

RESEARCHING HUMAN GENETIC VARIATION: AN EXAMINATION OF THE ETHICS OF GENETIC RESEARCH

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I RESEARCH, MEDICINE AND IMPROVEMENTS IN HEALTH CARE: PLACING GENETIC RESEARCH IN CONTEXT

Research is one of the central building blocks upon which modern medicine is based. Evidence-based research into treatments, new tools of diagnosis and pharmaceutical interventions have led to an improved quality of life and new and significant improvements in methods of treatment. As early as the fourth century BC, the Hippocratic Oath noted that, due to the 'uncertain' nature of medicine, in order to devise new treatments physicians were allowed to attempt new and untried remedies, so long as they maintained the maxim 'benefit and do no harm'.¹ The twelfth century philosopher and physician Moses Maimonides pleaded that he be granted the strength, time and opportunity to correct the knowledge he had acquired and to endeavour to 'extend its domain'.²

Until the development of important diagnostic aids, for example the microscope (seventeenth century), the thermometer and new methods of chemical analysis of the blood (eighteenth century) and x-rays (nineteenth century), the practice of medicine was severely restricted compared to today. That is not to say that medicine has not been a specialised discipline for a significant period of time. The oldest medical records date from around 2600 BC. Physicians not only existed in ancient Egypt, but were also divided into specialties we still see today (obstetricians–gynaecologists, proctologists, ophthalmologists, dentists and surgeons).³ It is only recently, however, in terms of medical history that medicine has ceased to be 'practiced against a background of incomplete scientific knowledge about the nature of disease process'.⁴ Medicine (at least up until the early nineteenth century) was considered more of an 'art' than a 'science', and until the nineteenth century medical understanding of disease relied almost entirely on a doctor's clinical skills at the bedside, supplemented with a knowledge of biology and anatomy that could be gained in the autopsy room.⁵

One of the most significant contributions to the practice of medicine occurred in the eighteenth century: the introduction of the concept of evidenced-based medicine by English physician Thomas Beddoes (1769–1808). Beddoes' primary concern was that medicine had become 'stagnant and secretive'. He advocated two solutions to this problem. First, he proposed the 'systematic collection and indexing of medical facts' which could be compared in order to 'sift good practice from bad'; and, secondly, he urged other physicians to publish their findings (presumably both the beneficial and the harmful) more often so that others could learn from previous practice.⁶ Beddoes believed that medicine was harming patients by its failure to collect and analyse information about what practice worked best in the treatment of patients. He presupposed not only that it was morally right to collect data and share it between physicians, but also that there was a duty to do so, if that information could be used to benefit the patient.⁷ One of the most significant early uses of statistical analysis

in medicine was undertaken by the French clinician Pierre Charles Alexandre Louis (1787–1872), who used it as a basis to prove that the practice of ‘bloodletting’ which had been a significant part of medical practice up until that time was not only non-beneficial, but ‘positively harmful’ in the treatment of disease.⁸

History tells us, therefore, that progress in medicine and scientific knowledge about the body and how it operates is crucial to mankind. While the ancient Egyptian physicians may have provided relief for their patients with their array of medicines, the linking of medical treatment with charms, incantations, amulets and prayers may have had little real therapeutic value. One of the continuing struggles in medical practice is how to improve the health and well-being of the patient, while minimising harm. As Beddoes and Louis envisaged, researching which practices worked and which did not was the first step. Following on from this, however, was a new method of scientific endeavour, the age of the physician–scientist who not only sought to treat the patient’s illness, but also to broaden understanding of disease with trials of new methods of treatment. This new era, involving experimentation on humans, brought advances in medicine along with new ethical challenges.

1.1 Human experimentation in the name of medicine: ‘Therapeutic’ research versus ‘pure’ scientific investigation⁹

To develop new treatments and methods of diagnosis it was necessary for physicians to develop techniques for research. In the ‘Age of Enlightenment’, during the eighteenth century, the scientific revolution continued and eventually shaped modern medicine with important progress taking place in the biological sciences.¹⁰ Since the mid eighteenth century the number of experiments on human subjects has increased. These early ventures into controlled research trials resulted in significant improvements in medical practice, providing medical treatments for scurvy (Lind, 1757), the vaccination for smallpox (Jenner, 1798) and an understanding of the circulation of the blood (Harvey, 1628).¹¹ Despite the obvious benefits of research, it is not without its risks. History records that at times medical research became a form of medical experimentation that was not in the interests of the patient but rather of medical science.

At times there is a blurring of the boundaries between research and innovative medical practice. Although research and practice can occur together, ‘practice’ is commonly now used to refer to medical interventions designed purely to ‘enhance the well-being of an individual patient’ and which have a ‘reasonable expectation of success’. Contrastingly, the term ‘research’ applies to investigations designed to ‘test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge’ which may be expressed in ‘theories, principles, and statements of relationships’.¹²

Human experimentation has been defined as ‘anything done to an individual to learn how it will affect him’.¹³ The main objective of human experimentation is to acquire new scientific information, rather than directly benefit the individual. While the terms ‘research’ and ‘experimentation’ are often used interchangeably, a distinction can be made. Research can be taken to apply to investigations conducted in accordance with a predetermined protocol, while experimentation (in contrast) refers to more speculative investigations, which adopt a more ‘ad hoc’ approach to the individual subject.¹⁴ Following the Nuremberg medical prosecutions, the full dangers became known of physicians sacrificing the interests of their patients to scientific endeavour. The World Medical Association responded by developing a Code of Practice for doctors, outlining the ethics of human experimentation. Central to the Declaration of Helsinki was the statement that ‘the health of my patient will be my first consideration’.¹⁵ This marked the first time a distinction was drawn between clinical research that was therapeutic, and research that was ‘pure’ clinical research, aimed primarily at acquiring new scientific information.¹⁶

Genetic studies such as those discussed later fall in many cases between these two categories. In most cases there will be no direct benefit to the research participant donating the sample for genetic analysis. The major benefit will most likely come from the development of a greater understanding of the relationship between genetic variation and disease, together with a fuller understanding of the complex interaction between genetic and environmental factors and their influence on health status generally. The information from this may, in the future, help to prevent and treat some diseases, but it is important to distance these long-term potential benefits from any perceived short-term direct benefit to the participant. On the other hand, medical genetic research involves only minimal harm to the participant if we think of harm in the purely physical sense. What biomedical genetic research does carry, however, are new kinds of harm from those traditionally considered in research ethics. These are harms to the psychological, emotional, cultural and (in some cases) economic well-being of the research participant. In the case of research on population-based groups, these harms can also include socio-political harms of the type not previously considered in research ethics.

2 RESEARCHING THE HUMAN GENOME

Research into human genetic variation has been gathering pace in the nineteenth century. This research was aimed at identifying the genetic basis for disease, and initially began by identifying genetic anomalies responsible for some of the commonest forms of Mendelian conditions. In 1938 British physician Lionel Penrose discovered the genetic origin of the condition phenylketonuria. Linus Pauling observed the biochemistry of haemoglobin in sickle-cell disease in 1949. Following the determination in the 1950s

of the exact number of chromosomes, more studies revealed the link between genetics and disease. These new investigations combined statistical genetics, cytology and biochemistry, and marked a new era in genetic research.¹⁷

Between 1981 and 2000, a total of 1112 genes were discovered which harboured mutations leading to monogenic diseases.¹⁸ Among the most serious disorders caused by single-gene defects are cystic fibrosis, Duchenne muscular dystrophy, Huntington disease, the thalassaemias, sickle-cell disease, haemophilia and some uncommon hereditary cancers. As more research is undertaken on the human genome, it is increasingly clear that most common diseases have a genetic component.¹⁹ Not all forms of genetic research are the same, and we should reconsider the assumption that one set of moral standards could act as a guidance for all types of genetic research. Genetic research to identify an autosomal recessive condition (such as cystic fibrosis) using family linkage studies may raise very different moral concerns from genetic research, on a targeted sub-population, into multifactorial conditions which focuses on the complex working of single nucleotide polymorphism (SNP) variation. Significantly, the outcomes from different genetic research may be quite distinct. While to date one of the most prominent uses of genetic information is in the context of reproduction (see Human Genome Research Project, *Choosing Genes for Future Children: Regulating Preimplantation Genetic Diagnosis* (Dunedin, New Zealand: Human Genome Research Project, 2006)), there are other potential uses of genetic information, such as to create an 'envirogenetic' profile, or to generate pharmaceuticals that will work optimally with an individual's unique genetic makeup (pharmacogenetics).

