Medical genetic services in developing countries

The Ethical, Legal and Social Implications of genetic testing and screening

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1 Executive summary

This report is the second in a series of reports produced by the Human Genetics at WHO to examine the ethical, social and legal implications (ELSI) of genetics and genomics. It focuses specifically on the ELSI of establishing medical genetic services in developing countries, particularly those issues associated with genetic testing and screening. This report draws from the increasing body of empirical evidence regarding the experience of developing countries in introducing and expanding their medical genetic services. In order to provide an up-to-date picture of the ethical issues currently associated with genetic services in developing countries, the report includes five original case studies based on background papers commissioned specifically for the report from geneticists working in developing countries. The goal of this report is to broaden and enrich the discussion of some of the major ELSI specific to medical genetic services in developing countries, and to suggest principles of effective management of the ethical legal and social issues raised by genetic testing and screening in these contexts.

The report begins with a *Primer of medical genetics and genetic services*, which focuses on the implementation of genetic services in developing countries. The primer gives an overview of: the basic principles of genetics and genetic diseases; the distribution of genetic diseases in the population and their impact on morbidity and mortality; genetic tests and their use; health interventions for the prevention and management of genetic diseases (medical genetic services); and the public health applications of genetics. Some of the common misconceptions about genetic services are also explored. The primer concludes with a discussion of the challenges developing countries face in providing equitable and effective genetic services, and the contribution of genomic epidemiology to public health.

The major part of the report addresses the ELSI of introducing genetic testing and screening in developing countries. The primary ethical issues associated with medical genetic services in developing countries are:

Distributive justice

- Access to necessary genetic services is inequitably restricted, usually accessible only to the wealthy sectors of the community.

Non-discrimination

- Stigmatization of, and discrimination against, people with genetic disorders and carriers of recessive genetic conditions result in direct harm to such groups and act as barriers to the effective implementation of genetic services.

Non-maleficence and beneficence

- A lack of appropriate safeguards to ensure quality and safety of genetic testing results in testing occurring outside of genetic serv-

ices, usually without adequate genetic counselling, informed consent, or referral for subsequent care.

Exploration of the issues and challenges facing developing countries is arranged around seven key themes:

- distributive justice;
- the social context in developing countries as it specifically relates to genetic testing and screening, including consanguineous marriage, religion and gender;
- stigmatization and discrimination;
- protection of privacy and confidentiality;
- facilitating patient decision-making;
- education; and
- patient safety and quality assurance in genetic testing.

Within these themes, a range of specific issues is examined, such as: consanguineous marriage; sex selection and bias against female children; directive genetic counselling and traditions of paternalism in medicine; discrimination and stigmatization on the basis of carrier status for recessive genetic conditions; and commercial genetic testing.

The report concludes with general principles for the effective management of the ELSI and a series of recommendations based on these principles.

Briefly stated, the general principles are:

1. Equity and distributive justice in health care involve balancing macro-allocation and micro-allocation issues.
2. Evidence relating to the cost-effectiveness of medical genetic services should play an important role in health resource prioritization.
3. Principles of fair process should be used in rationing scarce health care resources and access to medical genetic services to ensure public endorsement of rationing decisions.
4. Genetic testing should be publicly funded and governed in countries introducing genetic services because this promotes equitable access and facilitates regulation and oversight.
5. Decisions to participate in all genetic testing and screening programmes should be voluntary and informed.
6. A range of viable options should be provided to enable autonomous decision-making regarding the use of medical genetic services, including appropriate and accessible services for the care and management of genetic conditions and access to safe abortion for medical reasons.
7. Genetic testing and screening programmes should be supported by public education and genetic counselling.
8. Regulation and education are key tools in reducing discrimination and stigmatization.

The 16 recommendations focus on:

- **Training and dialogue.** Education and training of health professionals; and dialogue and cooperation between national governments, policy-makers, patients and families, geneticists, religious leaders and other stakeholders, to establish and implement genetic services in a manner that is culturally acceptable and maximizes the health benefit to patients.
- **Genetic counselling.** Ensuring adequate genetic counselling is available to support genetic testing and screening programmes.

Counsellors should be appropriately trained in accordance with available resources, and international organizations should develop guidelines on the minimum skills required for genetic counsellors to assist developing countries in designing interim short-term training courses in genetic counselling to assist with immediate increase in genetic counselling capacity. Patient support organizations should also be encouraged to work alongside medical professionals and genetic counsellors.

- **Legal measures to protect patients' interests.** Implementing legal measures to protect privacy and confidentiality, and to safeguard patients against discrimination and stigmatization on the basis of genetic information. The international community should aid capacity building in relevant public policy and legislation-drafting skills to support this endeavour.

- **Quality assurance and patient safety.** Fostering patient well-being and protecting patient safety through implementation of: appropriate quality assurance standards for genetic tests; regulations requiring genetic counselling and informed consent for genetic testing and screening; and appropriate enforcement mechanisms.

- **Unsafe abortion and sex selection.** Assessing strategies for national governments to address unsafe abortion and sex selection.

We recognize that the laws of nations differ with respect to these particular issues, and that laws are subject to debate, evolution and change. We recognize and respect the diversities of cultural, religious and social structures that shape and inform the public's ethical views in different countries. We also call for mutual respect and continued dialogue regarding these issues.

2
Introduction

This publication considers the primary ethical, legal and social issues associated with the establishment of medical genetic services in developing countries, in particular genetic testing and screening. While many other reports (see, e.g. *177; 21; 223*) have considered the ethical, legal and social implications of genetic testing and screening, few have focused specifically on the genetic ELSI raised in developing countries. WHO has previously published a comprehensive guide to the ethical issues in medical genetics that are relevant to both developed and developing countries (*267*).

For this report we take a different approach: we start by considering the implementation of genetic testing and screening in developing countries; then we identify some of the significant social features that affect the implementation of such services; we explore the ethical, legal and social issues associated with these features and highlight some of the methods employed by different countries to address them. The report therefore does not aim to cover *all* the ethical aspects of genetic testing and screening, but rather to discuss in more detail some of the major ethical, legal, social and human rights issues that are specific to developing countries. Many of these issues have been touched on in other international publications; this report brings these themes together, at a time when there is an increasing body of empirical evidence regarding the experience of medical genetic services in developing countries and the ethical issues raised. The goal of this report is to expand and enrich the discussion of some of the major ELSI specific to medical genetic services in developing countries, and to suggest principles for effective management of the ethical, legal and social issues raised by genetic testing and screening in these contexts.

The report does *not* specifically discuss the ELSI related to the integration of genomics into public health more generally, the role of genetics in common chronic diseases or genomic research. These issues are important and the associated ELSI deserve international attention. However, as this report focuses on the situation in developing countries, many of which are still in the process of establishing traditional medical genetic services, an analysis of these 'new' issues would distract from the core ELSI themes surrounding genetic testing and screening.

Nor does the report aim to provide a systematic analysis of the treatment, management and care options available for people with genetic conditions. The report focuses on the *ELSI* of genetic testing and screening. Issues relating to treatment and care of genetic conditions are raised only where they are relevant to discussion of the ELSI.

It is important at the outset to contextualize the health burden resulting from genetic and congenital disorders, within the wider picture of the often overwhelming health burdens facing developing, particularly low-income, countries. It is estimated that each year 11 million children die, the majority in developing countries, before their fifth birthday, mostly as a result of malnutrition or from diseases that are considered to be easily preventable in developed countries (*215*). In 2001, life expectancies in developed countries were in the range of 75 to 80 years, while in developing

countries they remained between 40 and 50 years (*235*). Many developing countries now suffer from the burden of infectious diseases, such as HIV/AIDS, malaria and tuberculosis, in addition to the burden of chronic diseases, such as cardiovascular diseases, cancer, respiratory diseases and diabetes. While this report discusses the burden of genetic and congenital disorders and makes recommendations about the services and systems required to support genetic testing and screening programmes, it is the responsibility of national governments to assess and prioritize the health needs of their populations. The priority assigned to genetic services, with respect to other health services, is a matter of public health policy in each country, and should be expected to differ accordingly (*267*). Differences in countries' epidemiology, demographic factors and health systems mean that no standard set of interventions can be applied globally (*266*). This report therefore discusses the *principles* of effective management of the ELSI of genetic testing and screening. These principles will have to be translated into specific *policies*, appropriate to the local context, by individual governments.

Nevertheless, genetics is an important, and often under-recognized, contributing factor to disease and ill health worldwide (*265*). Inherited conditions affect millions of families throughout the world. It is estimated that about 5% of all pregnancies result in the birth of a child with a significant congenital disorder, many of which are due in part to genetic factors. In developing countries hereditary conditions account for about 15% to 25% of perinatal and infant mortality (*267*; *190*). At least 7.6 million children are born annually with a severe congenital and/or genetic disorder. In the absence of appropriate facilities and care, most of these children die undiagnosed, early in life (*16*). The overriding ethical issue is the lack of accessible, affordable, safe, medical care and services for these children and their families.

2.1 Summary of ELSI

While some of the issues and challenges raised by genetic testing and screening arise globally, there are other concerns that are specific or more prevalent in developing countries. For example, discrimination and stigmatization can present informal barriers to health care access worldwide. Many international and national reports on genetic testing and screening have focused extensively on the potential for discrimination in relation to health insurance and employment *(180; 177; 121)*. While this is also a concern in developing countries, an additional concern regarding stigmatization relates to the discrimination of female mutation carriers in communities with a high prevalence of autosomal recessive genetic diseases and a cultural preference for arranged marriage. Other issues are equally relevant to developed and developing countries but have a greater impact in developing countries. For example, the concerns around commercial genetic testing are more acute in environments with lower levels of public testing facilities and limited (or no) regulatory structures in place to protect patient safety and provide quality assurance. Such environments are more prevalent in developing, low-income, countries.

The report will focus on seven major ethical, social and legal issues that apply to the introduction of medical genetic services. These are:

- distributive justice;
- the social context in developing countries as it specifically relates to testing and screening, including consanguineous marriage, religion, gender, and views and policies on abortion for medical purposes;
- stigmatization and discrimination;
- protection of privacy and confidentiality;

- facilitating patient decision-making;
- genetics education; and
- quality assurance and patient safety.

2.2 Terminology

For this report, we distinguish between *developed* and *developing* countries. Although this terminology is not ideal, it is still used extensively in the literature and there is at present no widely accepted alternative. For the purposes of clarity we use the World Bank classification of developed and developing countries which is attached in Appendix A. According to the World Bank classification, *developed countries* include all high-income economies except China Hong Kong Special Administrative Region (Hong Kong SAR), Israel, Kuwait, Singapore, and the United Arab Emirates. These five countries are classified as *developing* despite their high per capita income because of their economic structure or the official opinion of their governments (*260*). *Developing* countries therefore include all low-income and middle-income economies, as well as the five high-income economies mentioned above.

Medical genetic services, genetic testing and *genetic screening* are defined in chapter 3, Primer of medical genetics and genetic services.

A glossary of technical terms used throughout the report is provided in chapter 7, Glossary.

3
Primer of medical genetics and genetic services

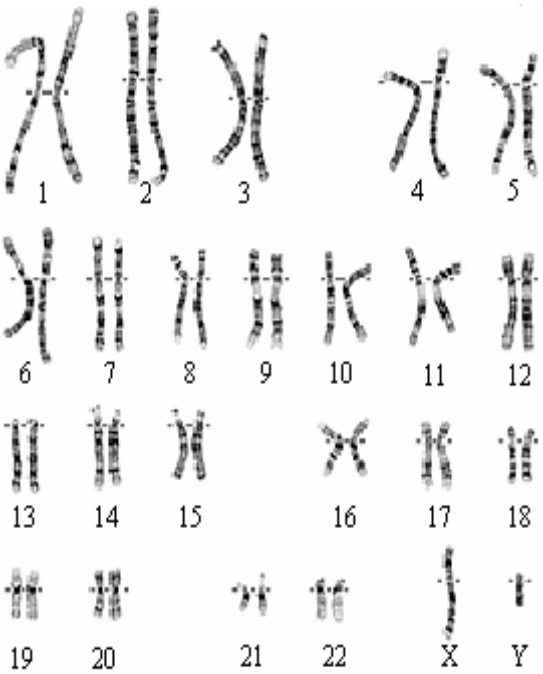
This section will introduce the concepts of genes, genetics and inheritance. It includes a review of current genetic diagnostic technologies, the types of genetic tests, their goals and their possible uses in public health in the context of medical genetic services.

In addition, the main strategies for the prevention and care of genetic diseases and their relevance for developing countries are presented.

3.1 Genes and chromosomes

The human *genome* is constituted by very long chains of *deoxyribonucleic acid (DNA),* packaged in structures called *chromosomes*, which are located in the nucleus of the cells. Humans possess two sets of 23 chromosomes, one set derived from each parent, carrying the same genes (except for the genes located in the sex chromosomes; see Figure 1). A gene is a segment of DNA that instructs the cell to produce a specific *polypeptide* (see Box 1).

Figure 1
Normal human male karyotype



The sex chromosomes are XY because this is a male karyotype; a female karyotype would have XX.

Source: Meyne (*162*).

Box 1
Deoxyribonucleic acid

DNA is the main chemical structure of the gene, and consists of two long strings of *nucleotide bases*. There are four bases: adenine (A), guanine (G), cytosine (C) and thymine (T). DNA's 'instruction code' is determined by the sequence of the four constitutive bases, in such a way that units of three bases form informational units, each with a 'meaning' that instructs the cell machinery to incorporate a specific amino acid during the assembly of a *polypeptide* or *protein*. Proteins, in turn, are chains of amino acids that fulfil essential biological functions, as structural proteins and as enzymes.

Two features of the human genome are of note. In the first place, the approximately 25 000 genes of the human genome constitute only about 2% of the length of the genome: the remaining 98% of the DNA does not code for any protein and its function is still largely unknown. Secondly, there is a very small fraction of coding DNA that is not in the chromosomes, but instead in special organelles in the cytoplasm of the cells, called *mitochondria*. Mitochondrial genes are essential in the production of proteins involved in energy metabolism and are transmitted to the offspring only by the mother.

Each individual inherits a single copy of the whole genome from the father and the mother, thus harbouring two copies of each gene, except for the genes located in the sex chromosomes. In addition, each individual inherits the mitochondrial genes from the mother.

