac.uk/downloaddoc.asp?id=820>



Annex D: Evidence

We drew on some additional evidence during our review of the arguments for and against genetically profiling babies at birth. As part of this, we held a useful meeting with researchers involved in the Avon Longitudinal Study of Parents and Children (ALSPAC). This demonstrated the need for carefully controlled studies of genetic and lifestyle factors relevant to child health and development.

GeneWatch UK (www.genewatch.org) provided the Joint Working Group with an overview of their concerns were any proposal for profiling babies at birth to go ahead. In relation to data storage requirements and costs, Dr Richard Durbin at the Wellcome Trust Sanger Institute in Cambridge provided us with some expert advice.

In addition, in May 2004, the Joint Working Group went to the At-Bristol Science Centre to speak to some young people about their views on the costs and benefits of genetically profiling babies at birth.

Can your genes forecast your future?

Bristol, May 2004

Students were drawn from King Edmund Community School and Fairfield School in Bristol, and Crispin School in Somerset. There was also a student whose family was involved with the Avon Longitudinal Survey of Parents and Children (ALSPAC).

As part of the day, students were presented with a number of scenarios. The scenarios were set at a future date and based on the idea that all babies were genetically profiled at birth. The topics raised by the Joint Working Group included issues around genetic discrimination in the workplace and in insurance, whether or not children should be given their profile by their parents, and what the implications of some genetic variations might be for reproductive choice of a person's children, grandchildren and so on.

Following the presentation of the scenarios, students worked in groups to discuss how genetic profiling might affect them and those around them. The general feeling was that if the genetic profiling of babies were to be introduced, then parents should only have information about their children if it was related to a childhood disease, or if preventative measures could be taken in childhood for an adult onset condition. Otherwise, the students felt they themselves were the correct people to make the decision about whether or not to know their own genetic profile.

A number of comments were made and below is a snapshot of these.

Worried about selective breeding – marrying because the genes are compatible, and not for love.

Worried about people wanting the 'perfect' child.

Genetic profiling should not be compulsory, but there should be choices, for example one solution might be that children are profiled, their GP checks for diseases, then the data is destroyed. We are aware of the costs associated with this and with redoing tests where the data had previously been destroyed.



Too much pressure on doctors on what information to tell parents – should we only be testing for certain diseases?

We should be able to choose what to disclose e.g. insurance companies shouldn't know unless told by person concerned etc. as this could lead to discrimination within the insurance industry.

Could suicide rates increase due to people being told they are likely to die at an early age?

Data protection issues – we feel strongly about computer hacking and the chance that our data will not be protected.

Can we test for aggressiveness and the likelihood of becoming criminals? Is this nature versus nurture? What would the consequences of this be?

Who will have access to our information? Employers, GPs, insurance companies?"

How would segregation be stopped if companies had this information? How would biases in employment be prevented?

Could people have access to your information and use this against you? Could it be accessed by the wrong people?

Before this goes too far we should decide 'yes' or 'no' as otherwise it could become like greed, once you know one thing you will want to know more.

Could this information be used for solving crime?

Would there be any benefits or problems for the NHS?

We should be able to opt out.



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