While current uses of genetic information focus on how that information can be used to avoid the genetic condition being passed on to offspring (for example, prenatal testing or preimplantation genetic diagnosis (PGD)), or to assist in diagnosing a serious hereditary disease (such as Huntington disease or sickle-cell anaemia), new genetic information may be useful to help individuals reduce their life-time risk of suffering from some of the most common and life-threatening diseases (such as heart disease, cancers, stroke and diabetes). In these latter cases, those at increased genetic risk can choose to make lifestyle changes.²⁰ While modern medicine can alleviate symptoms and prolong life for sufferers of these common ailments, it cannot yet cure them. One of the greatest challenges to modern medical practice has been its powerlessness against some of the most significant diseases of the twentieth century such as heart disease and cancer. While we know we can alter our lifestyle to reduce our risk of cancer, the absence of a cure seems at odds with the promise of what medicine would provide. In a century that began with some of the most significant improvements in health status following remarkable advances in medicine (consider the disappearance of diphtheria and poliomyelitis, the development of sophisticated diagnostic aids, the development of life-support systems and modern surgery, organ transplantation, chemotherapy

and the development of insulin) it seems that the reality of what medicine can do to fight these major killers is out of step with our expectations.²¹

Mapping of the human genome promised to provide a new range of information that was not available a decade ago. This information alone will not improve health or prevent disease. Advances of these kinds will come only after a deeper understanding of what this information means, and how genetic material controls the body at a molecular level.²² This first kind of research is already established, and has contributed some of the most significant advances in our understanding of genetics and health to date. Since many conditions are a result of both genes and environment, however, a second way to understand what the genetic data means is to gather genetic material from large numbers of persons and, over time, track their health states and disease outcomes, and map these against basic biographical information about how they live (such as their diet, exercise and living environment).²³

2.1 The role of polymorphisms²⁴

The human genome is made up of around 25,000 genes. If we compare the DNA of two different people we find a variation in genetic material at an average rate of 1 per 1250 base pairs.²⁵ Variations from a predominant allele occurring at an incidence of >1 per cent are called genetic polymorphisms.²⁶ Some polymorphisms will have no significance in terms of health status, but others will have a role to play in determining how an individual develops and responds to environmental factors. The frequency of a polymorphism can vary between different population subgroups.²⁷

'Polymorphism' is the name given to the small variations that occur in the sequences of bases in the genetic makeup of different people. As shown in Table 1, they can include either a change in a base pair at an isolated point along the genome (or SNP), or an alteration in the number of bases at different points along the genome (called a length polymorphism).²⁸ The most common polymorphism is the SNP. The majority of SNPs have two alleles, representing the substitution of one base for another (a C to T or A to G).²⁹ The number of SNPs in the human genome makes them suitable for generating 'ultra-fine-resolution genetic maps'; although, as a result of their abundance, there is no guarantee that the genetic map will be powerful enough to predict all disease association states.³⁰ There are many correlations between SNPs, making it difficult to distinguish the SNP that is associated with a phenotype from the other SNPs associated with it.³¹ Many association studies use SNPs, however, due to their potential to be genotyped on a large scale using new methods of automation.³²

TYPES OF POLYMORPHISM	
Single nucleotide polymorphism (SNP)	
ATTCCTTGGTATC	ATTCCTCGGTATC
TAAGGAACCATAG	TAAGGAGCCATAG
(e.g. a T–C substitution, forcing an A–G change in the other strand)	
Length polymorphism	
short tandem repeats (STRs) or variable number tandem repeats (VNTRs)	
GTATATATATATATATAC	GTATATATAC
CATATATATATATATATG	CATATATATG
(eight TA repeats)	(four TA repeats)

Table 1: Types of polymorphism

Source: Select Committee on Science and Technology, *Human Genetic Databases: Challenges and Opportunities* (2001) Appendix 7, Box 9

These variations can occur due to mistakes in the way DNA is copied during cell division, through damage to DNA (by for example chemicals or radiation) or, in the majority of instances, through the different combination of mixtures of DNA from two parents that occurs during sexual reproduction.³³ Some polymorphisms can create benign differences between individuals (such as eye colour and other distinctions in appearance), while others can affect a person's health.³⁴ Much research is now focused on polymorphisms that create a *susceptibility* to disease. In other words, the polymorphism does not make it inevitable that an individual will develop a particular condition (such as cancer or heart disease), but may make it more likely that, with the presence of other factors (such as poor diet, lack of exercise and environmental factors such as exposure to chemicals that trigger the disease), the individual will have an increased risk of developing the disease.³⁵ In some cases differences in polymorphisms may affect how some individuals respond to medications.³⁶ It is anticipated that an increased knowledge of polymorphisms will allow drug therapy to be tailored to coincide better with an individual's genetic makeup, thereby increasing its efficiency.

3 ETHICAL ISSUES ARISING FROM GENETIC RESEARCH

3.1 Non-therapeutic research: Special issues in genetics³⁷

The sequencing of the human genome provides data about our genetic makeup, but does not necessarily translate into immediate health benefits.³⁸ While some benefits may soon be available, many others will take years before they are realised. This poses special problems when we consider genetic research, much of which may be of a 'non-therapeutic' nature. As the United Kingdom Human Genetics Commission has succinctly described, '[r]esearch in human genetics relies upon early-stage work with no direct medical relevance. In this sort of work, sometimes known as "blue skies" research, the objective is to understand gene function rather than to pursue immediate practical goals'.³⁹

The time lag between the time when we gain knowledge of our genetic sequence and the later time when this knowledge translates into a health benefit has been termed the 'therapeutic gap'. This interval between pure scientific discovery and therapeutic benefit has caused some to issue guarded warnings about how we promote genetics, at the very least with regard to the exercising of caution when potentially creating unrealistic expectations in the mind of the public about what genetic research can deliver in terms of immediate health gains. As the House of Lords Select Committee on Science and Technology concluded in its deliberations on possible benefits, with a call for prudence in relation to genetics:⁴⁰

We fear that recent publicity may have led to misplaced expectation that benefits will be realised quickly. Accordingly, we urge that the Government and all those involved in explaining this complicated science to the public should, while stressing the benefits of research on human genetic databases, ensure that the likely time scales and other potential consequences are made clear.

Genetic research relies heavily on the donation of human genetic material for analysis. These samples are donated from research participants. Some samples will be donated by participants at known risk of genetic disease. They may either have a medical condition, the genetic origin of which is being researched, or they may be closely related to an individual who is known to have the condition in question. Initial investigations into the genetic nature of disease comprised these types of studies, known as 'linkage studies', in which researchers started gathering genetic material from known sufferers and expanded their pool of research participants to wider family members. In these cases, although the 'therapeutic gap' means that direct health benefits (in terms of improved treatments) may be a long way off, the research studies do offer some potential benefits to participants. First, they offer predictive testing which can be used to detect susceptibility for some hereditary conditions (such as the BRCA-2 gene which can be used as a predictive for some forms of

breast cancer). Secondly, research may lead to improved diagnosis, as in the case of the over 1100 disease-related genes (many are single-gene disorders), which allows ‘at-risk’ couples to use genetic screening to avoid the birth of a child affected by an identifiable genetic disorder.⁴¹

For conditions with a more complex mode of inheritance (see Table 2), where there is a complicated interaction between disease and environment, the form of genetic research may take a different direction. While it is still crucial to obtain genetic samples for analysis, this type of research typically differs from the traditional linkage studies in two ways. First, this research may not focus on obtaining participants from known at-risk family groups, but may instead seek to obtain samples from a range of people, many of whom may be selected from the general public rather than a select group of participants. Secondly, these studies require a high degree of personal information about influences such as the participants’ health status, lifestyle, diet and environmental factors. This type of research therefore requires ‘long-term epidemiological studies of large numbers of people ... to unravel the links between genetic background, environmental (or lifestyle) factors and the occurrence of disease’.⁴² It may also increasingly require the establishment of large-scale genetic databanks, a relatively new phenomenon in genetic research.

ENVIRONMENTAL AND GENETIC INFLUENCES ON DISEASE		
Wholly environmental ‘Accidents’	Environmental/genetic ‘Complex diseases’	Wholly genetic ‘Monogenetic disease’
Chemical poisoning Radiation sickness	Asthma Obesity Heart disease Breast cancer	Huntington disease Haemophilia

Table 2: *Environmental and genetic influences on disease*

Source: *Select Committee on Science and Technology, Human Genetic Databases: Challenges and Opportunities (2001) Chapter 3, para 3.6*

While research into complex diseases does not subject the participants to physical procedures evident in other forms of research (such as drug trials), it does involve the collection and retention of highly personal information, both genetic and non-genetic.⁴³ In this type of research any potential benefit to the participants may be hard to identify. ‘Participants in genetic research may therefore be invited to take part in projects in which the findings will only be predictive at the population level and

which the benefits for the community may be distant and uncertain'.⁴⁴ This type of research may aid in disease prevention, for which the best preventative measures in the case of common disorders may be dietary or lifestyle changes, rather than drug therapy or sophisticated medical intervention.⁴⁵

Research of this kind heralds a turning point in human genetic research. Not only does it involve sequencing large sections of an individual's unique genome, it requires this information to be held in a centralised database, and checked against highly personal biographical information. In addition to questions of consent, privacy, storage and use of such personal information, it also raises key issues around the benefits that this type of research offers participants. Is this type of research of potential 'therapeutic' benefit to the participant, or is it the 'pure' research type identified by the World Medical Association, aimed at acquiring new scientific information? The ethics around such research are further complicated when those targeted individuals belong to one identifiable sub-population in society. In these situations questions of benefit and potential harm extend beyond the individual researcher and research-participant relationship. The implications for the wider community, and those connected by the genetic material collected for research purposes, must also be considered.