The genome has the inherent characteristic of undergoing mutations, changes in its DNA sequence. Mutations may involve substitutions, deletions or duplications of bases, and have been occurring in the DNA of all species for millions of years. In humans, gene mutations occur

Box 2
Mendelian inheritance

If a man and a woman have identical alleles (gene copies) at the same gene locus, called 'A' for example, they can only produce germ cells (sperm or eggs) of type 'A', and consequently can only have children with an 'AA' genotype. If, on the other hand, 'A' exists in another form (or allele), and the genotype of the father is 'AA' and the mother is 'Aa', then although the father can only produce 'A' germ cells, half the mother's will be 'A', and half will be 'a'. The possible genotypes of their children can be worked out as follows:

		Father's germ cells	
		A	**A**
Mother's germ cells	**A**	AA	AA
	a	Aa	Aa

It follows that half the children (shown in the box) will have the genotype 'AA' and half 'Aa'. On the other hand, if both parents have the genotype 'Aa', then one quarter of the children will have the genotype 'AA', one quarter the genotype 'aa', and one half the genotype 'Aa' as follows:

		Father's germ cells	
		A	**a**
Mother's germ cells	**A**	AA	Aa
	a	Aa	aa

If the 'a' allele causes a disease, its appearance in families will depend on whether it is dominantly inherited (expressed in heterozygotes, 'Aa') or recessively inherited (expressed in homozygotes, 'aa'). If dominantly inherited, on average half the children of an affected parent will be affected (top figure). If recessively inherited, on average a quarter of the children of 'Aa' parents (heterozygotes or carriers) will be affected ('aa') (bottom figure).

Source: WHO, 2002 (*268*:26)

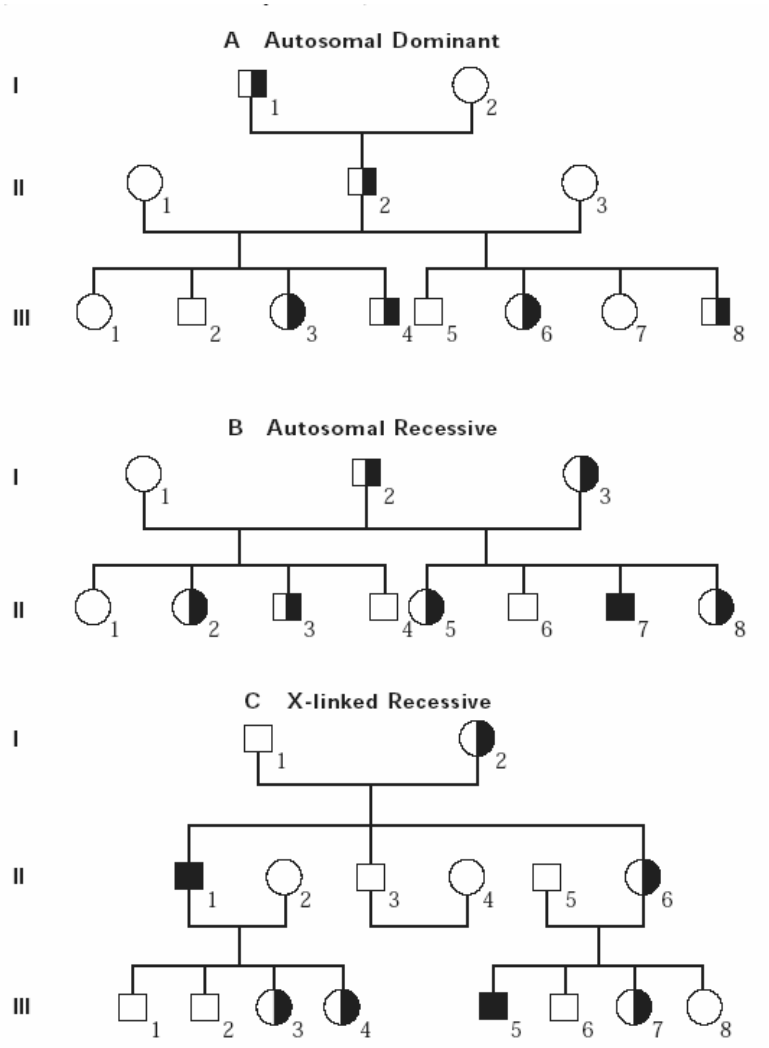
spontaneously or may be triggered by environmental factors such as radiation, infections or exposure to certain chemicals. When new gene mutations occur in the DNA of germ cells, they can be transmitted to offspring, accounting for the accumulation of such mutations in the population after tens or hundreds of generations. Thus, the genes of *all human beings* carry some variations (mutations) in their DNA structure. DNA mutations can (a) be neutral with respect to disease; (b) result in a small change in function affecting disease susceptibility; or (c) result in significant alteration of function. Some mutations in genes determine a change in the DNA instruction code; a subset of gene mutations can result in the production of an abnormal or deficient protein, or even the absence of a produced protein. Depending on the function and importance of the protein in question, disease may result. This chain of events is mediated by numerous other intervening factors (other gene products, environmental factors, etc.) such that it is rare for a gene mutation by itself to determine all the clinical manifestations (or lack thereof) associated with a particular condition.

Genes in families and populations

Genes are transmitted from parents to offspring through the reproductive cells (gametes): the male's sperm and the female's eggs. Each gamete contains a single copy of each gene (*haploid* number). The *diploid* genome (two copies of each gene) is reconstituted in the fertilized egg. The observable expression of a gene (trait, characteristic or clinical manifestations of disease) is called the *phenotype*. There are some autosomal diseases that are manifested when only one copy (*allele*) of the gene harbours a deleterious mutation. These diseases are called *dominant*, because the ill effect of the affected allele 'overpowers' the expression of the normal allele (see **Figure 2** and **Box 2**). In other autosomal diseases, the clinical manifestations occur only when *both* copies of a gene have a deleterious mutation: these are called recessive diseases. In the case of X-linked recessive diseases, where the deleterious allele is located on the X chromosome, males can express the phenotype when they have only *one* copy of the allele. Women who are carriers have the disease allele on one X chromosome, and a normal allele on the other, and so do not usually express the disease (see Figure 2).

Individuals who carry a single dose of an autosomal recessive mutation are healthy because the function of the normal gene is sufficient to avoid disease. These individuals are called *carriers*. It is important to recognize that for every patient with a recessive disease in a population, there exist many healthy carriers of a single dose of the affected *allele*; in other words, recessive genes exist in populations mainly in single doses, causing no disease in the carrier. The maintenance of a recessive gene mutation in a population occurs essentially through transmission from a carrier parent to the offspring. It is only when two prospective parents are *both* carriers of the same mutation that there is a probability of having affected children (those who inherit the mutation from *both* parents). The knowledge of this phenomenon is the basis for *carrier screening programmes* for recessive conditions particularly prevalent in some populations, which provide couples and individuals with information for reproductive purposes.

Figure 2
Pedigrees illustrating different forms of monogenic inheritance*



* The squares represent males and the circles females. The different generations are represented by Roman numerals and the number of persons in each generation by Arabic numerals. In the family showing autosomal dominant inheritance, the open symbols represent normal individuals and the half-shaded symbols affected people. In the two recessive forms of inheritance, the open symbols are normal, half-shaded are carriers (non-affected) and fully shaded are affected. In X-linked (sex-linked) inheritance, since males only have one X chromosome, they cannot transmit the condition to their sons but all their daughters will be carriers. Female carriers, on average, will have half of their sons affected, depending on which of the X chromosomes is passed down to them; similarly, half their daughters will be carriers.

Source: WHO, 2002 (*268*); from Weatherall, 1991 (*251*) with permission.

The evolving concept of genetic disease

The concept of genetic disease has been evolving along with advances in medicine, medical genetics and our ability to analyse the human genome. The molecular study of genes and their relationship to health and disease started with Linus Pauling's characterization of the molecular defect in the gene for one of the haemoglobin chains, which causes sickle cell disease (*188*). In the subsequent 50 years, hundreds of disease-causing gene mutations were identified, a process that was accelerated by the Human Genome Project, which sequenced the whole human genome. Of the approximately 25 000 genes presumed to constitute the human genome, 15 000 have been identified thus far.

A great amount of human genetic variation has been uncovered and the very concept of *genetic disease* is in revision. In fact, we now know that virtually all diseases have a genetic component, at the same time as we know that all diseases have environmental components. Environmental factors, in fact, account for most of the burden of disease and the variations in prevalence of diseases among populations, including diseases with a genetic component. In this report, we use a very broad definition of genetic disease: that of any condition in which there is an identifiable genetic component in causation. While this definition helps to include conditions such as cancer and cardiovascular diseases, the fact remains that the latter are due primarily to environmental factors. In fact, the uncovering of genetic influences in virtually all diseases will perhaps render the term 'genetic disease' obsolete, and we will soon be talking rather of diseases with major or minor genetic components, according to the relative weight of genetic factors in causation. Notwithstanding these considerations, this report will adhere to the current classification of the three major categories of diseases with genetic component: chromosomal abnormalities, monogenic diseases and multifactorial diseases.

Chromosomal abnormalities

The first category of genetic conditions, well known since the 1970s, is caused by *chromosomal abnormalities*, which are usually 'genetic accidents' occurring at the time of conception (such as the *non-disjunction* of *homologous chromosomes* in the formation of the gametes), as a result of which the fertilized egg is conceived with an excess or deficiency of chromosomal material. The most common example is Trisomy 21 (Down syndrome), where chromosome 21 is present in triplicate due to an accidental error in the formation of one of the gametes. Chromosomal disorders also include those occurring as a result of structural rearrangement of chromosomal material and micro-deletions of portions of the chromosome. Chromosome imbalances contribute to about 10–20% of the public health burden of spontaneous abortion, congenital anomalies, mental retardation and developmental disorders worldwide (*263*).

Monogenic diseases

A second category of diseases with a genetic component is that due to *major mutations* or *highly penetrant mutations*. Diseases resulting from a major mutation in a single gene are called *monogenic diseases, single-gene diseases*, or *Mendelian diseases*, because they are inherited in families following the laws of inheritance described by Mendel: autosomal recessive, autosomal dominant, and X-linked inheritance (see Figure 2). There are about 1500 monogenic diseases where the genetic defect has been identified. They tend to cause severe illness and a wide range of clinical manifestations depending on the function of the gene involved. Typical examples are the haemoglobinopathies (thalassaemia, sickle cell disease), cystic fibrosis, phenylketonuria, the haemophilias, muscular dystrophies, Huntington disease and neurofibromatosis. While individually rare, they affect collectively about 1% of the population worldwide (*263*).

Multifactorial diseases

A third category of diseases with a genetic component is the result of complex long-lasting interactions between environmental factors (nutrition, infections, exposure to toxins, living conditions and lifestyle, psychosocial stress, etc.) and gene variations of minor effect. These diseases are called *multifactorial* because many different factors contribute to their causation. Multifactorial diseases constitute the major bulk of the global burden of disease. They include congenital anomalies, coronary artery disease, cancers, mental illness, diabetes, obesity, hypertension and many others. While single-gene conditions refer to one end of a spectrum where the effect of a mutation in a single gene is sufficient to cause disease, in multifactorial diseases an overriding effect of any single gene is not evident and non-genetic factors are increasingly relevant. Here, mutations in any particular gene are neither necessary nor sufficient to independently cause a disease. Rather, the concerted interactions between several genetic variants and environmental factors combine to create a state of health or disease. The genetic component of these diseases is variable and does not usually account for more than 10–20% of the attributable risks *(256; 196; 114)*. This genetic component does not necessarily determine disease, and can be better understood as the impact of many genes of minor effect that increase or reduce the probability that an individual will develop a condition, in interaction with adverse environmental factors *(148)*. Variations in genetic susceptibility can also explain increased or reduced resistance to infectious agents *(78)*.

3.2 Distribution of genetic diseases in the population and impact on morbidity and mortality

The factors that influence the prevalence of genetic diseases in populations and their impact on the public's health are best understood by specific category of disease.

3.2.1 Chromosomal abnormalities

As stated above, chromosomal abnormalities occur mostly as a result of biological errors in the transmission of chromosomes from parents to offspring. The average birth prevalence of chromosomal abnormalities in liveborns is 1 in 200, and the most common example is Down syndrome. The following fundamental features of chromosomal abnormalities are of note:

- The occurrence of non-disjunction, and hence the prevalence of chromosomal abnormalities, is highly correlated with maternal age. Thus, the incidence of these conditions varies according to the maternal age structure of the population. For example the prevalence at birth of Down syndrome is 1 in 1000 among mothers younger than 30 years and about 1 in 100 in mothers over 35 years old. The occurrence of chromosomal abnormalities at each maternal age is similar in all populations.

- The main clinical manifestations of chromosomal abnormalities are congenital anomalies, mental retardation and infertility. Further, they are the main cause of miscarriages, as the overwhelming majority of chromosomally abnormal embryos are aborted spontaneously (an estimated 60% of spontaneous abortions involve a fetus affected by a chromosome abnormality). It is estimated that chromosomal abnormalities are responsible for about 10–20% of congenital anomalies and mental retardation in children *(263)*.

- The development of prenatal screening and prenatal diagnosis is reducing the prevalence of chromosomal abnormalities in countries where these services are available and accessible, as they are in developed countries (*45*).

- Socio-cultural circumstances and limited

access to family planning in developing countries contribute to a higher proportion of births at advanced maternal age, explaining a higher prevalence of chromosomal abnormalities (*264*). This is further compounded by the lack of prenatal screening programmes and accessible prenatal diagnosis services.

3.2.2 Single-gene diseases

As stated above, most of the several hundred known single-gene diseases are individually rare (prevalences at birth of 1 in 2000 to 1 in 100 000). However, they collectively affect about 1% of the population worldwide and tend to have serious clinical manifestations, high morbidity and early mortality, and primarily affect the paediatric population. Since these conditions are due chiefly to inherited gene mutations, their prevalence in a population depends on the frequency of deleterious mutations. In turn, the gene frequency of a particular mutation in a population depends on several factors (*210*):

- when the mutation appeared for the first time and in which population;
- the frequency of the new mutation;
- whether the mutation is expressed in a *dominant* or *recessive* manner (see Figure 2);
- its clinical manifestations and how these affect survival and reproduction of those who carry it;
- the process of natural selection;
- demographic phenomena such as reproductive patterns (for example, consanguinity, etc.), migrations and founder effects; and
- genetic drift due to chance variation.

Varying combinations of the above phenomena explain the variations in the prevalence of a particular single-gene disease in different populations. Well-known examples are: sickle cell disease, more prevalent in Africa and in people of African descent (and the Asian sickle cell disease haplotype more prevalent in populations in the Middle East, the Mediterranean basin the Indian subcontinent); thalassaemias, more prevalent in people of African, Mediterranean and South-East Asian descent; cystic fibrosis, more prevalent in populations of northern European descent; and Tay Sachs disease, more prevalent among people of Ashkenazi Jewish descent. In addition, some single-gene diseases have reached very high frequencies (clusters) in specific populations due to a combination of founder effect, genetic drift and genetic isolation. Examples are Huntington disease in Venezuela (*22*), spinocerebellar atrophy type 2 in Cuba (*103*), and oculocutaneous albinism in South Africa (*136*). Single-gene disorders cause a significant burden to public health either when they are widely prevalent, like the haemoglobinopathies (*252*), or when the phenomenon of founder effect and reproductive patterns determine a high prevalence in a particular population, as in the above noted examples.