While this new form of genetic research may seem to tend towards the 'pure science' end of the spectrum as far as research goes, the research is generally considered both scientifically valuable and ethically acceptable, so long as it is conducted in accordance with ethical standards – many of which have struggled to keep pace with new forms of research. Genetic research that promises to provide benefits at a community rather than individual level is tacitly supported and recognised as a potentially valuable field of investigation. The American Society of Human Genetics, for example, in its Code of Practice calls on members to 'promote public health, through the advancement of human genetic research and the provision of high quality genetic services'.⁴⁶ In the United Kingdom the Human Genetics Commission (HGC) describes this type of research as 'vital', and emphasises that 'as many people as possible should feel able to participate in genetic research, confident of the security and confidentiality of their personal genetic information and confident too, that ethical standards in research will be upheld'.⁴⁷ Since many of these research projects involve the creation of genetic databases, new ethical standards have developed to ensure that genetic *and* personal information is protected to a satisfactory level.⁴⁸ In a few cases specific targeted legislation has been passed to regulate genetic databases (such as those of Iceland and Estonia). In most cases, however, national bioethics bodies have issued a comprehensive range of reports and recommendations to provide guidance in this area (such as in France, the United Kingdom, Canada and the United States).⁴⁹ The World Health Organization is currently working towards a comprehensive set of recommendations and guidelines for researchers and research ethics committees worldwide.⁵⁰ The World Health Organization currently recommends that, in the case

of research seeking to create a database, the onus is on the researcher to justify its 'nature, purposes, content, and uses'.⁵¹

3.2 Recruitment

Most of the advancements in genetics to date have been in relation to identification of those genes that contribute to diseases which are highly penetrant and are caused by single genes (such as cystic fibrosis). The main method by which these genetic links to disease were discovered was through family linkage studies.⁵² For these studies many of those participating in the research were already patients or family members of patients. A study which restricts recruitment of participants to patients 'introduces a potential selection bias because their health status could cause them to be more motivated to participate in a research study compared with members of the general population'.⁵³ As a result, it is argued that follow-up studies of patient participants and their perspectives on aspects of the research procedure (such as informed consent) may not accurately represent the views of the general population about participation in population-based research.⁵⁴

Current genetic research, however, focuses on conditions that have a more complex etiology. What has proved difficult is the location of those genes that contribute to common diseases such as diabetes, heart disease and cancer. In the case of these conditions, the phenotypes are affected by not one gene but many, each having a small effect, together with the environment.⁵⁵ A new method of genetic research is therefore required: one which performs genetic analysis on a large number of participants, some affected and some not. Enrolling such a wide range of research participants poses new challenges for researchers. Resistance to these studies has occurred in some cases for a number of reasons, including fears about the misuse of information, confidentiality concerns, general fears of involvement with 'genetic studies' or an unwillingness to be involved in genetic research *per se*.⁵⁶

BOX 1: GUIDANCE FOR RESEARCHERS RECRUITING RELATIVES OF PARTICIPANTS FOR RESEARCH PURPOSES

Researchers wishing to recruit relatives of participants to the research must consider any potential for harm which might result from an attempt to recruit, and in doing so, should take into consideration the privacy and any known sensitivities of the relatives, and accepted processes of communication with the family. In general, recruitment should be through a family member who is already a participant in the research.

Source: *Winship and Marbrook. Ethical Considerations Relating to Research in Human Genetics, 1998 (amended 2000)*

Special concerns arise in relation to genetic studies involving population-based groups. While it may be tempting to obtain initial consent from group leaders (in cases where the targeted population belongs to a culturally or ethnically defined group) these persons may not be (or be perceived to be) entirely neutral in their views of the research. The role that community leaders should play in being the 'gateway' to genetic services has received much ethical attention. Issues of consent within the group and pressures within a targeted community to consent to research are some of the most complex ethical concerns arising from genetic research. These are discussed more fully later in this Report.

3.3 Informed consent

3.3.1 *Information that should be provided*

Consent is a crucial feature of any research on human subjects, as recognised by article 5(b) of the Universal Declaration on the Human Genome and Human Rights (1999) and article 8 of UNESCO's International Declaration on Human Genetic Data (2003). Consent is valuable for two main reasons. First, it provides the research participant with the information necessary to make an informed decision about whether to become involved in the research project. Secondly, it serves to remind the investigators of the ethical duty not only to advise the research participant of potential harms, but also to become aware themselves of potential dangers and to take steps in the development and design of any research protocol formulated to minimise potential harm to participants.⁵⁷ The principle of informed consent is firmly entrenched in medical ethics, and is a founding principle upon which any medical practice is based. Consent consists of three basic components: that adequate information is provided to enable an informed judgment to be made; that information is provided in a form and manner that will enable it to be understood by each individual; and that the consent is voluntary in nature (participation free from manipulation, coercion, inducement or any other undue influence).⁵⁸ Participants in any research study must be advised of the purpose, intended outcomes or benefits (to the individual and the community) of the treatment or research; all foreseeable risks, side effects or potential harm that are material to the research participants; and the right to withdraw from the research.⁵⁹

3.3.2 *Questions of coercion and group participation*

Participation in research must be voluntary and not subject to either coercion or inducement through either direct or indirect means. New Zealand's Operational Standard for Ethics Committees takes a broad view of what may constitute such coercion, stating that it includes 'financial or other rewards (such as promises of treatment), exploiting the vulnerability of individuals, or the influence and status of the health professional or researcher'.⁶⁰ Any reimbursement for participation

must be reasonable (such as covering the participant's expenses) and not amount to an 'inducement that compromises the voluntary nature of an individual's participation'.⁶¹

When genetic research is conducted by medical professionals or public health bodies with whom the participant has an ongoing relationship, the role of consent can become obscured by other factors causing new ethical challenges. Results from one study conducted in Sweden, a country with a strong welfare state and significant publicly funded health-care services, found that research participants did not view consent in the same way as envisaged by a traditional ethical framework. First, in some cases it seemed that ethical analysis focused too much on consent in relation to the donation of biological samples, and not enough on consent in relation to the supplying of biographical data. As was discussed earlier, new forms of genetic research (such as research into the role of SNPs and their influences on health and disease) require two types of information: a genetic sample, and biographical information. In focusing almost exclusively on the ethics of consent in relation to the donation of genetic samples, ethical analysis may overlook significant moral concerns in relation to the supplying of biographical information. In the study conducted in Sweden it was this latter type of information to which research participants felt most connected. This more personal information provided in questionnaires or interviews was seen as 'more intimate' than the genetic samples themselves.⁶² Secondly, research participants in an ongoing relationship with the health professional or public health authority may pay little attention to the information contained in consent forms, but instead place more significance on the personnel involved in the research study. This suggests, according to some, that decisions to donate are 'viewed as something other than an information-based, intentional act'.⁶³ Reasons for this may include a general desire to advance medical science, even if only one 'single soul' would benefit.⁶⁴

Associated with this must be the fact that the 'altruistic' act of donation of genetic samples is one that is relatively straightforward, involving only minimal risk of physical harm in the form of bruising to the site of venupuncture. Other studies have noted, too, that donation of genetic samples is sometimes seen as a 'good deed' which can be performed without significant cost to the participant.⁶⁵ In the Swedish example, research participants were selected from those persons who were undergoing a State-funded health check at the ages of forty, fifty or sixty at a public health centre. During the examination (which involved a range of medical tests) participants were 'invited' to donate a blood sample for research purposes. Researchers in this type of relationship with participants should be sensitive to the special nature of the obligations that may arise from research conducted in the context of a pre-existing doctor-patient relationship. In the Swedish study, research participants were described as already 'enmeshed in a set of duties and responsibilities in a state-citizen

relationship in which healthcare plays a central role'. In this case the claim that the decision to donate was a decision made by an autonomous individual was criticised as 'misleading', demonstrating one way in which, in the context of genetic research, questions of consent pose new ethical dilemmas.⁶⁶

It may be helpful to consider research as being separated into three distinct, but not unrelated, categories:⁶⁷ research aimed at pure scientific investigation in which no potential benefit to the research participant is envisaged; clinical research which utilises and develops pharmaceuticals or other therapeutic products; and research which will possibly lead to a direct health benefit for the patient or their family.⁶⁸ This helps to clarify the different relationship between the parties in each scenario. In the first category, the relationship is purely one of researcher and research subject. This is the type of scenario most likely to arise in relation to research aimed at creating long-term epidemiological studies of large numbers of people for the purposes of researching the role of polymorphisms and their association with common diseases (such as cancers and heart disease). This can be contrasted with the third category, in which the relationship is primarily one between health-care professional and patient. In this scenario there is a 'therapeutic alliance' which gives rise to stronger rights and duties. The primary obligation is on the health-care professional to 'do good for, and not harm to, her patient'.⁶⁹ It is the second scenario that arguably poses the greatest risk of potential conflict since the health-care professional acts as both clinician and researcher.⁷⁰ As the World Health Organization has warned, in some investigations it may be easy for clinicians to 'tip into the realm of research', and physicians should be 'mindful of their dual responsibilities'.⁷¹

Finally, one significant issue is the complex role of consent in studies involving 'population-specific' research participants. While the focus of ethical guidance is on consent to the research by individual participants, in some cases consent should be sought not just from an individual participant, but also from the wider ethnic group or community to which that participant belongs. In these cases, researchers would be required to undergo consultation with the community elders or extended family, while also making it clear that in these circumstances an individual is 'free to give or withhold consent'.⁷² The ethical issues in conducting population-based genetic research are discussed more fully later in this report.

3.4 Defining 'genetic information': What needs protection?

Information regarding genetic risk can potentially be of interest to many persons. It may be useful, for example, for insurance, in the employer–employee relationship, for forensic investigations, and in paternity testing. If genetic information relates to a group of participants connected through family relationships or under the wider ethnic/racial category, any misuse of information derived from a genetic study may

impact on that wider group. 'There is potential for harm to participants arising from the use of genetic information, including stigmatization or discrimination and researchers must take special care to protect the privacy and confidentiality of this information'.⁷³ Researchers are required to protect the privacy of participants and minimise any invasions of privacy. To minimise the risk of any unauthorised access to data researchers should take the appropriate steps to restrict access to the information, encrypt it and/or record it anonymously, and store it in secure facilities.⁷⁴

Public opinion surveys repeatedly reveal that behind concern about genetics is the belief that genetic information is 'special' and essentially 'a private matter' deserving of particular attention.⁷⁵ The term 'genetic information' is not, however, a unified concept, although much weight has been placed on the term which has been broadly defined as 'any information about the genetic make-up of an identifiable person, whether it comes from DNA testing or from any other source...'.⁷⁶ The term may be applied broadly, to refer to any information that relates to any characteristic or condition thought to have a genetic component. According to this interpretation, the term 'genetic information' would be indistinguishable from general sorts of health information.⁷⁷ In a narrow sense, however, the term 'genetic information' relates purely to the information derived from analysing genetic material. Under this narrow definition 'genetic information' would apply only to information resulting from analysis of an individual's genetic makeup. It is helpful to separate out the main ways of obtaining 'genetic information' into the four categories listed here.⁷⁸

3.4.1 Phenotypic observation

Observing a person can provide some basic genetic information about that individual, derived solely from examining their appearance and characteristics.⁷⁹ A simple example is that by observing a person's eye colour preliminary conclusions can be drawn about their genetic makeup.⁸⁰ While this does not pose too many ethical problems, some relatively serious and rare genetic conditions can give rise to an observable phenotypic change from which conclusions about genetic makeup can be implied. In the case of achondroplasia, for example, the condition is characterised by different body proportions from the average individual. The arms and legs are very short, the torso is more nearly normal size and the hands will most likely be short with 'stubby' fingers, with a separation between the middle and ring fingers. From these observable alterations in body shape a preliminary conclusion can be drawn about genetic makeup. A similar judgment can occur in relation to other conditions such as Down syndrome (in which those affected display physical characteristics in common such as an upward slant to the eyes, a flat facial profile, small ears, an enlarged tongue and a single crease across the centre of the palms), or albinism (an inherited genetic condition in which the body fails to make the usual amounts of a pigment called melanin, causing those affected to have little or no pigment in their eyes, skin or hair).