Autosomal dominant late-onset diseases

There are a number of *autosomal dominant late-onset diseases* that are particularly frequent in some populations because of demographic factors, such as founder effects and social or geographic isolation. In some cases, in particular population clusters, these diseases have reached levels that have a significant adverse impact on that population's health. One such example is spinocerebellar atrophy type 2 in the province of Holguin, Cuba, where hundreds of affected individuals, and thousands of at-risk individuals, live. A public health programme of pre-symptomatic testing of at-risk individuals, followed by genetic counselling and the offer of prenatal diagnosis, has been put in place by the public health system (*183*). A similar situation exists for Huntington disease in the Maracaibo Lake region of Venezuela, which is home to hundreds of affected individuals and thousands of people at risk (*22*).

3.2.3 Common multifactorial diseases

The common diseases resulting from environment–gene interactions and mentioned above are sometimes called 'diseases of affluence' because they acquired notoriety when developed countries started an epidemiological transition based on the control of infectious disease in the middle of the twentieth century (*132*). Common multifactorial conditions, often referred to as chronic diseases, are responsible for the majority of morbidity and mortality worldwide. They include coronary artery disease, many cancers, hypertension, diabetes, obesity, asthma and mental illness, among others. While it is true that these common chronic diseases, mostly of adulthood, are the most significant health problem in affluent societies, their importance is growing alarmingly in developing countries.

Conclusion

While the existence and prevalence of genetic diseases (excluding common multifactorial conditions) in developing countries is well documented, the recognition of their significance for public health is recent. Socioeconomic and cultural changes and improvements in maternal–child health, nutrition and control of infectious diseases in developing countries are causing an epidemiological transition whereby the contribution of genetic and congenital disorders to the burden of morbidity and mortality is more exposed *(191; 48)*. It must be noted, however, that over the last decade there has been a deterioration of the health situation in many developing countries, resulting from globalization, increased levels of poverty, privatization of services and inequities in health care. Previous improvements in health indicators are also being eroded by the HIV/AIDS pandemic, the resurgence or resilience of old infections such as tuberculosis and malaria, pervasive malnutrition, and the current obesity epidemic. Thus, a more accurate label of these phenomena is epidemiological *accumulation* rather than *transition*, as new morbidities are superimposed on old ones. Nevertheless, there can be no doubt that multifactorial conditions, including congenital anomalies and common diseases, contribute significantly to morbidity and mortality in developing countries *(48)*.

3.3 Genetic tests and their use

In the past couple of decades, a number of interventions aimed at the early detection, prevention and care of health problems caused by genetic factors, have been developed and implemented in developed countries. These developments have been facilitated by new or improved diagnostic technologies such as fetal ultrasound, improved cytogenetic techniques and biochemical analysis, direct analysis of genes causing monogenic disorders (DNA testing) and prenatal diagnosis. In fact, there seems to be considerable hype about genetics in developed countries, where the capacity of genetic approaches to prevent and treat common diseases is perhaps exaggerated (*105*). In contrast, developing countries have been lagging in their implementation of public policies for the care and prevention of genetic diseases *(191; 48)*.

It should be noted that both in developed and developing countries, even diseases with genetic components have overwhelmingly higher social, environmental and lifestyle attributable risks (*256*), and therefore their prevention will continue to require the control of those identified risks (exposure to toxins like tobacco, sedentarism, poor diet, psychosocial stress and others). Furthermore, the tendency to see genetic testing as *the* solution to the health problems posed by genetic diseases, out of the context of the health care system and genetic services, is not only ineffective but also fraught with a number of ethical risks. In this section, we will first review current genetic diagnostic technologies, the types of genetic tests, their goals and their possible uses in public health in the context of medical genetic services. In the next section we will analyse the main existing strategies for the prevention and care of genetic diseases and their relevance for developing countries.

The development of genetic technologies has been most fruitful in devising tests to detect genetic abnormalities at the level of the chromosomes and the genes. The application of these diagnostic technologies is most advanced in developed countries, where the diagnosis of genetic diseases is shifting from analysis of the clinical manifestations to analysis of chromosome or molecular defects. Further, genetic tests are being applied not only to individuals with symptoms or signs of disease (classically referred to as 'patients') but also to asymptomatic and healthy individuals (whom the term 'patients' does not fit well) to determine genetic predispositions and predict the future onset of disease.

The proliferation of new genetic diagnostic tools has been accompanied by confusion about terminology, and there are varying definitions of what constitutes a 'genetic test' (*21*). Indeed, the definition of genetic test suffers from the same ambiguities as the definition of what constitutes a genetic disease, as alluded to above. The confusion stems from the fact that genetic diseases can be diagnosed by many other approaches than DNA testing: family history, physical examination, imaging techniques such as radiographs and ultrasound as well as biochemical and morphological laboratory tests that do not look at the genetic material itself. For the purpose of this report, a genetic test is defined as a laboratory test that analyses a particular configuration of the genetic material, be it (a) by direct analysis at the level of a gene or a chromosome, or (b) by testing a direct gene product—ribonucleic acid (RNA), a structural protein or an enzyme or key metabolite. Many of the other tests that reveal genetic information, but which fall outside this definition of genetic test, are also considered in the report because they form an important part of medical genetic services, particularly in developing countries. Further, the ethical issues surrounding the use of genetic information are similar, irrespective of whether the information is generated through genetic tests or other investigations. Many national and international guidelines and regulations, discussed throughout the report, include their own definitions of genetic test, some of which differ from this specific definition.

3.3.1 Goals of genetic tests: testing and screening

The main purposes of genetic tests are:

- diagnostic genetic testing: to diagnose a genetic disease (chromosomal or monogenic) in a symptomatic patient;
- presymptomatic genetic diagnosis: to make a prediction of future development of a monogenic disease in an asymptomatic individual;
- predisposition genetic testing: to make a probabilistic estimation of the likelihood of future development of a multifactorial disease in a healthy individual;
- genetic carrier testing: to determine whether a healthy individual is a carrier of a recessive mutation that may increase his/her risk of having affected offspring; and
- prenatal genetic testing: to identify fetuses at increased risk of congenital abnormality.

Genetic tests can be applied to individuals in the context of health care, or to populations in the context of public health programmes. The term *genetic testing* usually refers to the use of genetic testing in individuals and families in the context of clinical care with the goals noted above. Genetic testing is defined as testing offered to people already known to be at increased genetic risk in order to achieve a definitive diagnosis (*266*). For the purposes of the report, we use Wald's definition of screening: the systematic application of a test or enquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action among people who have not sought medical attention

because of the symptoms of that disorder (*246*). Within this context, *genetic screening* refers to a basic test that is systematically offered to a defined population, in order to identify a group at increased genetic risk, who may then be offered further tests leading to a definitive diagnosis.

3.3.2 Characteristics of genetic tests

Three main attributes are used to assess the health benefit of a genetic test: its *analytical validity*, its *clinical validity*, and its *clinical utility* (*195*).

Analytical validity refers to the performance of a genetic test in the laboratory, that is, the test's ability to detect the trait it seeks to measure (DNA, chromosomes, proteins or metabolites). The main items to consider in the analytical validity of a test are its sensitivity (ability to detect an abnormality if it is present), its specificity (results should be negative if there is no abnormality), and its reliability (the probability of obtaining the same result consistently). The determination of the analytical validity of a genetic test is the responsibility of quality control state agencies.

The clinical validity of a test refers to the accuracy with which it predicts the presence or absence of a clinical condition or predisposition. The components of clinical validity include: the probability that the test will be positive in patients with the disease in question (clinical sensitivity); the probability that the test will be negative in patients without the disease (clinical specificity); the probability that patients with a positive result will develop the disease (positive predictive value); and the probability that patients with negative results will not manifest the disease (negative predictive value).

The clinical utility of a test refers to the actual usefulness of the test in improving the health and well-being of the persons tested, and it depends largely on whether the information provided by the test can be followed by effective and safe preventive or therapeutic interventions.

Given the increasing commercialization of genetic tests, it is not uncommon that they are marketed to the public without proper validation (based on analytical validity, clinical validity and clinical utility) in both developed and developing countries. The use of genetic tests that are not accurate, safe and effective is not only a waste of scarce health resources but also an unethical practice that puts the health and well-being of the public in jeopardy (*268*) (see 4.8.1). It is an essential function and responsibility of the public health agencies in each country to ensure the characterization and validation of genetic tests by determining their analytical validity, clinical validity and clinical utility before they are utilized in health care.

3.3.3 Types of genetic tests and their possible applications

In this section, the different types of genetic tests are discussed in conjunction with their applications. The availability and accessibility of all the different types of genetic tests are fraught with the usual inequities common to all health care services: access is better for individuals in urban centres, developed countries and the middle–upper classes, and worse in rural areas, developing countries and lower socioeconomic classes.

Chromosome tests

Techniques for the genetic testing of chromosomal abnormalities have been in place for the past 40 years and are being applied worldwide. Chromosome analysis is sometimes performed to confirm the diagnosis of a chromosome abnormality in patients suspected of having such conditions. Newer techniques combine the classic analysis of the number and structure of chromosomes (standard chromosome analysis), with high resolution and molecular cytogenetic analysis for the detection of sub-microscopic structural defects that may explain a patient's condition. These techniques are also widely used in oncology to detect genetic abnormalities in

tumour cells to define prognosis and guide treatment in a variety of cancers. The widest application of chromosome analysis is in the prenatal diagnosis of fetal chromosomal abnormalities in chorionic villi and amniotic fluid cells. Several hundred thousand pregnancies are subjected to prenatal chromosome diagnosis annually, primarily in developed countries.

DNA tests in the diagnosis of symptomatic individuals

There are currently over 1000 disease-associated genes that can be tested to aid the diagnosis of disease in patients suspected to have a monogenic disease or those at risk (*83*). This is indeed the major application of genetic testing in medicine thus far. The interpretation of results is not always straightforward, as there are often many nuances and subtleties. The clinical validity and clinical utility of each test vary according to the disease in question, the gene tested and the techniques employed.

DNA tests in prenatal diagnosis

The same principles and techniques used in DNA testing for diagnostic purposes in symptomatic patients can be used for the genetic testing of a fetus at high risk for a specific single-gene disease. Fetal cells are usually obtained from chorionic villi at 10 weeks of gestation or amniotic fluid at 14–16 weeks of gestation. Both procedures are associated with a risk of procedure-induced abortion of 0.5–1%, depending on the skills and experience of the operator.

Since the early 1990s, a procedure called *pre-implantation genetic diagnosis* (PGD) has been available to couples at risk of having a pregnancy affected by a genetic condition or chromosomal abnormality, as an alternative to prenatal diagnosis and termination of pregnancy. PGD involves a test performed on a single cell biopsied from the embryo at the 8–16 cell stage after in vitro fertilization and before embryo implantation in the uterus. Over 1000 procedures have now been performed in developed countries. PGD is a very expensive and high-tech procedure, whose long-term safety and efficacy is still under investigation (*241*).

DNA tests for predictive purposes

Genetic testing is also used to predict the probability that an individual might develop a gene-associated disease in the future. In cases of monogenic diseases that have not yet presented symptoms, predictive testing is usually referred to as presymptomatic genetic testing. This type of genetic testing is mostly used to predict the development of autosomal dominant late-onset genetic diseases (for example, Huntington disease, spinocerebellar atrophy, familial adenomatous polyposis) and is offered to high-risk individuals in families in which the disease is present. Presymptomatic genetic testing is most notably offered to the offspring of an affected individual, who face a 50% probability of having inherited the affected allele, in which case they would in all certainty develop the disease in the future. The ideal goal of presymptomatic genetic testing is to implement preventive or therapeutic measures to stem the development of the disease or reduce its severity. Unfortunately, there are at present no such safe or effective health interventions for most known late-onset genetic diseases, making the clinical utility of their presymptomatic diagnosis rather low.

For other monogenic conditions, like haemochromatosis and Factor V Leiden, genetic testing in the absence of symptoms or positive family history has low predictive value because of low penetrance and the presence of, as yet, poorly understood concurrent factors (both genetic and environmental).

Genetic testing for multifactorial diseases aims to detect genetic variants associated with an increased probability of developing one of those conditions. This is called *predisposition genetic testing*, where a positive result would theoretically mean a higher than average susceptibility to develop the disease when environmental risk factors (usually more important in causation) are also at play. Much research is targeted at detecting susceptibility alleles for common diseases in the hope that this

knowledge may illuminate the mechanisms of disease, the causative role of genetic and environmental factors, and the development of newer methods of prevention and treatment (*53*). However, for the vast majority of multifactorial diseases, the genetic underpinnings of disease remain unknown and most predisposing mutations uncovered so far have very low penetrance and hence very low clinical validity. The only example of predisposition testing in a multifactorial condition demonstrating preliminary clinical validity is testing for mutations in the *BRCA1* and *BRCA2* genes in the assessment of breast and ovarian cancer risk in women with positive family history. The high clinical validity of this testing depends on the careful selection of patients (those at high risk because of family history) and on the fact that the mentioned genes are known to have high penetrance (quasi-dominant). Even when patient selection is adequate, the risk of future disease predicted by the test remains around 60% *(131).* Other examples of predisposition tests of potential clinical validity include tests for colon cancer, thyroid cancer, cardiomyopathies and Alzheimer disease.

The term 'genomic hype' has been used to describe the belief that detecting individuals with higher than average genetic susceptibility to multifactorial diseases is the right approach to conquering diseases like coronary artery disease, diabetes, obesity and many cancers. For most of these diseases, environmental and lifestyle factors have attributable risks higher than 80% (*256*), and the whole population is therefore at risk. Furthermore, public health interventions aimed at the general population are thought to be safer and more effective (for example, programmes to promote tobacco cessation and avoidance of exposure to possible carcinogens, physical exercise, diet, among others) (*80*).

DNA tests for carrier status for reproductive purposes

Genetic testing can be used to detect healthy carriers of recessive genes, with the aim of detecting couples in which both spouses carry the same recessive gene and, thus, are at risk of having affected offspring; or women who are carriers of an X-linked recessive disorder. It is important to note, however, that in practice many tests used to identify carriers are not DNA-based 'genetic' tests. Carrier genetic testing can be indicated in individuals with a positive family history of the disease in question. Individuals tested can use their genetic information to make informed reproductive decisions.