While this may be a blunt tool upon which to base any genetic diagnosis, we should not forget that judgments based on appearance, from which genetic information is *assumed* about an individual, can be just as potentially discriminatory as the results of any more sophisticated laboratory-based genetic analysis.

3.4.2 Family history

Another way of gaining information about a person's genetic inheritance is through obtaining personal and family information about medical conditions, biological inter-relationships and descriptions of phenotypes.⁸¹ By matching this health information with family connectedness some preliminary conclusions can be drawn about a person's genetic makeup. Take the example of Huntington disease, in which each offspring of a parent with Huntington disease has a 50 per cent chance of inheriting the gene. By obtaining a family history, one can determine that a child with a parent who has Huntington disease has a 50 per cent chance of also having that condition. If a child inherits the gene, then he or she will inherit the disease. If the child does not have the gene then they will neither have the condition nor pass it on to their subsequent offspring. The information that can be surmised from this basic medical and family information is that a person does or does not have a 50 per cent chance of having Huntington disease. This would count as 'genetic information' under a broad definition of the term; and, interestingly, these sorts of statements were possible even *before* the existence of genes was established, when all that had been proved was the existence of Mendel's laws of inheritance.⁸²

3.4.3 Laboratory-based analysis of bodily tissues and fluids

A third way through which genetic information can be obtained is the analysis in the laboratory of blood or other body fluids or tissues. This can be done through biochemical analysis of proteins or other biochemicals associated with DNA contained in body fluids (such as blood or urine) and tissues. Tests can be conducted to detect the presence or absence of the *activity* of the protein (as in the case of PKU), or *of the protein itself*.⁸³ This sort of genetic information may be highly predictive of future health status (such as the tests for Tay-Sachs disease or cystic fibrosis), or it may provide evidence of a disease susceptibility that without information about environmental and lifestyle factors may indicate a higher than average risk only. This latter sort of genetic information may not be highly predictive of future health status. It may reveal merely a causal mechanism of disease, with the genetic element being but one factor that contributes to the disease progression, along with others factors such as environment, diet and lifestyle. Since this information is derived from a more complex laboratory process than the first two categories outlined earlier, it would count as genetic information on the narrow definition of the term, notwithstanding issues of vagueness in its predictability. In these cases where tests only indicate a

susceptibility, although the laboratory testing may reveal a high level of accuracy about the underlying genetic condition, this 'genetic information' alone does not translate to information about future health status. This is because in these cases the genetic component has a relatively small degree of influence.

3.4.4 Direct DNA or RNA analysis

A final method through which genetic information can be derived is direct analyses of DNA (deoxyribonucleic acid) or RNA (ribonucleic acid). A number of methods can be used such as sequence analysis, mutation scanning or mutation analysis to detect a mutation in a gene.⁸⁴ One way of doing this is to test a genetic sequence by targeting a segment of DNA or RNA using a process known as polymerase chain reaction (PCR). This process (developed in 1985) allows the DNA from a single cell to be amplified (i.e. reproduced in large amounts) for testing.⁸⁵ This method of obtaining genetic information is contrasted with 'linkage analysis' (which was previously called indirect DNA analysis).⁸⁶ For direct analysis to be used it is necessary for the gene or genes (or genomic region) associated with the disorder to be known.⁸⁷ This can be contrasted with linkage analysis, in which it is not necessary for the gene association to be identified.⁸⁸

3.5 Protecting genetic information

As demonstrated, the first question we are presented with when we try and protect genetic information is the rather fundamental one of what we take that term to mean, and what category of information we are aiming to protect. With so many ways of arriving at genetic information, does the method by which we obtain genetic information affect the degree of protection provided? Should the term refer solely to conditions that are significantly influenced by genetics, or also to those conditions that are perceived to be influenced by genetics, despite the genetic component being of lesser significance than other factors?⁸⁹

Alternatively, should it refer to 'information obtained solely from sophisticated methods of analysis (such as direct DNA analysis) and exclude information based on assessments of a more general nature (such as phenotypic observation)? In favour of adopting a broad definition of 'genetic information' is the argument that information about a person's genetic heritage should be protected no matter how it is derived.⁹⁰ Since, however, laboratory-based genetic analysis has the capacity to yield information not in just in relation to one, but many, conditions, and can provide more accurate information about our genetic makeup, the alternative argument can be made that it is entirely appropriate to define 'genetic information' narrowly, so that it refers solely to the results of DNA tests.⁹¹

Additional questions arise when we consider to what extent it is appropriate to separate out the types of genetic information, not by the method by which they were revealed, but by the personal or social significance of that information.⁹² The HGC (UK) has rightly observed that genetic information, no matter how it is arrived at, may either be of a highly sensitive nature to the individual, or may not be considered sensitive at all.⁹³ In its report *Inside Information* (2002), the HGC rejected an approach it had tentatively favoured in its earlier work, which restricted 'genetic information' to information derived from DNA or other direct testing, in favour of a broader approach, in which the term, 'genetic information' would encompass all forms of genetic information howsoever derived.⁹⁴ 'We consider personal genetic information to be information about the genetic make-up of an identifiable person, whether derived directly from DNA (or other biochemical) testing or indirectly from any other source.'⁹⁵ In reaching this conclusion the HGC is consistent with the findings of the International Bioethics Committee (UNESCO), which similarly recommended that a 'broad rather than narrow definition of human genetic data' was preferable.⁹⁶

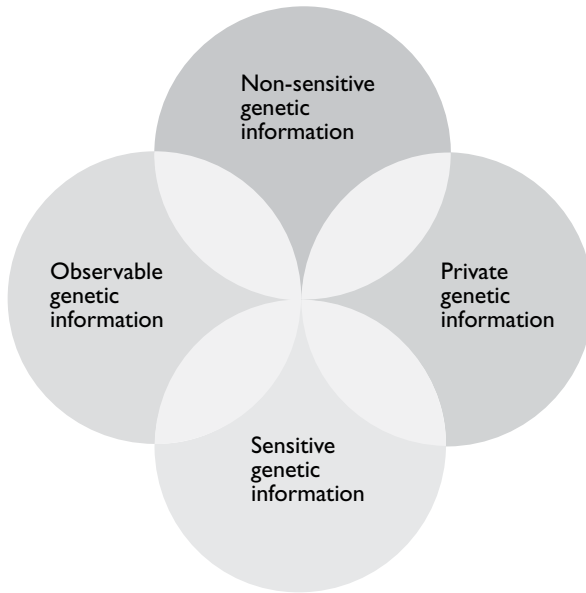
The HGC was persuaded by the fact that what matters is the use – or misuse – of information, not how the information was derived. It argues that this places the emphasis on the social context of the genetic information. If genetic information is used to discriminate against an individual, what matters is how that discrimination affects the person, not whether the information was derived from direct genetic testing or phenotypic observation. The HGC identified four categories which were helpful in considering genetic information. The overlap between the categories is best demonstrated in Figure 1. The HGC concluded that not all personal genetic information should be treated the same. Different levels of protection (such as requirements of confidentiality and consent) differed *depending on the specific circumstances*.⁹⁷

The desirability of this solution can be illustrated with the example of Duchenne muscular dystrophy.⁹⁸ While Duchenne is a genetic condition caused by the mutation of a gene (called the DMD gene), it can be diagnosed in a number of different ways. First, due to distinct observable physical symptoms (progressive muscle weakness and muscle wasting, a 'waddling' gait and difficulty climbing stairs, and muscle contractures in the legs, occurring only in boys) it could be diagnosed initially with phenotypic observation. This may be assisted by linkage studies joining family history with observable phenotypic changes. Secondly, since the DMD gene encodes the muscle protein 'dystrophin', a muscle biopsy may be undertaken to assist diagnosis, upon which analysis is undertaken to determine whether abnormal levels of dystrophin occur in the muscle. Finally, DNA analysis may also be undertaken which may employ a variety of methods such as looking for large changes in the gene (deletions or duplications, for example) or other changes in gene sequencing. All these observations or procedures result in personal genetic information relating to

the same genetic condition. Adopting a definition of genetic information that protects this information, notwithstanding how it is arrived at, is preferable to construing the term narrowly.

Figure 1: Categories of personal genetic information, showing overlap between observable, private and sensitive information

Source: HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data*, May 2002, 28.



Of ethical significance to this discussion is UNESCO's *International Declaration on Human Genetic Data*. It declares that human genetic data (defined as 'information about heritable characteristics of individuals obtained by analysis of nucleic acids or other scientific analysis') has a 'special status' (Article 4). Also provided in the Declaration is the specific direction that 'every effort' should be made to ensure that such human genetic data is not used in a way that infringes human rights, fundamental freedoms or human dignity. This applies to both the individual and to a family, group or community (Article 7). Article 14 sets out detailed provisions for the protection of privacy and confidentiality in relation to human genetic data. The most complex of these provisions relate to the obligation that researchers do not to keep such data in a form which allows the research participant to identified 'for any longer than is necessary for achieving the purposes for which they were collected or subsequently processed' (Article 14(e)).

3.6 Future Use of Stored Samples

Adding to the complexity of protecting research participants' privacy interests, is the fact that, once obtained, genetic samples may be stored where they could potentially be used for other research. This raises questions about in what circumstances it is appropriate to use samples obtained for one purpose for other additional research purposes. There is a need for clear guidelines to protect the interests of participants against future unauthorised use of stored samples. The extent to which these samples remain in the control of the research participant is a complex legal and ethical problem dependent on a number of variables.⁹⁹ The question has been canvassed in New Zealand by means of a Ministry of Health consultation in relation to proposed guidelines on the use of human tissue for future unspecified research purposes.¹⁰⁰ Since extracted DNA is not 'human tissue' (as currently defined in the guidelines) these proposed guidelines would appear to apply to genetic samples (which contain human cells or include a human cell) but *not* extracted DNA (which is the genetic material within the cell).¹⁰¹ The manner in which extracted DNA is protected is a separate legal question, which falls outside the scope of this report.

Regulatory complexity aside, a number of ethical issues are involved in the question of future use of stored samples, the most pressing of which is whether it is ever possible for research participants to consent to donation of samples for future research purposes of which they may have limited understanding, due to the ever-changing research in this area.¹⁰² What happens, for example, if a sample is later analysed and results suggest that the research participant is at risk of a genetic condition for which they have had no previous counselling? If samples were de-identified, the researcher would not be able to report back to the participant that he or she was at high risk. If the sample were still traceable, however, it is not clear that the researcher *should* report back in all cases. There may also be purposes for which some participants do not want their samples used. The current Operational Standard for Ethics Committees in New Zealand states that 'consent should be obtained before human tissue or bodily substances may be used for any purpose other than that for which consent was originally given'.¹⁰³

This may mark a change in the way stored samples may be used in New Zealand. Previous guidance did suggest a more flexible approach, allowing that stored genetic samples obtained for research purposes should only be used for future research purposes in the following circumstances:¹⁰⁴

- (i) The future research has the same, or closely related, research goals and the possibility of such future research has been discussed with the research participant and the participant has given consent and a new research proposal is submitted to an ethics committee (and approved) *or*,

- (ii) Genetic material and information is made anonymous and a new research proposal is submitted to an ethics committee and approved.

Research participants are entitled to know at the start of the study for how long the data or tissue will be stored, who will be responsible for the secure storage and how the data or tissue will be destroyed.¹⁰⁵ Genetic samples that have been obtained during routine clinical care can be used for research without the consent of the patient if the purpose of the research has been approved by an ethics committee.¹⁰⁶ The current Operational Standard for Ethics Committees states that ethics committees may 'waive the need for informed consent for storage, preservation or use of human tissue or bodily substances' in cases where it is not practicable to get consent, or where the committee satisfies itself that 'the potential public benefit in allowing the research to proceed outweighs the very strong need to protect an individual's right to consent'. The guidance provides, however, that this will be uncommon and only occur in limited circumstances.¹⁰⁷ This in essence echoes the guidance found in UNESCO's *International Declaration on Human Genetic Data*. Article 16 provides that human genetic data collected for one purpose should not (without additional consent of the research participant) be used for different purposes 'incompatible with the original consent'. A proviso exists, however, in cases where the proposed use 'corresponds to an important public interest reason and is consistent with international law of human rights'.

3.7 Reporting results to research participants

The current Operational Standard for Ethics Committees provides that research participants should 'continue to be informed throughout the duration of their participation in the research or innovative practice. This includes being kept apprised of any developments that could potentially impact on them and being informed of the results of the innovative practice or research'.¹⁰⁸ While the Human Genome Project has provided an unprecedented amount of genetic information, this new data about the human genome has not translated to a greatly improved ability to improve health and prevent disease.¹⁰⁹ This 'therapeutic gap' (as it has been termed) raises significant ethical questions. What should be done with the results of genetic research? Is it appropriate to advise participants of results that do not translate to clinical treatment? Is genetic information itself valuable, irrespective of how that information may be used in clinical practice? While much discussion has centred around the potential harms in advising research participants of results which do not provide any firm clinical advice, there is little evidence yet of how these risks affect research participants and their families.

In the case of research into conditions for which genetic influences are thought to be highly predictive, and which occur among close family members (such as BRCA1/2), it is well established that research may result in potential psychological harms to research participants and their families.¹¹⁰ In addition to psychological implications for the research participant and their family, genetic data arising out of research can also have potentially significant economic implications. For results that may be useful for insurance purposes the reporting back of genetic data can involve concerns about whether that information, once known to the research participant, must be disclosed to an insurer. In the United States, for example, the fear that genetic information about an increased risk of serious illness could harm an individual's 'ability to maintain healthcare coverage or to obtain health, life, disability or other insurance' has been taken seriously.¹¹¹ Since the 1990s there have been a burgeoning number of legislative attempts to prevent discrimination of this kind arising from unauthorised use of genetic data.¹¹² When research participants are connected in family or other population groups, the potential risks from the release of information to the community as a whole should also be considered. At the start of any research study participants should be made aware of what research findings will be reported back to them, and the manner in which this will be done.¹¹³ When research is conducted on population-specific groups, the implications of reporting back should be considered in terms of the implications on the group as a whole. Genetic research which analyses the genetic information associated with an identifiable population has the potential to raise new risks for population groups such as indigenous communities. 'All members of a socially identifiable population may be placed at risk by identification of genetic features linked with their common identity'.¹¹⁴

4 RACE AND GENETICS

The relationship between genetics and race has been described as having a 'turbulent history'.¹¹⁵ Race itself is a contentious topic, having grown out of the European practice of 'naming and organising the populations encountered in the rapid expansion of their empires'.¹¹⁶ There is currently a debate revolving around the role racial classification plays in medicine and biomedical research,¹¹⁷ and what value (if any) there is in using self-identified race or ethnicity to help identify factors that may contribute to health or disease.¹¹⁸ Some have argued that 'there is no basis in the genetic code for race', calling for the exclusion of racial or ethnic grounds of classification in biomedical research.¹¹⁹ The terms 'race' and 'ethnicity' are themselves so loosely defined, and carry such 'complex connotations' reflecting culture and socioeconomic and political status, that they can appear biologically meaningless.¹²⁰ Despite this, some argue that outward signs often associated with race and ethnicity (such as skin pigmentation, facial features and hair type) also indicate other differences such as character, disease susceptibility and temperament.¹²¹

At times the debate about race and genetics becomes subsumed in a larger debate about the role of genetics in explaining disease *per se*. According to Francis Collins (Director, National Human Genome Research Institute, United States) there is 'increasing scientific evidence ... that genetic variation can be used to make a reasonably accurate prediction of geographical origins of an individual'. He cautions, however, that the connection is blurry 'because of multiple other nongenetic connotations of race, the lack of defined boundaries between populations and the fact that many individuals have ancestors from multiple regions of the world'.¹²²

Within these parameters, genetics can play a role in health disparities associated with some racial or ethnic groups. This is most obvious when there is an unequal distribution of disease-associated alleles for recessive disorders such as sickle-cell disease or Tay-Sachs disease.¹²³ Increasing research endeavours are being directed at understanding the role race plays in determining disease susceptibility. An international research project (the HapMap Project) has been established to map common patterns of human genetic variation. It is hoped that this will encourage a fuller understanding of the role genetic variation has on health and disease. The Project maps the genome of four different groups: European American, African (the Yoruba in Ibadan, Nigeria), Japanese and Han Chinese. It excludes Native Americans and Pacific Islanders.¹²⁴ While the HapMap Project aims to identify genetic influences for disease and health status, it has been described as 'naïve' to think that the results would not be applied to other more contentious issues such as group identity and their correlation to social as well as health outcomes:¹²⁵ '... the proposed haplotype map project cannot be considered in isolation from the more general, ongoing discussion of the implications of using socially constructed identities in genetic research'.¹²⁶ While it is true that racial categories have been misused in the past to discriminate against some racially defined groups, some make the case that the risks of potential abuses need be weighed against the potential benefits of conducting epidemiological and clinical research using racial and ethnic categories as criteria for 'generating and exploring hypotheses about environmental and genetic risk factors'.¹²⁷

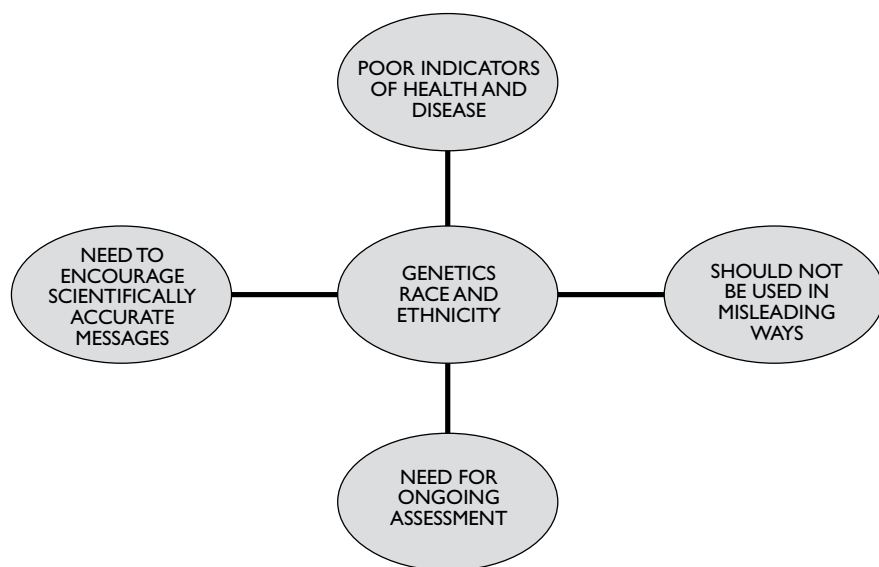
4.1 Race and ethnicity as indicators of disease

The greatest influence on genetic differentiation has been described as geography.¹²⁸ Distances in geographical boundaries have affected patterns of inheritance by directly altering patterns of mating and reproduction. This has resulted in a genetic substructure in some population groups that follows geographic lines.¹²⁹ This has been noted in both indigenous groups and groups that migrated to geographically remote areas. Canada, for example, was one of the first countries to develop multidisciplinary regional genetics centres and, as early as the 1970s, Canadian geneticists, together with genetic counsellors and laboratory scientists, established

centres for providing genetic services which were specifically ‘assessed and configured to fit local health service requirements’.¹³⁰ Many of these were created in Quebec, where the link between genetic disease and settlement structure is so marked that the ‘histories of populations and the histories of their alleles’ in some ways reflect each other.¹³¹ French settlers to Quebec brought with them their unique genetic makeup, which was passed on to future generations as a result of both traditional marriage patterns and relative geographical remoteness.