Carrier genetic testing can also be aimed at the population at large, or at specific subpopulation groups, defined by age, gender or ethnicity. When carrier genetic testing is aimed at populations it is usually referred to as *carrier genetic screening*. Screening for carriers of recessive mutations should be a function of the public health system and should meet a number of requirements before being undertaken:

- the condition in question should have high prevalence;
- the condition in question should impose a significant health burden on the population;
- the gene in question should be easily and inexpensively tested;
- the analytical validity and clinical validity of the test should justify the screening;
- genetic counselling and prenatal diagnosis should be available; and
- termination of affected pregnancies, for women who voluntarily choose to use this service, should be a feasible option.

In addition, steps should be taken to educate communities and their leaders, and the population should have a clear interest in the programme. Programmes should be strictly voluntary and there should be no pressure of any kind on anyone to be tested or to take any specific steps after results are delivered (such as marrying, embarking on a pregnancy, having prenatal diagnosis, continuing or terminating an affected pregnancy). Carrier

screening programmes and the associated services should be implemented in a manner that is responsive to, and sensitive of, the population's religious and cultural views. Examples demonstrating where and how this has been achieved are presented throughout the report. A number of successful carrier genetic screening programmes supported by education, counselling and access to prenatal diagnosis are in place in both developed and developing countries, particularly for the haemoglobinopathies (*170*) and diseases common among Ashkenazi Jews (*122*).

Newborn screening

Newborn screening is the 'dean' of genetic screening programmes applied on very large and systematic scale for the past 40 years, both in developed countries and in some developing countries. It began in developed nations in the 1960s with screening for phenylketonuria (PKU), which was followed soon after by screening for congenital hypothyroidism (CH). The rationale for newborn screening accords with the paradigm of public health: early detection and (preventive) treatment before symptoms begin. Again, many tests used in newborn screening are not DNA-based tests.

There are a number of prerequisites for the development and implementation of newborn screening. First, the condition to be screened for must be:

- severe;
- frequent; and
- amenable to easy, safe, reliable and inexpensive laboratory diagnosis on a very large scale.

Second, a treatment that is cost-effective and makes a significant difference when it is started soon after birth rather than after symptoms are established should be available.

Third, there should be an effective treatment and follow-up programme for the affected infants identified, and every step of the programme should be the responsibility of the State and should ideally be offered free of charge. Finally, the country should have a functional and well-structured public health system and good centralized laboratories to provide infrastructure for the screening programme. Most importantly, newborn screening should have public support and be supported by adequate and sustainable public funding.

Over the last 20 years, new conditions have become candidates for newborn screening, and their addition to the testing panel has followed political, economic, medical and societal pressures. All developed countries have instituted newborn screening programmes for PKU, congenital hypothyroidism and a variable number of other conditions (*113*). Developing countries have been slow to implement newborn screening and most have not yet started, as the above mentioned prerequisites are rarely fulfilled. In Cuba and some large urban centres in Argentina and Brazil, newborn screening is available for PKU and CH (see Case study 1).

Only Cuba, however, can claim more than 50% coverage of their newborn population (in Cuba coverage is in fact over 95%).

Developed countries are increasingly resorting to DNA testing for some newborn screening tests, and some are implementing tandem mass spectrometry to increase the number of conditions tested (*93*). The main challenge is to ensure accessibility to diagnostic confirmation studies, treatment and follow-up services. Developing countries should: (a) weigh carefully their priorities in health care in general and in genetics in particular; (b) consider the required infrastructure and services; and (c) analyse issues of cost-effectiveness, before embarking on newborn screening programmes.

3.4 Medical genetic services

Medical genetic services are those that provide health interventions for the prevention and management of genetic diseases. The goal of health interventions in genetics is the care and prevention of diseases with a significant genetic contribution in their causation. Health interventions in genetics are organized as (a) medical genetic services as part of general health care services, which address primarily the care and management of individuals and families with, or at risk for, genetic diseases and congenital defects, and (b) as public health genetic programmes aimed at populations, with the main purpose of prevention.

The essential components of genetic services and public health genetic programmes suitable for developing countries have been described in several publications *(191; 48)*. Common themes in all recommendations are as follows.

- Genetic services and public health genetic programmes should combine prevention with the best possible care for affected individuals and their families.
- Genetic services and public health genetic programmes should prioritize simple, low technology and cost-effective activities, according to the prevalence and severity of existing genetic diseases and the expectations and cultural traditions of the community (in a way that does not perpetuate or reinforce existing discriminatory practices). Programmes should be focused on genetic risk detection and subsequent referral.
- Genetic services should be rooted in primary health care, and linked with regional secondary and tertiary levels of care in a rational manner.
- Primary health care personnel should be properly trained to perform defined tasks, such as finding out and interpreting a family history, detecting reproductive genetic risks, and detecting signs and symptoms that require referral to the next level of care.
- Genetic testing and screening should be voluntary, offered only in the context of comprehensive genetics service delivery and accompanied by proper genetic counselling appropriate to the test and clinical context.
- Proper attention must be paid to the ethical, legal and social issues associated with genetic testing and screening.

From the outset it is important to dispel some common misconceptions regarding the role of genetics in health care and the relevance of these issues in developing countries. See **Box 3**: Dispelling misconceptions.

Box 3
Dispelling misconceptions

Misconception #1: Genetic variations are the main cause of ill health at the global level

While it is true that virtually all diseases have a genetic component, it is equally true that all diseases have environmental components and that *disease is the result of environment–gene interactions*. In fact, and except for chromosomal abnormalities and monogenic diseases—which collectively affect less than 2% of the population anywhere in the world (*266*) — the bulk of morbidity and mortality largely results from environmental factors *(256; 16),* even for diseases where genetic predispositions are significant. Although the genetic constitution of individuals is important, the main reasons that the common multifactorial diseases have a larger proportional share of morbidity and mortality (as opposed to infectious diseases and malnutrition) in developed countries than in developing countries is precisely because of differences in environmental circumstances (nutrition, toxic exposures, immunizations, lifestyles, sedentarism, access to health care, etc.). The burden of disease in developing countries is still loaded with infectious disease and malnutrition, and aggravated by poverty and lack of access to health care, primarily prenatal and delivery services and infant care (*173*).

Misconception #2: Genetics is not relevant in developing countries

As already stated above, and emphasized in numerous publications (see, e.g. *191; 48)*, genetic and congenital diseases in developing countries do exist and contribute to excessive morbidity and mortality. The fact that other scourges (like poverty, HIV/AIDS, tuberculosis, malaria, malnutrition and conditions secondary to poor prenatal care and delivery conditions) have made genetic diseases somewhat invisible thus far does not mean that the health system should neglect them. Most importantly, a number of them can be prevented or managed. Further, care and management should be available to all patients with genetic and congenital diseases. Genetic and congenital diseases contribute to economic, social and developmental stagnation because of the severity of their manifestations, the stigmatization they engender, and the high costs of their treatment and care.

Misconception #3: There is a dichotomy between care and prevention of genetic and congenital diseases

From the public health point of view, care and management of these complex chronic conditions are expensive and require many human and technical resources. In this field, however, prevention of the occurrence of disease and care of the affected, go hand in hand. Indeed, cost-effective prevention approaches reduce the number of affected individuals and free resources for the care of individuals with the disease. In turn, care of patients with the condition is not only an ethical obligation based on the right to health, but also increases the trust of the population in the goals of the public health system. The experience of successful programmes in Cuba, Cyprus, the Islamic Republic of Iran, Thailand and many more countries, supports this contention *(191; 48).*

Misconception #4: Genetic testing and screening have a value in themselves, out of the context of genetic services

The aggressive marketing of genetic tests without proper validation and outside the context of clinical genetic services is common both in developed and developing countries. This practice, however, is at odds with the WHO recommendations that genetic testing and screening should not be implemented where there are no genetic services and that genetic services should be part of health services accessible to the entire population (*268*).

3.4.1 Genetic counselling

Genetic counselling is an indivisible part of the delivery of genetic services. Genetic counselling has been defined as

> the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and the ways this may be prevented, avoided or ameliorated (*100*)

and as

> an educational process that seeks to assist affected and/or at risk individuals to understand the nature of the genetic disorder, its transmission and the options open to them in management and family planning (*125*).

Central to the process of genetic counselling is its educational, voluntary and non-directive nature. The main goal of genetic counselling is to empower individuals and couples to make their own informed decisions when facing genetic risks, according to their own values (see section 4.6.2). Patients and individuals at genetic risk need unbiased and objective information on which to base difficult decisions regarding health and reproduction issues. Autonomous decisions should enjoy the support of health providers.

In the same way that medical practice and health care in general vary in different countries and cultures, a number of features of genetic counselling may vary. For example, in some countries genetic counselling is considered part of medical practice and provided by specially trained medical personnel (*193*); in other countries non-physicians are trained in genetic counselling to provide the service. At present there is a shortage of health personnel adequately trained in genetic counselling in all countries, but particularly in developing countries. Given the contextual differences in health care, social, cultural, religious and legal factors, the modalities for delivering genetic counselling, including the personnel who provide the service, should be left to each country to determine. Defining the minimum training required for health personnel to provide genetic counselling is the basic priority. Training primary health professionals (general physicians, nurses, social workers, etc.) in genetic counselling in developing countries would help to address these shortages.

3.4.2 Clinical genetic services

Historically, clinical genetic services were developed in major hospitals in large urban centres, in both developed and developing countries, to provide diagnosis and counselling to patients with, or at risk for, genetic diseases and congenital anomalies. In developing countries, the major bottlenecks to increasing access to genetic services have been fundamentally the shortage of trained specialists, the lack of appropriate technology, the scarcity of funding and the lack of links with the primary health care level. The responsibilities of clinical genetics centres have been expanding from dealing with rare diseases to dealing with the genetic components of common diseases, particularly genetic susceptibility to cancer. In addition, medical genetic services have traditionally dealt with, and will probably continue to deal with, prevention and management of congenital anomalies, irrespective of their cause (most congenital anomalies are environmental or multifactorial in nature).

The challenge for developing countries is to define the type of genetic services needed according to the prevalence of genetic diseases. The development and implementation of services with a base in primary health care that follow sustainable cost-efficiency models are crucial *(191; 8; 203)*.

3.4.3 Prenatal genetic services

Prenatal genetic services are essential components of all public health programmes. These services are aimed at detecting genetic reproductive risks, through programmes such as carrier screening for prevalent recessive conditions and prenatal screening for neural tube defects and chromosomal abnormalities. Experience shows that these programmes can only be successful when couples identified as at risk have access to diagnostic tests, free access to genetic counselling and the option to terminate affected pregnancies (*170*). These services should be adequately regionalized in tertiary care centres to ensure cost-efficiency and quality of service. An important limitation to the development of these services in developing countries is the prevalence of legal prohibitions that preclude selective abortion in cases of fetal abnormalities. However, this is slowly changing and abortion for fetal abnormality is now legal in a number of developing countries, such as China, Cuba, Cyprus, India, South Africa and important localities in Mexico, among others (see 4.3.3).

3.4.4 Genetic testing and screening

As mentioned above, genetic testing and screening are an essential component of genetic services and of public health genetic programmes. Genetic testing and screening should be backed by proper genetic counselling, and should not be offered out of the broader context of health care service delivery. Genetic testing and screening programmes should be implemented in a manner that is sensitive to the population's cultural practices and religious views and in accordance with national legislation.

3.5 Public health applications of genetics

The main goal of public health applications of genetics is the reduction of the impact of genetic disorders on health and well-being, through primary prevention, prevention through reproductive options, and secondary prevention. The following general strategies for primary prevention in genetics were identified at the meeting of WHO experts (WHO/HGN/WAOPBD) in 1999 *(264)*.

3.5.1 Primary prevention

Primary prevention aims to reduce the occurrence of specific genetic diseases and congenital anomalies. General strategies for primary prevention include:

- public efforts to improve health, nutrition, education and reproductive autonomy, particularly of women;
- avoidance of unintended pregnancies and proper birth spacing through access to contraception and other methods of family planning;
- improved access to, and quality of, prenatal care;
- improved quality of newborn care;
- control of possible occupational mutagenic risks;
- voluntary premarital genetic screening and counselling (screening should be strictly voluntary, implemented through non-directive genetic counselling, and not coerced through direct or indirect social pressures);
- pre-conceptional and peri-conceptional supplementation of vitamins, including folic acid, for women in the reproductive age group to reduce the risk of neural tube defects and possibly other birth defects;
- encouraging women to procreate at the optimum reproductive ages (20–35 years) to reduce the risk of non-disjunction chromosomal abnormalities; and

- avoidance of exposures to mutagens and teratogens (such as, radiation, rubella, alcohol, tobacco and self-medications) during pregnancy.

Primary prevention strategies are usually centrally planned and population-based, and are implemented at the level of primary care by health personnel trained in genetics and community education. Perhaps the best known application of genetic knowledge in primary prevention of congenital conditions with a genetic component is the supplementation of folic acid to women of reproductive age and the fortification of staple foods with adequate levels of folic acid in many countries. This approach is based on the knowledge that neural tube defects are due in part to a deficiency of folic acid. A significant reduction in the prevalence of neural tube defects at birth has consistently followed these interventions *(26; 111; 257)*. Prevention of exposure to mutagens, teratogens and other environmental toxins should have a larger role in public health than currently accomplished.

3.5.2 Prevention based on reproductive options

Most public health applications of genetics have so far been directed at the prevention and control of *chromosomal abnormalities* and of specific *recessive conditions* particularly prevalent in defined populations.

Chromosomal abnormalities

Chromosomal abnormalities affect approximately 1 in 200 live newborns and are a common cause of congenital malformations and mental retardation (*263*). They are largely non-hereditary, that is, they occur sporadically, without significant ethnic, socioeconomic or geographic variations, worldwide. Maternal age is positively correlated with the prevalence at birth of the most common type of chromosomal abnormalities: the autosomal trisomies like Down syndrome and the sex chromosome aneuploidies. The effect of maternal age is so strong that for over 30 years it has been the basis for selecting pregnancies at increased risk for chromosomal abnormalities (usually those above 35 years of age) as targets of preventive public health programmes.

In addition, a number of biochemical markers in maternal blood and fetal ultrasound markers are now also used to identify pregnancies at increased risk of chromosomal abnormalities (usually over 0.5%) *(67; 248; 158)*. The preventive model followed by health care systems in developed countries is to institute such prenatal screening as part of routine prenatal care, followed by the offer of voluntary prenatal cytogenetic diagnosis on fetal cells obtained by chorionic villus sampling (CVS) at 10 weeks or amniocentesis at 14–16 weeks of gestation. These programmes should be implemented according to the principles of voluntariness, non-directive genetic counselling and informed consent. Whether or not these principles are actually adhered to in practice, is discussed later in the report (see section 4.6.3). These programmes have been very effective in significantly reducing the prevalence at birth of chromosomal abnormalities in developed countries (*48*). In developing countries these services are often not implemented in a way that maximizes public access or cost-effectiveness; they are often available and accessible only to the wealthier 20% of the population *(48; 192)*.