Figure 2: Race and Genetics – summary

Source: Collins F. *What We Do and Don’t Know About ‘Race’, ‘Ethnicity’, Genetics and Health at the Dawn of the Genome Era.* *Nature Genetics Supplement* 36(11), ss 14–15, 2004



In the case of Mendelian disorders, race can have a perceptible role in the manner in which the conditions occur. Genetic mutations that occur less frequently than 2 per cent are thought to be ‘nearly always race-specific’, and in some cases are found particularly in a single ethnic group within a wider racial classification.¹³² Examples of such groups are French Canadians, Ashkenazi Jews, Amish and ‘European gypsies’, all of which are thought to descend from a small number of founders.¹³³ Conditions that occur with between a 2 to 20 per cent frequency are often associated with a single racial group. Hemochromatosis (associated with a mutant allele C282Y) occurs in all European groups at a frequency of between 8 to 10 per cent), but not in non-white

groups.¹³⁴ Conditions that are a more complex mix of genetic and environmental factors are more difficult to research, although the few examples do suggest that race and ethnicity still play a contributing role.¹³⁵

While this suggests that race and ethnicity can have an important role to play in the understanding of genetic disease, theoretical evolutionary models explaining how this has occurred are complex.¹³⁶ Even in instances where a genetic variation is present in a number of ethnic groups, it may have a different effect in different populations. Homozygosity in the E4 variant of APO4 (associated with increased risk of Alzheimer's disease) increases the risk in Japanese by a factor of 33, in Europeans by a factor of 15 and in African Americans by a factor of 6.¹³⁷ While genetic research has revealed the genetic basis for a number of high-profile Mendelian (single-gene) disorders, using family linkage studies, this has created an 'unrealistic expectation' regarding the power of linkage studies to identify a genetic basis for common disease in humans.¹³⁸ For these common diseases 'no single factor is either necessary or sufficient' to describe the etiology of the disease.¹³⁹

4.2 Researching genetic variation among Māori: Examining new concepts of harm¹⁴⁰

Although Māori make up around only 12 per cent of the New Zealand population, research indicates that, compared with non-Māori, they suffer an increased burden in terms of health status. Common health problems such as cardiovascular disease, cancer and diabetes are all more prevalent in Māori than non-Māori.¹⁴¹ One response to these statistics has been to seek to identify genes that might influence this greater disease burden. The Institute of Environmental Science and Research Limited (ESR) has established a strategic partnership with Māori (Te Iwi o Rakaipaaka of the Hawke's Bay) to determine their health status, develop a computerised health registry, obtain genetic samples and create a genetic database of up to 3000 people, who trace their ancestry back to the Rakaipaaka iwi.¹⁴²

This type of genetic research poses significant ethical questions, which have as yet been under-explored in the context of Māori. While research into genetic variation has the potential to improve health in relation to these common health problems, it also creates new ethical challenges. Some of these potential problems have already come to light in New Zealand, when research (also conducted at ESR) was used by the researchers to identify what was described as genetic determinants for a range of 'antisocial disorders' (criminality, gambling and the so-called 'warrior gene').¹⁴³ Why are common health problems (such as cardiovascular disease, cancer and diabetes) all more prevalent in Māori than non-Māori?¹⁴⁴ What accounts for this disparity? To what extent do genetic variations influence such health burdens?

First, and most importantly, health disparities can have many causes and genetics may have a very minor role to play. 'In many instances, the causes of health disparities will have little to do with genetics, but rather derive from differences in culture, diet, socioeconomic status, access to health care, education, environmental exposures, social marginalization, discrimination, stress and other factors.'¹⁴⁵ While genetic explanations may highlight some causative factors that have previously been overlooked, we should not forget that for most conditions health status is a complex result of genes interacting with environmental factors. The higher incidence of disease can also be attributed to basic health-care issues, such as a lack of access to early health care (i.e. the early detection of cancers, diabetes and heart disease) or a failure in education about disease prevention through changes in lifestyle. While new developments in genetics may encourage a deeper understanding of the role genetics may play in these health disparities, genetic theories of causation for health disparities between racial groups may overstate the importance of genetics and may lead researchers to miss other explanatory factors such as unequal quality of, for example, health care, education and employment.¹⁴⁶

Research in the United States, for example, demonstrates how disparities in health status may result from 'long-standing, pervasive racial and ethnic discrimination'.¹⁴⁷ Factors such as substandard housing, increased environmental exposure to chemicals, hazardous working conditions and psychological stress caused by 'perceived racial discrimination' (producing higher rates of depression and high blood pressure) have all been cited as factors associated with poor health status in minority groups in the United States, contributing to a significant, non-genetic, theory of causation.¹⁴⁸ Notwithstanding this, to focus solely on non-genetic factors, if genetic influences do play a significant role in determining health status of minority groups, could be considered equally as problematic and raise serious ethical concerns.¹⁴⁹

4.3 Genetic research involving indigenous populations

Genetic research conducted on indigenous populations has been open to much criticism in the last decade. In the past, genetic research on indigenous groups has been clouded by past practices that threatened to breach a general understanding that biological samples would be used to help improve the health of the community, not prove (or disprove) theories of ancestry. A new range of harms needs to be considered for indigenous populations compared with other research participants who are usually otherwise unrelated to one another. Genetics may be used to question cultural beliefs and challenge claims of indigenous ancestry. They may be used to stigmatise further groups who are already the subject of discrimination. Sociopolitical harms may also arise in cases where one dominant population group in society uses genetic information to reinforce cultural stereotypes about a minority

group. These types of harms are commonplace in genetic research involving any sub-populations in society, but they are particularly relevant when the research involves indigenous populations. There have been a number of recent examples of genetic research being conducted in a way that both challenges cultural beliefs, and breaches tacit understandings between researcher and research participant. In the late 1990s, for example, international concern was sparked when samples from a First Nations group in British Columbia (Canada), which were donated by more than 800 persons of Nuu-chah-nulth origin to examine high rates of arthritis in that group, were used to examine the origins of the Nuu-chah-nulth people.¹⁵⁰ Even groups that have an established interest in genetic research to improve health and reduce disease burden can feel the negative effects of genetic research if they begin to lose control over how findings are disseminated and interpreted. This is demonstrated by the range of genetic studies being conducted on Ashkenazi Jews. While this research was initially welcomed and supported by the Jewish community, as more research demonstrated a high prevalence of mutations in Ashkenazi Jews, causing higher rates of breast, ovarian and colon cancers, concerns were expressed that 'anyone with a Jewish-sounding name could face discrimination in insurance and employment as companies struggle to keep down health-care costs'.¹⁵¹ In response, leaders of the Jewish community called for guidelines to protect the community.

These examples suggest that new types of ethical concern exist in the context of genetic research on population-based groups. Traditional ethical analysis of the potential impact of genetic information identifies problems with protecting confidentiality and privacy of research participants. In response to these concerns bioethical analysis has focused on concepts of individual autonomy and informed consent to safeguard against the use of genetic information for discriminatory purposes.¹⁵² These traditional responses have been criticised, however, for failing to address concerns about the potential for discrimination and stigmatisation resulting from what has been termed 'population-specific genetic variation'.¹⁵³

In response to breaches of expectation new ethical guidelines have been established for research conducted in indigenous communities and other identifiable populations. Many of these guidelines are based on a model of 'participatory action research', a model which is designed both to empower those involved and recognise the importance of self-determination.¹⁵⁴ There is still ongoing discussion, however, about the role of community involvement in the development and review of genetic research. On one side of the debate are those who argue that communities involved in population-specific genetic studies should be involved in development and ongoing evaluation of the research. A number of models have been proposed to facilitate this involvement.¹⁵⁵ In some cases social units upon which the community already relies when making health-related decisions can be used to engage the community

in the evaluation of genetic research proposals. In other cases, alternative approaches may need to be found to facilitate community involvement. Contrastingly, others argue that these approaches for gaining community approval are impractical and of little real value. Moreover, attempts to do so may be construed as ‘paternalistic’ and ‘inherently demeaning’. At the extreme end of the spectrum are those who deny any collective risk to socially identifiable groups.¹⁵⁶

Table 3: *Criticism of indigenous genetic studies*

PRIMARY AREAS OF CRITICISM FOR GENETIC STUDIES INVOLVING INDIGENOUS PARTICIPANTS

1. Lack of involvement of indigenous community in the planning and design of research
2. Insensitivity to cultural beliefs about condition
3. Fears about the potential for stigmatisation of community following research results
4. Lack of feedback to community on completion of project
5. Disputes about the commercial ownership of DNA
6. General feelings of exploitation of communities
7. Concern over use of stored DNA and cell lines for unauthorised research.

Source: *Arbour L. and Cook D. ‘DNA on Loan; Issues to Consider When Carrying Out Genetic Research With Aboriginal Families and Communities’, Community Genetics 9: 153-60, 2006*

4.4 Developing a new ethical framework¹⁵⁷

The three central principles to consider regarding the ethics of clinical research on humans are respect for persons, beneficence and justice.¹⁵⁸ This approach has been criticised for being too focused on individual rights, and for failing to recognise that research participants may be part of a wider family group or community to which duties are owed. Some argue that a new ethical principle needs to be adopted to recognise respect for wider communities and ties beyond the research participant. This could be a principle that confers respect on the community and an obligation on the investigator to ‘respect the values and interests of the community in research and, wherever possible, to protect the community from harm.’¹⁵⁹ Research into specific sub-populations in society raises new ethical concerns. These stem from the fact that the effects of some research are far-reaching and transcend the confines of the traditional researcher–research participant relationship. While these may have been

overlooked in the initial stages of genetic research, targeted groups are now becoming aware of the need to ensure that genetic information that was intended to improve their health and well-being does not confer a disadvantage on the community in the form of discrimination, stigmatisation and the perception that the group carries a higher disease burden than others.¹⁶⁰

To date, much of the focus of research on humans has been on the potential harms to the research participant. The assumption is often made that research subjects are strangers who have no connection to each other aside from their participation in the research study. New forms of genetic research challenge this assumption. It is not uncommon for genetic research to target specific racially or ethnically defined groups. In these cases the potential for harms extends beyond the traditional boundaries of the research participant and researcher. Information about genetic risk may impact not only upon the individual but also upon the wider ethnic or racial group. The potential for stigmatisation of or discrimination towards the group subjected to the research is a real ethical concern. Moreover, the wider community impact of genetic research may be overlooked by research ethics committees, which have traditionally kept their focus on potential harm to the research participant.

Ethical guidelines have been reconsidered and rewritten in an attempt to keep pace with new potential harms as a result of genetic research. *The International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Council for International Organizations of Medical Sciences, 2002) provides that the investigator in all biomedical research involving human subjects must ensure that the 'potential benefits and risks are reasonably balanced and risks are minimized' (Guideline 8: 'Benefits and Risks of Study Participation'). Those investigations that are of 'direct diagnostic, therapeutic or preventive benefit' should be justified by the 'expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative'. The guidance states that any risk of this kind of 'beneficial' intervention must be justified in relation to 'expected benefits to the individual subject'. For those investigations where there is no prospect of 'direct diagnostic, therapeutic or preventive benefit for the individual', risks are required to be justified in relation to expected benefits to society (generalisable knowledge). The *Guidelines* state that in these cases the risks to the individual must be reasonable in relation to the 'importance of the knowledge to be gained'.

How does genetic research into the SNP variations for ethnically or racially defined groups fit into this framework? What if research discloses information that groups would rather not reveal? Traditional responses would be to suggest that individual research participants could withdraw from the study, or that their anonymity could be preserved in the publishing of genetic data; but these responses fail to address the concerns of a sub-population in society that may be easily identifiable even though the

identities of the individuals themselves are protected. In these cases, it is appropriate for research agreements between the research participants and investigators to be thorough and detailed when addressing the possibility of such information surfacing. Appendix 1 of the International Ethical Guidelines for Biomedical Research Involving Human Subjects provides that among those items to be included in a research protocol are the ‘circumstances in which it might be considered inappropriate to publish findings, such as when the findings of an epidemiological, sociological or genetics study may present risks to the interests of a community or population or of a racially or ethnically defined group of people’.¹⁶¹

4.5 Conducting genetic research on Māori: New Zealand ethical standards

What the previous analysis suggests is that indigenous communities have unique concerns in relation to genetic research. The impact of genetic information on them as communities is potentially greater than the impact on other, less defined groups. Greater assurance needs to be given that the research will be conducted in accordance with robust ethical guidelines and that it will meet their expectations. Any research relationship must respect the indigenous cultural beliefs and be in keeping with their values. This extends to the use of genetic samples which may be considered ‘on loan’ to the researchers for the specific purpose for which consent was obtained.¹⁶²

PRINCIPLES OF COMMUNITY-BASED PARTICIPATORY RESEARCH

1. The research is required to respect the needs of the community and to be considered by all parties an appropriate research question to explore
2. The research must demonstrate an acceptance of indigenous culture, knowledge, tradition and values
3. Respect for these cultural elements should be developed through an understanding of the indigenous social, political and cultural structures
4. The indigenous community should be involved with the research from its initial stages, i.e. when the research question is first asked
5. The research should offer some benefit to the community
6. Research results should be reported back and data considered to be either mutually owned by the researcher and community, or owned by the community with ‘data stewardship’ held by the researcher.

Table 4: *Community-based participatory research*

Source: Arbour L. and Cook D. *Community Genetics* 9:153–60, 2006, 2–3

In New Zealand, any research on Māori health burdens should take steps to minimise harm to Māori arising out of the research. Researchers are required to minimise harms, which generally fall into four categories: physical, psychological, social, and economic. For research involving Māori, researchers are additionally obliged under the current *Operational Standard for Ethics Committees* to minimise harms that may occur to the whānau (family or community), hinengaro (emotional well-being and state of mind), wairua (spirit) and tinana (the body or physical self).¹⁶³ The concept of harm is broad enough to include ‘pain, stress, fatigue, emotional distress, embarrassment, cultural dissonance and exploitation’ (para 66). The New Zealand ethics committee guidance requires researchers to take steps to minimise potential harm to participants. The guidance proposes that this be achieved through inclusion of Māori as ‘partners and participants in the design, implementation, management, and analysis of research about Māori or Māori health’.¹⁶⁴

Any research on Māori conducted in New Zealand should be based on the following three principles (as set out in the *Operational Standard for Ethics Committees*, para 380):

- (i) *Partnership: working together with iwi, hapū whānau and Māori communities to ensure Māori individual and collective rights are respected and protected*
- (ii) *Participation: involving Māori in the design, governance, management, implementation and analysis of research, especially research involving Māori*
- (iii) *Protection: actively protecting Māori individual and collective rights, Māori data, Māori culture, cultural concepts, values, norms, practices and language in the research process.*

The guidance describes consultation as the ‘key component’ in developing research on a Māori health issue (para 381). Recalling past experiences, where consultation was not undertaken in a satisfactory manner, the guidance affirms that consultation is a ‘dynamic and flexible process’ involving a ‘two way communication process for presenting and receiving information before final decisions are made, in order to influence those decisions’ (para 382). Consultation means:

- *setting out a proposal not fully decided upon*
- *adequately informing a party about relevant information upon which the proposal is based*
- *listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal)*

- *undertaking that task in a genuine and not cosmetic manner*
- *reaching a decision that may or may not alter the original proposal (para382).*

The guidance also calls for Māori participation ‘in the governance and management of research’, particularly research focusing on Māori health (para 383), and for researchers to ensure that Māori participants have ‘the same protection as all other participants in research, with particular acknowledgement of cultural diversity for Māori’ (para 384). The guidance specifically states that this is to include ‘protection of individual and collective rights and ownership of data as well as protection from harm’ (para 384). Researchers are obliged to ‘support’ and ‘protect’ Māori culture, language, cultural beliefs, practices, values and norms (para 384). Importantly (in the context of genetic research) ethics committees are asked to consider whether mechanisms are in place ‘to ensure the Māori individuals and groups are not marginalised in the research process or by the presentation of the research results’. (See Appendix 2.)

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APPENDIX I

REPORT OF THE FIRST COMMUNITY CONSULTATION ON THE RESPONSIBLE COLLECTION AND USE OF SAMPLES FOR GENETIC RESEARCH

September 25-26, 2000

Ten major recommendations for genetic research involving populations and communities are, in brief:

- 1. Define “Community” in Appropriate and Meaningful Ways.** “Community,” a social construct, can be defined in many different ways, and individuals may consider themselves members of multiple, fluid communities. Reliable criteria are needed for defining communities for genetic research, and all potential stakeholders should be included in the definition of community for a particular research study.
- 2. Understand the Potential Benefits and Risks for Communities and Community Members.** As much as possible, all benefits and risks should be identified and understood in consultation with the community during the planning, conduct, and followup of a research study. Special efforts may be needed to maximize the benefits and to minimize the risks or harms to communities and their members.
- 3. Obtain Broad Community Input for All Phases of Research.** Communities participating in genetic research may have a strong desire to be involved in all aspects and stages of the research. Researchers should give special attention to soliciting broad input throughout the community, and NIH should establish criteria, goals, and mechanisms for obtaining input from communities.
- 4. Respect Communities as Full Partners in Research.** Lack of reciprocity between communities and researchers undermines the research process. Effective research depends on the full participation of communities and on mutual respect and a continuing, interactive dialogue between researchers and communities. Researchers should be encouraged to be sensitive to communities’ perspectives and needs.
- 5. Resolve All Issues Pertaining to Tissue Samples.** Continued efforts are needed to clarify the legal status of tissue samples; establish criteria for the collection, use, and storage of samples; understand the potential risks and benefits for individuals and communities providing samples; and assure appropriate procedures for obtaining informed consent regarding samples. Communities should participate fully in these efforts.

6. **Establish Appropriate Review Mechanisms and Procedures.** Researchers are, and should be, held accountable for any research involving communities. NIH should ensure the transparency of this research to communities and foster the participation of communities, public advisory groups, and institutional review boards in initial and ongoing reviews of community-based research studies.
7. **Facilitate the Return of Benefits to Communities.** Communities participating in research often do not believe that they receive any benefits, or returns, from their participation. Researchers should make an effort to provide these benefits, and NIH should extend support for follow-up studies of the benefits of research for communities and their members. The ownership of research results and data needs to be clarified.
8. **Foster Education and Training in Community-Based Research.** To enhance researchers' understanding and skills for conducting community-based genetic research, support is needed for education and training of predoctoral investigators and for continuing education for established investigators and research reviewers. Curricula should include community issues; ethical, legal, and social implications of genetic research; and model programs.
9. **Ensure Dissemination of Accurate Information to the Media and Public.** NIH should disseminate widely the results of genetic research which shows that genetic variation within populations is greater than that between populations; foster education of health professionals about these findings; and promote dialogue with the public about the ethical, legal, and social implications of genetic research.
10. **Provide Sufficient Funding and Encourage Partnerships.** NIH should provide sufficient funding to ensure that meritorious community-based genetic research can be conducted adequately. Specifically, NIH should expand funding to foster community involvement and participation in this research and encourage partnerships among government, industry, and academia.