Recessive conditions

The public health model followed worldwide for the prevention of *recessive genetic conditions* prevalent in particular populations follows the sequence: (a) detection of carriers of the particular gene through genetic screening; (b) ascertainment of carrier–carrier couples and subsequent genetic counselling; (c) offer of prenatal diagnosis in pregnancy, and (d) offer of termination of affected pregnancies.

This model requires that: (a) the condition is particularly prevalent in the defined population; (b) the condition causes a significant health and economic burden to society; (c) DNA testing and

prenatal diagnosis for the condition is available, cost-effective and equitably accessible through the health system to everyone at risk; (d) there is a preventive public health policy based on voluntary decisions by the public with proper respect for reproductive rights; (e) there are adequate plans for treatment of individuals with the condition without stigmatization or discrimination; and (f) there are appropriate human resources for non-directive genetic counselling to all individuals and couples identified as being at high genetic risk (*170*).

These requirements have been met in a number of countries or population groups for several recessive conditions (this list is not complete):

- thalassaemia in Cyprus (*19*), Greece, Italy and immigrant groups in the United Kingdom, and more recently in Thailand and the Islamic Republic of Iran;
- sickle cell disease in Cuba (*103*);
- sickle cell disease and thalassaemia in the United States; and
- Tay Sachs disease and other recessive diseases common in Ashkenazi Jews (*122*).

3.5.3 Secondary prevention

Secondary prevention aims to minimize the clinical manifestations of a genetic condition after the birth of an affected infant; or to detect a genetic predisposition for a condition that presents later in life.

The most important application of genetics in secondary prevention and early detection of genetic diseases is exemplified in *newborn screening*, whereby all newborns in a population are subjected to systematic testing for a list of specified conditions (as discussed in 3.3.3). The inclusion of a particular condition for screening in newborns depends on a number of factors, including the impact of that condition on the public's health, the feasibility of accurate and cost-effective screening and diagnostic methods, and the effectiveness of treatment, with a much better outcome if started immediately after birth. It is expected, then, that the conditions screened vary from country to country, and even within countries, as is the case in the United States, in which each state determines the conditions it screens for. Typical conditions screened at birth are phenylketonuria, congenital hypothyroidism, haemoglobinopathies, cystic fibrosis and congenital deafness *(113, 178. 187)*.

Newborn screening should be implemented as a *public health* programme, run by the *public health system*, which covers all steps in the sequence: screening (of all newborns); diagnostic confirmation (of those newborns who screened positive); referral for proper care (usually lifelong); and genetic counselling for the parents. Genetics and genomics have so far played little role in newborn screening as the technologies for screening are biochemical or immunological. However, diagnostic confirmation of those screened positive relies increasingly upon DNA techniques, and it is expected that genomics will play an ever increasing role in all steps of newborn screening (*93*).

Whether or not a country needs to institute a newborn screening programme is a matter of high complexity that should be decided by a vigorous analysis of the epidemiology of specific conditions technically amenable to screening. Consideration must also be given to economic and social factors in addition to alternative options for the use of scarce health funds.

3.6 Challenges

The specific barriers to increasing the equitable provision of genetic services in developing countries vary according to local community, region and country. There are, however, common themes that affect most developing countries. These include poverty; scarcity of trained health professionals; low priority given to genetic services by policy-makers; and cultural and religious factors

including ethnicity, language, gender norms and practices, and geographic isolation *(48:227)*. Tensions may exist between providing treatment and focusing on the prevention of disease, which is exacerbated by the fact that the impact of preventive programmes can be difficult to measure in the absence of sound epidemiological data. Barriers also include lack of education (low literacy rates and little or no knowledge about genetics) and misconceptions at the public, medical and health policy planning levels. The list below, compiled from results of a WHO consultation on genetic services in Latin America (*117*), highlights the main barriers to effective and equitable genetic testing and screening programmes, and is applicable to most other developing countries. These are:

- competing health priorities, as the burden of other unmet health needs resulting from infectious disease, malnutrition, prenatal care, labour and delivery care and neonatal care remain;
- opinion among the medical profession and public health officials that genetics is not a health priority;
- misconceptions that genetic services are expensive and relevant only to rare diseases;
- lack of understanding of the full range of options available for prevention of genetic disease, with prevention often misperceived as being limited to the abortion of affected fetuses; and
- insufficient public education about genetic risks and the range of preventive options.

It is important to note that the first of these barriers is a legitimate concern. Developing countries face a range of unmet health needs and this report does not advocate prioritizing genetic diseases above all other demands on health resources. A just and fair health system will: (a) consider the burden of genetic disease in proportion to the total burden of ill health; (b) consider the potential strategies to address it; and (c) distribute resources accordingly. It follows that sound epidemiological data are required to assess these needs. The resources devoted to medical genetic services compared to other health services will vary from country to country depending on the needs and resources of their populations.

The final four barriers listed above demonstrate where the problem lies. Health planners are not able to weigh fairly the demands of genetic disease control against other health needs because the prevalence and burden of genetic diseases is under-recognized, and prevention is misconceived as expensive and dependent on sophisticated technologies. Again the importance of sound epidemiological data should be emphasized: in the absence of adequate data it is hard to convince policy-makers of the need for, and impact of, genetic services.

This report attempts to dispel these misconceptions, as have other publications (*48*; *1; 16*). The case studies and other examples discussed throughout the text, demonstrate the innovative, varied, culturally sensitive, cost-effective ways that genetic screening and testing have been used in developing countries to improve public health.

Cost-effectiveness

Cost-effectiveness analysis (CEA) is an analytical method of illuminating the trade-offs inherent in decisions regarding scarce health care resources and competing health demands. The point of CEA is to display which, among a range of alternatives, either: (a) maximizes the desirable consequences, given a fixed set of resources, or (b) minimizes the cost in order to achieve a desired outcome. In the context of health policy, CEA is usually employed to compare alternative courses of action that result in similar health benefits, in order to compare which is the most cost-effective (*24*). The results of a CEA feed into the macro-allocation issues of priority setting in health care.

3.7 Genetics/genomics research and public health

Common chronic diseases of adult life are responsible for a high proportion of the public health burden worldwide. It can confidently be stated that most common chronic diseases have a genetic component, conferred by variant versions of many genes, each one with small causal effect. Their occurrence is the result of complex environment–gene interaction. This concept includes infectious diseases, where variations in the human genome may explain differences in clinical responses to the infectious agent (*78*).

The main role of genetics/genomics thus far is in the development of much better genetically-based diagnostic tools for many diseases with a discernible genetic component (*126*). Similarly, genetics/genomics is playing an increasing role in the diagnosis of infections, as tools are developed to identify infectious agents by their DNA footprints. Furthermore, there is the potential of pinpointing the genetic predispositions for common diseases like coronary arteriosclerosis, some types of cancer, some types of dementia, diabetes and hypertension, among others. This assertion, however, does not deny that environmental factors (exposure to mutagens and other toxics and teratogens, smoking, unhealthy diet, lack of physical exercise, stress, etc.) are, and will continue to be, the major factors in disease expression, even for some conditions classically considered 'genetic' (like sickle cell disease or cystic fibrosis).

Prevention and treatment of diseases, in which genes play a significant role (particularly in common adult diseases) rely, and will continue to rely, on the control of adverse environmental factors (*256*). This realization is essential to avoid reductionistic approaches to the prevention and control of conditions of public health significance that have a genetic component in their causation. Nevertheless, and given that common conditions with a genetic component contribute heavily to the global burden of disease, it is logical to expect that genetics and genomics will have a significant role to play in their prevention and control in public health, both in developed and developing nations (*159*).

Genomic research and epidemiology

Epidemiology as a discipline is at the scientific core of public health, involved primarily in studying "the distribution and determinants of health-related states or events in populations and the application of these studies to control health problems" (*137*). Epidemiology is concerned with determining the risk factors for diseases, identifying those at highest risk, and evaluating the effectiveness of health interventions. In turn, *genomics* is concerned with determining the effect of variations in the human genome on the risk of disease. Thus, the two disciplines blend in the field of *genomic epidemiology*, which studies how genetic factors influence the occurrence of disease in populations and families *(163; 128).* A related field is *molecular epidemiology*, which looks at the occurrence of disease through the study of biological markers of exposures, susceptibilities and effects *(199).* The fields of genomic epidemiology and molecular epidemiology rely increasingly on high technology tools such as DNA microarrays and gene expression profiles. These techniques enable the study of thousands of genes simultaneously, in order to determine the effects of gene variations on disease as well as the effects of environmental factors on the genome and its expression.

Epidemiological methods are essential to quantify the impact of gene variants on the risk of disease and its phenotypic manifestations and to measure the effect of environmental risk factors that interact with gene variants to cause disease *(244).* Further, epidemiology is the appropriate tool to assess the clinical validity of new genetic tests (often this does not occur and tests are put on the market with inadequate proof of their validity in predicting the risk of disease). Finally, epidemiological methods permit the monitoring of genetic test utilization in the population and of the effects of genetic knowledge on the health of different populations *(97).*

The role of genome epidemiology is thus to: use genetic variants routinely in the study of gene–environment interactions in disease; use biological markers of exposure, susceptibility and outcomes; evaluate allelic variants in relation to health outcomes; evaluate genes as disease risk factors and to provide a basis for assessing clinical validity of genetic tests for disease susceptibility *(129; 127).* In sum, genomic epidemiology can determine the scientific validity of purported gene–disease associations (*97*).

Genetics/genomics research applied to health care

Some of the key objectives of current genetics/genomics research applied to health care are to identify:

- human genome variants associated with susceptibility to common non-communicable diseases;
- human genome variants associated with immune responses to infectious agents, which may influence individual susceptibility or resistance to infections or determine abnormal responses which may lead to chronic autoimmune diseases; and
- human genome variants involved in the metabolic pathways of drugs and medications, which may explain individual variations in the responses to these agents (*pharmacogenomics*).

As useful as such research may prove to be in providing new means of preventing, diagnosing and treating diseases, some public experts are concerned that excessive emphasis on unproven genomic approaches to disease prevention may divert scarce resources from generally applicable public health measures (promotion of good diet, regular exercise, smoking cessation, etc.) which in spite of being well proven are not fully applied, particularly in developing countries *(23; 80).*

Additionally, it is unclear whether genomic research will lead to improved approaches for disease prevention and health promotion at the population level. This research requires genetic screening and testing of individuals, families and populations to uncover the role of genomic variations in health and disease. Genetic epidemiology enables a scientific assessment of the real validity of genetic screening and testing in disease prevention and health promotion.

3.8 Conclusion

Compared with developed nations, developing countries are burdened by high levels of poverty and structural deficiencies; and their resources to combat disease and promote health are scarce. Disease profiles in these countries are characterized by a higher proportion of nutritional, infectious and social conditions leading to ill health and death. Superimposed on this reality, there is an increasing visibility of diseases traditionally associated with developed countries (namely, congenital conditions and non-communicable diseases). Facing this hard reality, developing countries must carefully assess their disease burden, set their priorities and use their scarce health budgets wisely, making sure that the prevention and care of genetic and congenital conditions is not neglected and finds an appropriate place among other health priorities.

A number of WHO-convened advisory groups have articulated the criteria for applying genetics and genomics to the health problems of developing countries (*263; 264; 266; 268; 271).*

The following are the main recommendations for developing countries resulting from the WHO/HGN/WAOBDP meeting of experts convened in 1999 *(264)*:

1. Need to recognize the burden imposed by genetic disorders and birth defects.

2. Need for political will and commitment to support the implementation of genetic services.

3. Improve epidemiological knowledge about genetic disorders and birth defects.

4. Define the goals of genetic services in terms of both individual/family well-being and public health.

5. Improve prenatal and perinatal services.

6. Organize genetic services in a comprehensive and integrated manner, with roots in the primary health care level.

7. Select programmes and targets according to prevalence, severity and predicted outcomes.

8. Respect ethical principles and cultural diversity.

9. Train health professionals in medical genetics.

10. Educate the public in genetics.

11. Encourage the formation of parent/patient organizations.

4
Discussion: ethical, legal and social issues

Medical genetics is the field of medicine most centrally involved in providing services to people with genetic disorders and to their families. As defined by WHO consultants, the goals of medical genetic services are:

> to help people with a genetic disadvantage and their families to live and reproduce as normally as possible, to make informed choices in reproductive and health matters, to assist people in obtaining access to relevant medical services (diagnostic, therapeutic, rehabilitative or preventive) or social support systems, to help them adapt to their unique situation, and to become informed on new relevant developments (*267*).

Medical genetic services include services that encompass all or most aspects of genetic testing, from genetic screening, to referral for testing, through to testing, post-test counselling and treatment.

There are a number of ways in which genetic information is considered to be different from other health information, although the degree and impact of these differences remain under discussion. For example: (a) genetic information may have medical and social implications for an entire family, rather than only the affected individual; (b) genetic discoveries may be predictive of future adverse health events for an individual or family member who is currently unaffected; and (c) genetic information and the choices made in the present may affect future generations. These features of genetic information generate specific ethical considerations, particularly concerning the implementation of medical genetic services.

Ethics is a field of philosophy concerned with articulating moral values and rules for action, and with analysing and resolving conflicts among these values and rules. Bioethics is the study of ethical, social, legal, philosophical and other related issues arising in health care and the biological sciences (*121*). The following four principles, outlined in the WHO 2001 *Review of ethical issues in medical genetics* (*267*), are widely accepted as philosophical tenets of bioethics:

- **Justice:** treating persons and groups equitably, and distributing benefits and burdens of health care as fairly as possible in society.
- **Autonomy:** respecting the self-determination of individuals and protecting those persons with diminished autonomy.
- **Beneficence:** giving highest priority to the welfare of persons and maximizing benefits to their health.
- **Non-maleficence:** avoiding and preventing harm to persons or, at least, minimizing harm.[1]

The ethical issues arising in relation to genetic testing and screening in developing countries cannot be readily compartmentalized according to these principles, because the issues often involve questions relating to more than one principle. Throughout the report we will highlight the impact of certain social, medical and legal practices on the realization of these principles.