APPENDIX 2

MINISTRY OF HEALTH, OPERATIONAL STANDARD FOR ETHICS COMMITTEES: APPENDIX 8 RESEARCH INVOLVING MĀORI

Ministry of Health 2006

376. This appendix has drawn on a number of publications including those produced by the purchasers of Māori research and Māori researchers themselves. Source documents are referenced in the Bibliography.

377. The National Ethics Advisory Committee is currently developing a Māori framework for ethical review of health and disability research. For further information on this work see www.newhealth.govt.nz/neac.

378. Māori health research practice and theory is developing rapidly. A number of guidelines and standards for undertaking research with and about Māori have been developed over the years. Examples include the Health Research Council *Guidelines for Researchers on Health Research Involving Māori*, Pomare et al (1995) *Hauora: Māori Standards of Health III*, and the *Hongoeka Declaration for Māori Health Researchers* (refer to Te Pumanawa Hauora ki Te Whanganui-a-Tara (ed) (1996). *Hui Whakapiripiri: A Hui To Discuss Strategic Directions for Māori Health Research* (Wellington: University of Otago). Many of the issues important to Māori researchers and research participants are covered in the text of this document. Other issues which should also be considered include:

- *the Rights of Indigenous Peoples over their cultural and intellectual property (the Mataatua Declaration, UN Commission of Human Rights (1993))*
- *the recognition of diverse Māori realities*
- *the opportunity for Māori to monitor, critique, and discuss, including in hui and public forums, all research impacting on Māori health*
- *the strengthening and development of Māori health researchers.*

379. Other indigenous approaches are important comparators to the Māori research developmental approach and this is reflected in a recent agreement on indigenous health research between New Zealand, Canada and Australia (Canadian Institutes of Health Research, National Health and Medical Research Council of Australia, and Health Research Council of New Zealand, 2001).

Principles

380. The three Treaty of Waitangi principles of partnership, participation and protection should inform the interface between Māori and research.

- *Partnership . working together with iwi, hapū whānau and Māori communities to ensure Māori individual and collective rights are respected and protected.*
- *Participation . involving Māori in the design, governance, management, implementation and analysis of research, especially research involving Māori.*
- *Protection . actively protecting Māori individual and collective rights, Māori data, Māori culture, cultural concepts, values, norms, practices and language in the research process.*

Partnership

381. Consultation is a key component in the development of research on a Māori health issue and for involving Māori as partners and participants in the research process.

382. In the past there have been many instances of misunderstanding resulting from differences in opinions as to what constitutes consultation. Consultation is a two way communication process for presenting and receiving information before final decisions are made, in order to influence those decisions. It is a dynamic and flexible process, which is well summarised by Justice McGechan: .Consultation does not mean negotiation or agreement. It means:

- *setting out a proposal not fully decided upon*
- *adequately informing a party about relevant information upon which the proposal is based*
- *listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal)*
- *undertaking that task in a genuine and not cosmetic manner*
- *reaching a decision that may or may not alter the original proposal.*

Participation

383. Māori participation in the governance and management of research must also be enabled. Participation by Māori in the research process is especially important in research that focuses on Māori or Māori health. The full range of research

methodologies may be applied to Māori and Māori health. This range covers many innovative approaches, especially including kaupapa Māori methodologies, which have been developed by Māori researchers and Māori research units.

Protection

384. Māori participants must be afforded the same protection as all other participants in research, with particular acknowledgement of cultural diversity for Māori. This includes protection of individual and collective rights and ownership of data as well as protection from harm. In addition, Māori culture, language, cultural beliefs, practices, values and norms must also be supported and protected. Te reo Māori, one of New Zealand's two official languages, is a special case in point, as are the respective roles and rights of Māori collectives whānau, hapū, and iwi, and individual Māori.

Informed consent

385. While written consent is the usual method of recording informed consent in research, some Māori may prefer to give their consent orally.

Points to consider

386. Ethics committees should consider the following points.

- Are mechanisms in place to ensure that Māori are involved as research participants in ways that do not undermine their cultural integrity?
- Are there any special problems, such as confidentiality and reporting, that might arise in sensitive research such as research about child abuse or sexual practices of rangatahi?
- Are special needs of rangatahi Māori, such as counselling and confidentiality, accounted for in the research design?
- When is it appropriate for parents or other whānau members to be present during the conduct of the research?
- If conditions present in participants have implications for other whānau members, health statuses, are appropriate mechanisms proposed for dealing with the larger family unit (for example, genetic risks or HIV infection)?
- Are mechanisms in place to ensure that tikanga Māori will be observed?
- Are mechanisms in place to ensure the Māori individuals and groups are not marginalised in the research process or by the presentation of the research results?

ENDNOTES

- 1 Jonsen A. 1998, 125.
- 2 Goodman K. 2003, 2.
- 3 Adler R. 2004, 3.
- 4 Weatherall D. 1995, 27.
- 5 Weatherall D. 1995, 46.
- 6 Goodman K. 2003, 4.
- 7 Goodman K. 2003, 5.
- 8 Weatherall D. 1995, 47.
- 9 I am thankful for discussions with Sheila McLean on the subject of the distinction between non-therapeutic research and experimentation, and also the question of the extent to which research on indigenous groups differs from other kinds of research.
- 10 Weatherall D. 1995, 42.
- 11 Jonsen A. 1998, 125.
- 12 The Belmont Report, 1979.
- 13 Bassiouni M.C. et al. 1981, 1597.
- 14 Mason J.K. and McCall Smith R.A. *Law and Medical Ethics* (London: Butterworths, 1999) 453.
- 15 World Medical Association, Declaration of Helsinki, 1964.
- 16 Bassiouni M.C. et al. 1981, 1610.
- 17 Jonsen A. 1998, 173.
- 18 World Health Organization, 2002, 11.
- 19 World Health Organization, 2003, 5.
- 20 I am thankful to Tony Merriman and Genevieve Matthews for their helpful discussions and suggestions on matters raised in these sections.
- 21 Weatherall D. 1995, 5.
- 22 Select Committee on Science and Technology, 2001.
- 23 Select Committee on Science and Technology, 2001.
- 24 My thanks to Tony Merriman, Nikki Kerruish and Genevieve Matthews for discussions relating to this section.
- 25 Environmental Genome Project. Available at: <http://www.niehs.nih.gov/envgenom/polymorf.htm>. Accessed 8 December 2006.
- 26 Guengerich F.P. 1998.
- 27 Environmental Genome Project. Available at: <http://www.niehs.nih.gov/envgenom/polymorf.htm>. Accessed 8 December 2006.
- 28 Taken from a helpful description provided in Appendix 7 of the House of Lords Select Committee on Science and Technology, 2001.
- 29 Crawford D. and Nickerson D. 2005, 303.
- 30 Crawford D. and Nickerson D. 2005, 304.
- 31 Crawford D. and Nickerson D. 2005, 303.
- 32 Crawford D. and Nickerson D. 2005, 303.
- 33 House of Lords Select Committee on Science and Technology, 2001, Appendix 7, para 21.
- 34 House of Lords Select Committee on Science and Technology, 2001, Appendix 7, para 22.
- 35 House of Lords Select Committee on Science and Technology, 2001, Appendix 7, para 22–5.
- 36 House of Lords Select Committee on Science and Technology, 2001. Appendix 7, para 27.
- 37 I am thankful to Nicola Peart for her comments, suggestions and time spent in discussing this section of the report in particular.
- 38 Select Committee on Science and Technology, 2001, Chapter 4, para 4.2.
- 39 Human Genetics Commission (HGC), *Inside Information: Balancing Interests in the Use of Personal Genetic Data*, May 2002, 89.

- 40 Select Committee on Science and Technology, 2001, Chapter 4, para 4.30.
- 41 For a thorough review of the techniques by which screening is provided, and the ethical and regulatory concerns relating to this, see Wensley, D; *Acceptable Limits of Reproductive Genetics: A Discussion of Ethical Principles and Regulatory Mechanism of Control* (A report prepared for the Law Foundation of New Zealand, July 2004) and Human Genome Research Project, *Choosing Genes for Future Children: Regulating Preimplantation Genetic Diagnosis* (Dunedin, New Zealand: Human Genome Research Project, 2006).
- 42 House of Lords Select Committee on Science and Technology, 2001, Chapter 4, para 4.6.
- 43 HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data*, May 2002, 89.
- 44 HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data*, May 2002, 90.
- 45 Evidence presented to the House of Lords Select Committee on Science and Technology for the preparation of its report, Select Committee on Science and Technology, 2001, Chapter 4, para 4.5.
- 46 American Society of Human Genetics, Code of Ethics 2006.
- 47 HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data*, May 2002, 90.
- 48 World Health Organization, *Genetic Databases: Assessing the Benefits and the Impact on Human and Patient Rights*. See also, UNESCO, World Medical Association, Council of Europe.
- 49 As per information provided in World Health Organization, *Human Genetic Databases: Towards a Global Ethical Framework*.
- 50 As per information provided in World Health Organization, *Human Genetic Databases: Towards a Global Ethical Framework*.
- 51 World Health Organization, *Genetic Databases: Assessing the Benefits and the Impact on Human and Patient Rights*, 10.
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