4.1 Introduction

Achieving *justice* is the primary ethical issue in relation to the development of medical genetic services in developing countries. Justice involves: (a) balancing genetic services against other population health needs, and (b) equitable and safe access to genetic services once they have been introduced. From this theoretical platform, this section moves to some of the relevant features of the social context common to a number of developing countries, which affect the implementation of medical genetic services in health care. For example, because reproduction predominantly occurs within marriage, marriage structures and preferences (for example consanguineous marriage) can affect the rate of expression of recessive genetic diseases, and can conversely provide opportunities (for example, arranged marriage) for screening, testing and counselling. Religion can affect the acceptability of certain services associated with genetic testing, namely termination of pregnancy. Abortion for medical reasons is a controversial issue; this section examines where and under what circumstances it is legally permitted; and looks at the problem of unsafe abortions, particularly in countries where abortion is illegal (definitions of the terms *abortion* and *termination of pregnancy* are available in section 4.3.3). Gender is another relevant feature of the social context because traditional gender roles and gender inequality can affect reproductive decisions and patterns of discrimination within a community.

The combination of genetic screening, arranged marriage and gender inequality generates a specific concern about the stigmatization of female carriers of genetic diseases and the potential for discrimination in marriage because the process of formal marriage introductions presents opportunities to exclude these female carriers. The report considers different examples of community-specific responses to this concern. An important tool in preventing discrimination and stigmatization more generally is the protection of patients' privacy and confidentiality. We look at the relevant regulations introduced in some developing countries to protect medical, and specifically genetic, information.

A further tool to prevent discrimination and stigmatization is public education. Genetic information can be complex and difficult to understand, and as discussed above, it can have special implications for the patient's future health, for the health of their children, and for other family members. For these reasons, patient and public education and engagement are essential components of medical genetic services. Genetic testing and screening should be supported by public education, and genetic counselling should be made available to patients and communities. To effectively integrate medical genetic services into public health more generally, primary health care providers such as physicians and nurses need to be able to recognize those at risk of genetic conditions, be aware of the genetic services available, and refer patients to the appropriate facilities.

This section finishes with a discussion of patient safety and well-being. In a sense, patient well-being encompasses many of the topics discussed previously, as all aim to reduce or prevent harm to patients and their families (non-maleficence) and benefit patients (beneficence). However, this subsection looks specifically at quality assurance mechanisms in place in developing countries and the implications of commercial genetic testing for patient safety and well-being.

The *topics* covered in this report do not form an exhaustive analysis of all of the ELSI of medical genetic services. Rather, the report highlights some of the more significant ethical challenges faced by

those developing countries that are establishing genetic services, giving priority to topics not comprehensively covered in previous reports. Similarly, the *examples* included do not cover all countries. The report as a whole provides examples from a selection of different countries and regions. As is widely acknowledged, epidemiological and project evaluation data are lacking for many developing countries; the range of the countries covered in the report has been constrained by the examples available in the literature. To help provide an up-to-date picture of the ethical issues currently associated with genetic services in developing countries, the report includes five case studies based on background papers commissioned specifically for the report from geneticists working in developing countries. Each case study highlights a primary concept covered in the report; but also encompass a wide range of other ethical, legal and social issues in the context of that country.

4.2 Justice

> Today's global health situation raises urgent questions about justice. In some parts of the world there is a continued expectation of longer and more comfortable life, while in many others there is despair over the failure to control disease although the means to do so exist (*270*).

The issue of equitable access to genetic services must be considered against the backdrop of existing global health inequalities. The benefits of modern medicine have still not reached many parts of the developing world. As noted in the introduction, many developing countries now suffer the double burden of infectious disease and malnutrition in combination with increasing rates of chronic disease (*268*:124). The vast majority of global research funds are spent on diseases that account for only a small proportion of the global disease burden. The term 'the 10/90 gap' refers to the fact that "less than 10% of the worldwide expenditure on health research and development is devoted to the major health problems of 90% of the population" (*146*).

In the context of such large and steadily increasing global health inequalities *(249; 63),* there is significant concern that health benefits drawn from future developments in genomics and genetics will not be shared with the developing world (*184*). In 1985, a WHO Advisory Group on Hereditary Diseases concluded that "the broadest of the real ethical issues is the limited availability of genetic services" (*274*). As a result, women bear seriously affected children, and the situation is exacerbated by the realization that it could have been avoided (*274*).

Justice is one of the four foundational bioethical principles. The *concept* of justice relies on the idea of fair and equitable treatment in light of what persons are owed or entitled to. Equity can be understood as the state of being just, impartial and fair. Formal justice demands that equals be treated equally and unequals be treated differently. The principle of formal justice disallows arbitrary, unjustified distinctions between things or people who should be considered equal. As is discussed in more detail below, the failure to weigh fairly the need for medical genetic services against other health services is a breach of the formal principle of justice (*24*). Medical genetic services may be rejected because of the erroneous assumption that they are always complex and expensive. Policy-makers have a duty to consider the growing evidence regarding the cost-effectiveness of medical genetic services in developing countries.

For the purposes of this discussion, we use the term justice to refer to *distributive justice*, defined as the fair, equitable and appropriate distribution of benefits and burdens within a society. Benefits and burdens can be interpreted very broadly, including: rights and obligations; opportunities and barriers; and access or restriction to resources (including services, facilities, money and taxation, among others) (*24*:327). Questions of justice are exacerbated by conditions of scarcity, where the resources required to meet essential needs must be divided fairly between competing demands. Considerations of justice, in the context of medical services, cover the *macro-allocation* issues of which medical services and goods should be provided, and *micro-allocation* questions of who

should have access to these services and on what basis. The allocation of health resources should maximize the benefits from limited resources and distribute those benefits fairly.

4.2.1 Challenges

It is important to note that, in some cases, the neglect and underutilization of genetic testing and screening options is an *ethical* failure. To ignore the evidence of the burden of congenital disorders, or any other demonstrable health burden, and to rely on the false assumption that genetic services are always sophisticated and demanding, is to fail to adhere to the principle of distributive justice. Evidence regarding the control of congenital anomalies should be compared to the evidence for competing health priorities. Failure to do this results in harm occurring that could have been prevented. In turn, failing to prevent avoidable harm breaches: (a) the principle of non-maleficence and (b) the principle of distributive justice, because it distributes health care burdens unfairly within the community.

The following case study of the newborn screening programme in Brazil (Case study 1) illustrates the process of establishing a nation-wide genetic screening programme. The case study highlights the challenges involved with trying to achieve a balance between, on the one hand, a realistic staged roll-out of the programme to match existing resources and, on the other hand, the desire to standardize services nationwide to ensure that all patients are treated equitably and receive a similar level of service.

Case study 1
Newborn screening in Brazil

2001—ongoing

Background

In Brazil, there are no dedicated governmental programmes for the prevention, diagnosis, registration, or treatment of the majority of genetic diseases. Since 1992, however, the public Single Health System [*Sistema Único de Saúde*, SUS] was responsible for neonatal screening to diagnose phenylketonuria and hypothyroidism. However, its provision of screening services varied by region and did not include facilities for diagnostic confirmation, clinical evaluation, treatment, family education or genetic counselling. In response to these limitations, in 2001 the Ministry of Health established the National Newborn Screening Program [Programa Nacional de Triagem Neonatal, PNTN] (*168; 165; 164; 151*). In 2002, 65% of all newborns were screened. The Brazilian government has made a commitment to providing resources for the early diagnosis, treatment and follow-up for disorders caused by inborn errors of metabolism. The Ministry of Health is currently focused on the goal of 100% newborn screening (165). Data from 2003 indicated that the total cost of the PNTN was U$ 15.2 million and the total number of newborns screened was estimated to be 2 360 960, which equates to approximately US$ 6.4 per newborn screened *(167; 213)*.

Description of the project

The PNTN's specific aims are to ensure equitable access to genetic screening for all Brazilian newborns; reduce morbidity and mortality as a result of genetic diseases; organize state screening networks; ensure therapy and follow-up for each disorder detected; provide guidelines to standardize regional services; and create and support a National Newborn Screening Database to collect epidemiological data. The PNTN has been operating nationally since 2001, and is run by municipal and state health offices under the guidance of the Ministry of Health. A technical team was established to develop, evaluate and assess quality and safety standards.

As a result of cooperation between the three governmental levels, the PNTN has organized the State Screening Network in 24 states, and the federal district.* The State Screening Network includes collecting stations in all municipali-

continued...

…Case study 1

ties that have amaternity hospital, which must be under the control of reference services (no less than one per state).maternity hospital, which must be under the control of reference services (no less than one per state).

The PNTN was implemented in three stages due to existing regional inequalities in health care structure: Stage 1, testing for hypothyroidism and phenylketonuria, for which testing is legally compulsory and is available in all 24 states of Brazil, and the federal district; Stage 2, testing for haemoglobin diseases, for which 13 states are now capable of screening; Stage 3, testing for cystic fibrosis, which is available in the 3 states with the most developed screening structures already in place (*213; 165; 151*). A prerequisite for transition from Stage 2 to Stage 3 is the demonstration of 70% screening coverage of newborns in the state for Stage 1 and 2 conditions. A state wishing to transition must also show epidemiological data justifying the need for Stage 3 screening.

Each state must have at least one reference service, a centre that identifies conditions for diagnosis, treatment, follow-up and genetic counselling. Reference services are in charge of collecting and managing samples, and receiving and registering patients; and they are also responsible for integrating services with the health assistance network to ensure general health support. Each service must minimally consist of a paediatrician, an endocrinologist, a nutritionist, a psychologist and a social worker. The inclusion of a clinical geneticist is officially recommended, although not compulsory, due to the lack of clinical geneticists in some regions (*166*).

Challenges

After almost four years, initial evaluations show that the PNTN has been successful in some regions. However, many regional public health care services are not able to fulfil all the programme requirements (*204*). After the implementation of the programme in 23 states, almost half of the teams did not have enough experience in newborn screening, and two-thirds did not include a member with any training in, or understanding of, genetic counselling (*165*). The State Screening Network has designed a training programme to ensure that all teams have appropriately trained staff to fill each of the required roles.

States with few or no genetic, clinical or laboratory facilities have found it financially challenging to meet the requirements of the programme. Clinical protocols and therapeutic guidelines are being developed to standardize the delivery of services, and the Ministry of Health is providing financial support for buying and distributing medications and dietary supplements to support treatment.

Finally, the process of coordinating all levels of government vertically (national, state and local) and horizontally (across a developing country the size of Brazil) has been politically challenging. In response, the Ministry of Health technical team is engaged in a national campaign to ensure the involvement and support of state and local public health officials. Clinical protocols and therapeutic guidelines are also being developed to standardize the delivery of services.

Ethical, legal and social issues raised by the project

There are still challenges in the oversight and standardization of genetics services in Brazil, and a specific concern is the shortage of clinical geneticists. Further, there is no official system of genetic counselling in Brazil and the current resources of newborn screening teams do not allow for regular genetic counselling. The PNTN procedures do not include an informed consent process, and parents are often informed about newborn screening shortly after the birth and without sufficient information about the scope of screening or the potential social and medical consequences.

Identification of misassigned paternity is not uncommon during newborn screening and is sometimes handled improperly. Stigmatization, genetic discrimination, and breaches of privacy have occurred, particularly in relation to the detection of sickle cell carriers (*112*:114). There has been controversy among physicians, health care workers, sickle cell disease associations and African descendants' associations over how best to handle information on individuals who are carriers for sickle cell disease (*3*).

Samples are collected and stored; however, there are no specific rules regarding their use in the future and it appears that their privacy is not always adequately protected.

* The 'federal district' refers to the Brazilian capital, which has the status of a state. Brazil therefore has 27 federal units consisting of 26 states and one federal district.

...Case study 1

This study of the The National Newborn Screening Programme in Brazil is based on information provided by Dr Antonia Paula Marques-de-Faria, Department of Medical Genetics, State University of Campinas School of Medicine, Brazil

4.2.2 Cost-effectiveness

An issue that is specific to genetic conditions in developing countries is the persisting misconception that medical genetic services depend on sophisticated, expensive technologies unsuited to the developing world context. We will therefore present some of the evidence that demonstrates medical genetic services can be cost-effective in developing countries.

Cost-effectiveness is analysed in two ways. *Prospective* analysis of cost-effectiveness is applied where there is no programme in place, but the efficacy of such a programme is predicted from known data. The difficulty with such analysis is that much of the data used is only an estimate, for example of the anticipated rate of uptake of screening, or the expected rate of termination of identified affected fetuses. In some countries, the cost of lifetime treatment for the genetic condition in question has never been measured, and therefore an estimate is again used. The preferable alternative is *retrospective* analysis, where a programme is analysed after either the full programme or a pilot programme has been implemented and data generated and collected. In practice, both types of analysis are used: prospective, to argue for the implementation of a trial or pilot programme; and retrospective, to argue for the expansion and continuation of the programme. Examples of both types of cost-effectiveness analysis (CEA) are discussed below **(country examples 1 and 2)**.

Country example 1
Cost-effectiveness analysis of fragile X screening in Israel

A *prospective* analysis of a proposed fragile X (an X-linked genetic syndrome that is a leading identifiable cause of mental retardation) carrier screening programme in Israel was based on four figures:

(1) data regarding the prevalence of fragile X syndrome in families with no history of fragile X or mental retardation (1 women in 113 is estimated to be a pre-mutation carrier);

(2) the cost of lifetime care for an individual with mental retardation, estimated at US$ 680 000;

(3) an estimated 50% acceptance rate of the screening programme; and

(4) an estimated 100% termination of affected pregnancies.

Estimates were based on data from Israel and/or the Netherlands. (For example the actual cost of lifetime care for mental retardation in Israel is not known and estimates were based on the cost of care in the Netherlands—similar in size and with a comparable system of social medicine to Israel. These estimates were adjusted relative to the respective GDPs of the two countries.) These estimates showed that the expected net benefit of running a fragile X screening programme in Israel is a saving of approximately US$ 5.5 million per annum. This preliminary analysis shows that a programme for fragile X screening should be cost-effective in Israel *(222)*. The establishment of a pilot screening programme would provide an opportunity to collect specific Israeli data to better estimate cost-effectiveness on a national scale.

Country example 2
Cost-effectiveness analysis of thalassaemia screening in Hong Kong SAR, China

The prenatal screening programme for a-thalassaemia and ß-thalassaemia in Hong Kong SAR was *retrospectively* analysed for cost-effectiveness in 2004 *(143)*. Since 1995, universal prenatal screening for thalassaemia has been offered at Tsan Yuk Hospital. Over the course of the programme, 18 of 19 affected fetuses were terminated, representing a 95% preference for termination. The total cost of the programme to date (HK$ 10 million) was far less than the expected postnatal service cost for 18 individuals with ß-thalassaemia (HK$ 40.4 million). The *postnatal service cost* was based on the cost of managing a patient with ß-thalassaemia major for 45 years, including bone marrow transplant/cord blood stem cell transplant, which equates to HK$ 2.7 million per patient. It was concluded that the programme was cost-effective due to the high prevalence of thalassaemia in the area.

The following example of family-based screening in Pakistan (Country example 3) illustrates how different social contexts can vary the outcome of a CEA in relation to specific genetic services.

Country example 3
Cost-effectiveness analysis of family-based (cascade) screening in Pakistan

Targeting extended families for screening is an efficient model of genetic screening in communities where there are high rates of consanguineous marriage. One study of cascade screening for haemoglobin disorders in Pakistan demonstrated that extended family screening can yield a large amount of useful information about carriers and couples at risk *(4)*. All identified carriers in this study reported having used the information provided to them during the genetic counselling and testing process for family planning purposes. Although family-based screening involves considerable labour in terms of collecting family medical information, it can identify a subpopulation who are at risk for the disorder, and thus avoids the need to screen much larger populations. It thus excludes some individuals from unnecessary testing, which can conserve the limited resources of developing countries.

Labour costs are relative to a country's resources and are therefore comparatively low in developing countries. Instead, it is the cost of reagents that is the primary financial barrier to screening for many developing countries. The labour-intensive aspect of cascade screening may therefore not be a serious cost concern. As a result, cascade screening, which places higher demands on staff time but lower demands on the use of reagents (the reverse of population screening), presents a cost-effective alternative for many developing countries.

Family-based screening can also be more effective, as it decreases the likelihood that affected individuals will be missed. In addition, family-based screening overcomes some of the barriers present in population screening that result from limited public education about genetic disorders, because family members have often had personal contact with someone with the disease *(4)*.

Ethical issues

CEA assumes a consequentialist moral standard. Consequentialism (one form of which is utilitarianism) is a moral theory that advocates only one basic principle of ethics: to maximize benefits and minimize harm (*24*). Most ethical criticisms of CEA stem from critiques of consequentialist moral theory generally, and include questions about:

(a) the *construction* of CEA in health care:

- such as, whose values should be used to define the desirable outcomes (for example, comparing impaired functions with shortened lives or no life at all)?

(b) questions of distributive justice in the *use* of CEA in a priority setting:

- such as, when should small benefits to a large number of persons be prioritized over large benefits to a small number of persons (for example: where rare genetic conditions cause *severe* suffering and hardship within a *limited* number of affected families)?

Attempting to maximize the health outcomes of a society as a whole, with limited resources, necessarily involves deciding between the health services required by one group and the health services required by another, whether these groups are defined geographically or in terms of health needs. As illustrated by the Brazilian newborn screening programme (4.2.1), distributing scarce resources equitably and in a cost-effective manner can be very challenging. Should medical genetic services be located in urban centres where they reach the most people or distributed throughout the country so that families in rural communities also have access to the services? Locating services in urban centres is likely to improve the health outcomes of the population as a whole, but it is also likely to widen the gap between the health outcomes of urban and rural communities. This example demonstrates the tension between cost-effectiveness and health maximization on the one hand, and the principle of equity on the other.

CEA of prenatal testing and screening

One issue relevant to prenatal genetic screening is the evaluation of the cost-effectiveness of this kind of medical service. Necessarily such screening has to evaluate the costs and benefits of early detection of serious genetic and/or congenital disorders. There are moral implications in choosing whether to evaluate programmes involving prenatal diagnosis in terms of parents' opportunity to make an informed decision, including the decision to end an affected pregnancy. A key controversy in this debate is how—if at all—to value lives. For instance, it can be argued that evaluating prevention of disease or disability involves evaluating a prenatal decision that the quality of life of a (future) person would be worse than non-existence. Aside from the difficult technical problems involved in making this comparison, many people are uncomfortable with the conceptual problems involved in the tangled process of evaluating burden of disease, when entwined with evaluating the value of a life *(41; 64)*.

Conclusion

Cost-effectiveness analysis can play an important role in macro-allocation decisions, but these data must be weighed against issues of equity and access. The Brazilian newborn screening programme (4.2.1) demonstrated that achieving a balance between cost-effectiveness and equitable access can be difficult. The ethical debate surrounding the rationing of scare health care resources, and CEA in particular, is complex and in many cases far from resolution *(40; 62; 24:*293). However three points can be made:

1. Evidence relating to the cost-effectiveness of interventions should play an important role in health resource prioritization. The intent of finding the least costly way to deliver effective care and maximize health

outcomes can be congruent with the principle of distributive justice, and represents an important technique for health care systems with limited resources.

2. However, the health policy process must consider not only the impact of different policies on health expenditure and population health outcomes, but also the distribution of improved health outcomes between different groups.

3. In the absence of consensus, a fair process for determining a legitimate distribution of health care resources is necessary (*62*). A list of the elements of fair process is available in Appendix C. The fair process model mirrors many of the elements of effective genetic testing and screening services that will be raised throughout the report: community consultation and education (section 4.7); active dialogue with relevant stakeholders (section 4.3.2); and ongoing responsiveness to community needs (4.7.1, Case study 5).

4.3 Social context

This section will take a more in-depth look at the features of the social context in some developing countries that affect both the need for genetic testing and screening services, and the acceptance and use of these services in specific communities. The elements of the social context discussed include traditional cultural patterns of marriage; religion; the legality of, and access to, safe abortion; and gender issues. The purpose of this section is not to discuss the features of the social context as barriers that must be overcome before genetic services can be implemented; rather it is to illustrate the framework within which genetic services should be developed. With cooperation between cultural, religious and political leaders, and in full consideration of the social context, genetic services can be developed that are applicable and effective within different social contexts. It is important not to simply transfer systems for delivering genetic services established in developed countries to contexts in developing countries where they may not be appropriate.

4.3.1 Marriage

Cultural traditions such as consanguineous and endogamous marriage can have an impact on the prevalence of recessive genetic diseases within a community, and therefore affect the need for genetic services such as testing and screening. A further way in which marriage norms can impinge on genetic services is the process of arranged marriage, which can affect the culturally appropriate time to conduct carrier screening (see section 4.4.1).

Some communities may use social constructions of kinship in addition to biological constructions, for example, referring to someone as 'uncle' when they are neither a genetic relative nor a member of the extended family by marriage. This can have an impact on genetic counselling, highlighting the importance that counsellors have the ability to understand the social circumstances of the 'clients', including for example the distinction between social and biological concepts of relatedness. Social concepts can likewise affect the family's understanding of genetic inheritance. Consanguinity and concepts of relatedness should be viewed as an integral part of the social and cultural framework within which genetic services must work (*15*).

Consanguineous marriage

Consanguineous kinship is characterized by the sharing of common ancestors. The word is derived from the Latin *com sanguineus*, 'of common blood'. Two or more individuals are said to be consanguineous if they have a common recent ancestor (usually not further back than three or four generations) (*38*). In clinical genetics, a consanguineous marriage is most typically defined as occurring between a couple related as second cousin or closer (resulting in a coefficient of inbreeding (F) in the progeny of $F = 0.0156$) (*31*:89). The coefficient of inbreeding *(F)* measures the

probability that a person with two identical alleles of the same gene received both alleles from a common ancestor. *F* is therefore determined by the genetic relationship between the parents, and what proportion of their genetic material is shared.[2]

Consanguineous marriage is practised for cultural and economic reasons that vary among communities. However, motivations that are common among consanguineous communities include strengthening family ties and the maintenance of family property, especially landholdings; reduced requirement for dowry; and the belief that the bride will enjoy a more harmonious relationship with her in-laws (e.g. *118*).

Relationship between consanguineous marriage and genetic diseases

Most people carry a number of recessive disease alleles but, because they are rare in the general population, there is a very low chance of two carriers reproducing and producing affected offspring (*169*). Consanguineous marriage is associated with an increased prevalence of recessive genetic diseases and infant mortality (*72*:45; *31; 33*). When close relatives mate, the chance that both will carry the same recessive allele for a trait is higher, and therefore they are more likely to have a child who is homozygous for that trait. However, it is important to recognize that most recessive characteristics are harmless; only a minority are associated with major diseases (*169*). Consanguinity in and of itself does not cause disease; it only increases the chance that reproduction will occur between two carriers for the same recessive genetic conditions.

The recognition that recessive conditions occur at a higher rate in consanguineous communities can facilitate the early identification of carriers and carrier couples (as discussed in Country example 3 on family-based screening in Pakistan). Carrier couples in a randomly mating population are often only identified after the birth of an affected child (*169*). However, in a consanguineous community extended family studies can make the identification of carrier couples much simpler (*169*). Early identification of carrier couples allows for premarital or preconception counselling and the avoidance of affected births.

It is not possible to provide data regarding the *absolute* risk associated with consanguinity because the risk depends on the prevalence of recessive alleles in the particular community, i.e. the background community risk. The only meaningful data therefore is the risk *relative* to non-consanguineous couples in the same community. Available data regarding the impact of consanguineous relationships on the prevalence of recessive genetic conditions indicate that this risk varies considerably both between communities and at the individual family level. Empirical studies involving the progeny of first cousins have indicated that morbidity levels are between 0.7% and 7.5% higher than in the offspring of unrelated couples (*33:*573). On average worldwide there is about a 4–5% increase in the risk of premature mortality among the offspring of first cousin unions *(37; 169).* Available data demonstrate that with each 0.01 increase in the coefficient of inbreeding (*F*), the birth prevalence of infants with recessively inherited diseases increases by about 7/1000 (*48:*242).[3]

Prevalence of consanguinity

Many communities in North and sub-Saharan Africa, the Middle East and West, Central and South Asia exhibit a strong cultural preference for consanguineous marriage (*31*:90; *169*). Even in regions and countries where consanguinity is common, there is a wide variation between subgroups. Pakistan, for example, has very high levels of consanguinity (*119*): a national study in the early 1990s found an average rate of 62% *(5).* However smaller surveys of subpopulations have indicated rates of 30–76% *(36; 245; 101; 120)*. Saudi culture also exhibits a strong preference for consanguineous marriage: the current average rate in Saudi Arabia is 58%; but this varies by region from a low of 34% to a high of 80% *(71; 161)*. In Jordan the frequency of consanguineous marriage ranges from 50–66% (*72*:45). In the Kingdom of Bahrain, the rate of consanguinity in 1995 was 39%,

although it is of note that this had significantly decreased from 46% consanguinity in the previous generation *(6; 7)*.

The size of the potential marriage pool may affect the observed levels of consanguineous marriage in the population. In small communities, prospective non-consanguineous pairings may be limited. As a result, the prevalence of consanguineous marriages may be elevated irrespective of the cultural and social preferences for consanguinity.

Although there is a preference for consanguineous marriage in many countries, in others, marriage between close relatives is legislatively prohibited. Under Chinese law, for example, marriage is generally prohibited between relatives of first and second degrees of kinship (see Appendix B), which includes first cousin marriages and uncle/niece and aunt/nephew marriages (*152*, Art. 6(1)). However, first cousin unions in China may be permissible for members of communities that traditionally have practised consanguinity. The *Hindu Marriage Act* in India bans uncle/niece marriage, but a study of marriage patterns in parts of southern India revealed that more than 21% of Hindu marriages were between uncles and nieces (*35; 28*). Under Islamic law, uncle/niece marriages are banned, although double first cousin marriages are permitted. This distinction is interesting from a biological perspective because these pairings have identical coefficients of inbreeding, F=0.125 (*28*).

While consanguinity influences the prevalence of recessive genetic conditions, it should not be assumed that this is always the major risk factor within consanguineous communities. In a study of the first 500 people to attend the 1993–1994 premarital thalassaemia screening programme in the Kingdom of Bahrain, only 15.4% of carrier–carrier couples were consanguineous (as compared to a 25.9% rate of consanguinity in the total study group); therefore trying to discourage consanguineous pairings through premarital counselling would not alone be sufficient to decrease the overall rate of affected births in the community (*11*). Preference for consanguineous marriage is a feature of the socio-cultural context within which medical genetic services must work.

To summarize, consanguinity is a risk factor for hereditary genetic conditions; however, there are many variables associated with the impact of consanguinity, such as the preference for consanguinity within subpopulations, the degree of consanguinity, and the prevalence of recessive disease alleles in the population. Consanguineous marriage should not be discouraged; instead, voluntary premarital screening to identify carrier couples should be offered to consanguineous communities, in combination with services for prenatal diagnosis and selective abortion of affected fetuses.

Endogamous marriage

Endogamous marriage refers to marriage within a specific group, such as a tribe or clan, as required by custom or law. In India, Pakistan and Bangladesh, which collectively account for more than 20% of the world's population, marriage continues to be arranged within caste and *biraderi* boundaries that probably date back some 3000 years. There are an estimated 50 000 to 60 000 separate endogamous communities in India alone. In effect, each of these groupings form separate breeding pools (*29; 32*). Among Muslims in Pakistan, endogamous marriage requires matching ethnic and tribal affiliations and at times social stratification based on familial occupation. According to Hussain, the strong preference for endogamous and/or consanguineous marriages is driven by multiple factors, including the pride associated with staying within the bounds of *biraderi* or social group identity, and the ease of arranging marriages within the family (*118*; *119*). In addition to consanguineous unions, a 1994 study in Pakistan showed that a further 38% of marriages had been contracted within *biraderis* (*217*).

Patterns of endogamous marriage also result in higher rates of expression of autosomal recessive diseases. The net effect of endogamous marriage is that disease mutations that have arisen recently may be restricted or even unique to individual ethnic groups, sub-castes, tribes or clans (*34*). In general, the less common a disorder, the greater the influence of consanguinity on its prevalence (*33*).

This applies to both monogenic diseases and multifactorial disorders. For this reason, many genetic diseases have been first diagnosed in highly endogamous communities *(28; 34)*.

In cultures where consanguineous and endogamous marriages are favoured, premarital genetic screening can be an effective strategy to increase the reproductive choice of couples and reduce the birth of affected children. This approach is discussed more thoroughly in the section of the report addressing arranged marriages (section 4.4.1).

4.3.2 Religion

Religious views may have an influence on understanding of, and attitudes towards, the nature of genetic disorders, and their diagnosis and treatment. In particular, they may affect an individual's reproductive decision-making (*185*:1300). Appreciating the prevailing beliefs in a local community is critical to achieving effective health care. Such understanding is necessary to ensure that information is imparted to individuals sensitively and in a way that facilitates understanding. The success of testing and screening programmes rests in part on their acceptance by the religious and wider community.

One 1995 study of sickle cell disease in Nigeria found that although the majority of carriers and affected individuals surveyed understood how the disorder was passed on, as many as 8% of carrier fathers and 30% of carrier mothers believed that the disorder was an 'act of God' (*68*, Table 2). Similar studies were conducted in Saudi Arabia among parents of children with a range of genetic diseases, who were interviewed about their understanding of the cause of the disorder. All parents interviewed believed that God determined their health status, granting either health or illness. At least half understood the inherited basis of genetic diseases; nevertheless, many of them rejected it, citing instead religious explanations for the cause of disease (*185*). As one respondent stated: "the disease runs in my family…but only God knows why some children are fine and others are not" (*185*). This did not prevent parents from seeking those treatments permitted by Islamic beliefs, demonstrating that religious views about disease causation and secular scientific explanations of heredity are not necessarily mutually exclusive.

Religious beliefs may affect attitudes to medical genetic services, particularly selective abortion for fetal abnormalities, and, by association, prenatal diagnosis. While many religions do not prohibit termination of pregnancy for medical reasons, provided termination can be performed early on in pregnancy (*16*), in some countries religious beliefs will preclude the abortion of fetuses diagnosed with a genetic disorder (*221*; *112*). For many couples this will exclude abortion as an option following prenatal diagnosis. Where anti-abortion views are prevalent, it is important to provide public education about the range of relevant reproductive choices available (including premarital screening, partner selection, adoption and the option not to have children).

These educational activities must be sensitive to gender norms about discussing reproductive choice, particularly the socially acceptable ways in which women are permitted to participate, in order to present information in a manner that maximizes accessibility for, and encourages active participation of, both women and men.

In many countries, the timing and rationale for abortions may be determined in accordance with religious teaching. In 1990 the Islamic Jurisprudence Council of the Islamic World League issued a *Fatwa* that allowed abortion in the first 120 days following conception: if the fetus was proven beyond doubt to be affected with a severe malformation not amenable to therapy; if born, there would follow a life of misery for the individual and his/her family; and if both parents consented (*13*; *12*). This example demonstrates the potential for religious teaching to accommodate and respond to new scientific developments and research.

Religious belief plays an important part in many people's lives, particularly in relation to marriage, reproduction and views on life and death, and can therefore have a significant impact on the way genetic services are implemented within a particular community. Dialogue and cooperation between religious leaders, policy-makers and scientists must be encouraged in order to ensure that genetic services are implemented in a manner that is culturally acceptable and maximizes the health benefits to patients and families.

4.3.3 Termination of affected pregnancy

At present, there are many congenital disorders that are not open to effective management, for example Trisomy 18 (Edwards syndrome), Trisomy 13 (Patau syndrome), Tay Sachs disease and anencephaly [description of disorders available in the glossary]. The number of conditions falling into this category is greater in developing countries, where treatment options are further restricted due to limited resources. For example, the condition phenylketonuria requires a highly specialized and expensive diet for approximately the first 16 years of life as well as during the female patient's own pregnancies (*48*). Although this diet is accessible to many of the affected individuals in developed countries, the cost can be prohibitive for affected persons in developing countries. Attitudes towards termination of pregnancy are relevant in the context of genetic testing and screening because abortion of fetuses affected by disorders that cannot be effectively managed within the local socioeconomic context is one preventive option.

This report uses the terms *abortion* and *termination of pregnancy* to refer to the deliberate interruption of pregnancy following the detection of fetal abnormality (unless otherwise noted). (The discussion of unsafe abortion is one such exception.) Unless otherwise specified, reference to abortion as an option for individuals and couples, following prenatal diagnosis, assumes that this procedure is not legally prohibited in the country concerned.

Contrary to popular belief, a large proportion of developing countries *do* permit abortions when medically indicated (*264*). At present, such services are available in China, Cyprus, India, the Islamic Republic of Iran, South Africa, some south-east Asian countries including Cambodia and a minority of Latin American and Caribbean countries, among others (*191*; *135*, Art. 8). Data on abortion rates (the number of abortions per 1000 women aged 15–44 years) are not available for all countries; the known rates for the countries listed above demonstrates the significant differences within countries where abortion is legal: China, 26.1; Cuba, 77.7; India, 2.7; South Africa, 2.7; and Tunisia, 8.6 (*232*).

The specific circumstances under which an abortion is legal vary by country. For example, under Ecuadorian regulations, termination of pregnancy is available where the fetus has been diagnosed with a genetic disorder and the termination is approved by both a gynaecologist and a geneticist (*189*). Termination for thalassaemia is accepted in Saudi Arabia and Pakistan up to 17 weeks into pregnancy, (*49*) in line with the Islamic *Fatwa* discussed above (*13*). In Pakistan, prenatal diagnosis in the first trimester and consequent termination of affected pregnancies is widely endorsed: research shows that 89% of couples who have a fetus affected with thalassaemia chose to terminate the pregnancy *(4*).

In many developing countries, however, medical abortions remain illegal. For example, termination of pregnancy is prohibited in most countries in Latin America and the Caribbean, except for Cuba, Ecuador and isolated jurisdictions such as Mexico City (*193*; *189*). Termination under any circumstances is prohibited by law in Chile (*221*). Termination is technically illegal in Brazil, except where the pregnancy is the result of rape or will endanger the life of the mother if allowed to continue (*112*). According to Horovitz et al., however, Brazilian courts have allowed termination where the fetus suffers from severe abnormalities that are 'incompatible' with survival outside the womb (*112*). Termination is prohibited in Jordan unless continuation of the pregnancy

endangers the mother's life (*72*). Full listings of the countries where abortion is legal, and under what circumstances, are available from the United Nations Population Division Department of Economic and Social Affairs (*234*).

Box 4
Grounds on which abortion is permitted—percentage of countries

- To save a woman's life 98%
- To preserve physical health 63%
- To preserve mental health 62%
- Rape or incest 43%
- Fetal impairment 39%
- Economic or social reasons 33%
- On request 27%

Source: United Nations Population Division 1999. See WHO (*269*)

The statistics in Box 4 demonstrate the breadth of reasons for which a pregnancy might be terminated, and how widely each is legally permitted. Thirty-nine percent of countries allow abortion for fetal impairment, although their definitions of what constitutes an 'impairment' will differ.

These differing definitions sit within the context of the broader question of how communities define ill health and impairment. Case study 2 highlights a complex aspect of this question—whether carrier status constitutes impairment.

Case study 2
Ethical issues in Duchenne muscular dystrophy screening in India

Background

Duchenne muscular dystrophy (DMD) is an X-linked muscle disorder, the severe effects of which almost always occur in boys. If the offspring of a carrier female is male, there is 50% risk he will be affected; if the offspring is female there is a 50% risk she will be a carrier.

The incidence of DMD is similar in all countries, and the frequency at birth is about 1 per 3300 male births. Therefore, in India with 25 million annual births, almost 3780 boys are born with this disorder every year. A boy with DMD is expected to live into his late teens or early twenties, depending on treatment; therefore about 75 000 boys in India are affected at any one time. Affected boys usually walk late, tend to have poor balance and lose the ability to walk at about 10–12 years. This chronic genetic disease results in a significant health burden for affected individuals, families and the State because there is currently no cure, only treatments to improve the individual symptoms, such as a pacemaker for cardiac symptoms, physiotherapy, surgery and medication.

The clinical diagnosis of DMD is confirmed by DNA testing, which shows deletions in the dystrophin gene in almost 65% of cases. The DNA diagnostic test is expensive (about US$ 75 in India) and parents must pay for the test themselves. However, if the test is conducted by a government-funded institution the service is state-subsidized (i.e. parents pay approximately half of the $75 cost). Determination of the sex of the fetus is a necessary component of prenatal testing for X-linked diseases.

Prenatal diagnosis of the disorder is now possible, and the service is available in five institutions in India. Prenatal diagnosis of DMD costs about US$ 300, a price that is significantly cheaper than in developed countries, but is still expensive for many families in India.

Case description

A couple with a son affected by DMD and a non-carrier daughter requested prenatal diagnosis for a subsequent pregnancy. The mother's brother was also affected with DMD and died at the age of 20 years. This indicated that

...Case study 2

the mother was an *obligate carrier* of the mutant gene (i.e. she was a definite carrier, as contrasted with a case occurring in the absence of a family history of DMD, where the mother is considered to be a *probable carrier*).

A prenatal diagnosis was conducted and the fetus was diagnosed as a female carrier of DMD. The information regarding sex of the fetus is available to the laboratory but this was not disclosed to the couple. They were informed that the fetus was normal and did not have DMD. The information conveyed to them could mean one of three things: that the fetus was an unaffected male, a non-carrier female or a carrier female.

The couple was not satisfied with this information, and insisted that they be told the sex of the fetus. They said that they would be happy to continue the pregnancy if the fetus was a normal male, or a normal female, but would like to terminate the pregnancy if the fetus was a female carrier of the DMD mutation. The parents argued that a carrier female would face difficulty in finding a husband and would subsequently require invasive, inconvenient, and costly tests during pregnancy. The laboratory refused to disclose the information requested by the couple because Indian law is clear that the sex of the fetus should not be disclosed, except in cases where the information relates to the diagnosis of a genetic disease.

Ethical, legal and social issues

X-linked genetic diseases pose significant ethical issues in developing countries. In arranged marriages, family medical histories are often discussed, and the potential bride's parents can be faced with a difficult decision about whether to reveal to the potential husband's family that their daughter may be a carrier of a serious genetic disorder.

The couple discussed above was counselled on two occasions—once when the affected child was brought for diagnosis and therapy, and again when the mother was pregnant. There are about 15 genetic counselling centres in India, a number totally insufficient for the demand generated by such a large population. Where there are no genetic counselling centres available, the treating specialists (paediatricians and neurologists etc.) provide genetic counselling.

In the absence of public health insurance, the Indian population has to bear the personal anguish and the significant socioeconomic burden associated with the birth of a child with a genetic disease.

In cases like the one discussed above laboratories differ in their policies regarding disclosure of sex of the fetus, and whether to reveal that a female fetus is a carrier. Families also differ in how they react to this information—some continue the pregnancy with carrier females and some do not.

* For a description of X linked inheritance see Figure 2.

This study of the management of Duchenne muscular dystrophy in India is based on information provided by Dr Ishwar Verma—Senior Consultant and Head of the Department of Genetic Medicine, Sir Ganga Ram Hospital, New Delhi, India (References: 73; 243; 242; 200; 201).

Unsafe abortion

Prenatal diagnosis provides information for prospective parents about the health of their fetus. It is common for parents to decide to terminate a pregnancy if prenatal diagnosis reveals a fetal abnormality. Access to safe abortion services allows parents to safely terminate an affected pregnancy if they wish. However, many women around the world do not have access to safe abortion. Unsafe abortions are defined as abortions carried out either by persons lacking the necessary skills or in an environment that does not conform to minimal medical standards, or both.[4] Access to safe abortion for affected fetuses is an important part of comprehensive genetic services.

Prenatal diagnosis and detection of a fetal abnormality, in the absence of safe abortion services, may mean that some women resort to unsafe abortions, thereby placing them at increased risk of death or serious complications. Horovitz et al. comment that in Brazil:

Those who can afford to pay for a safe abortion usually choose to terminate the affected pregnancy with no health or legal consequences. On the other hand, for most couples the option is between continuation of an affected pregnancy against their will, or an illegal and unsafe abortion, with its risks of social ostracism, prison, health damage, and even death (*112*).

Unsafe abortion is a serious and neglected health care problem in developing countries that severely affects women and, more specifically, women's health (*272*). Unsafe abortions are responsible for 17% of the maternal mortality in Latin America, resulting in a rate of 30 unsafe abortion deaths per 10 000 live births. Africa has even higher rates: 100 unsafe abortion deaths per 10 000 live births (and in East Africa this figure rises to 140 unsafe abortion deaths per 10 000 live births) (*272*). This should be a grave concern for developing countries with limited health budgets. For example, a review of the literature found that it is not uncommon for half of all obstetric admissions to be for complications related to unsafe abortions.

Legal prohibition of abortion does not prevent them from taking place (note that not all illegal abortions are unsafe; and conversely not all legal abortions are safe). In fact, restrictive legislation is positively associated with a high incidence of unsafe abortion (*272*). For example, an estimated 4.5 million terminations are undertaken every year in Latin America, 95% of which are illegal and most of which occur in unsafe conditions, especially those obtained by poorer women (*193*). Romania significantly restricted abortion laws in 1966 and witnessed a rise in the number of abortion-related deaths, from 20 per 100 000 live births in 1965 to 150 in 1983. When abortion was legalized in 1989, maternal deaths caused by abortion dropped to 60 per 100 000. This case demonstrates a clear correlation between restrictive abortion legislation and abortion-related death (*272*).

The vast majority of unsafe abortions are *not* related to genetic disorders. Women and couples can, however, be put under emotional and psychological strain and serious physical risk in societies where prenatal diagnosis of congenital disorders is available, but abortion of affected fetuses is not. Personal views on abortion vary and couples will therefore differ in their response to the knowledge that the fetus has a congenital disorder, but it must be acknowledged that a proportion of such couples will wish to abort affected fetuses for medical reasons. As discussed in section 4.3.3, research in Pakistan indicated that 89% of couples who had a fetus affected with thalassaemia chose to terminate the pregnancy (*4*).

The role of abortion within medical genetic services

Despite the relationship between prenatal diagnosis of congenital anomalies and abortion, genetic services can offer a range of health benefits that are independent of abortion. For some pregnant women and couples, prenatal diagnosis and genetic counselling can provide a valuable service in the absence of legal and safe abortion services, as they can help families, particularly mothers, prepare for the birth of an affected child (*272*). However it should be acknowledged that this benefit is only realized if women actually have access to prenatal services and are able to attend counselling. Culture, religion and social factors influence not only the views and practices surrounding pregnancy and termination, but also affect a woman's ability to access these services. Lack of social mobility, lack of access to household resources in order to pay for services and social norms of permission-seeking behaviour, can limit women's access to genetics and prenatal services.

Premarital family planning and preconception genetic counselling are other ways of preventing genetic diseases independent of abortion. Potential carrier–carrier couples have the option of finding other partners to significantly reduce the risk of their child being affected by a genetic disease; alternatively couples can choose not to have children, or in some cases to adopt. A small number of couples in developing countries may have access to, and the funds to pay for, in vitro fertilization (IVF), and pre-implantation genetic diagnosis.

None of these options involves the termination of affected pregnancies.

In light of the divergent, often strongly felt, views about the moral acceptability of abortion, it is important to foster dialogue between patients and families affected by genetic diseases, geneticists, physicians, public health officials, government, religious leaders and other relevant interest groups. Public engagement should take account of the socio-cultural taboos surrounding reproduction and abortion, and the division of social space in which men and women can discuss these issues, to ensure that the views of both men and women are included in the decision-making process. A comprehensive nationally coordinated set of genetic services must consider the relationship between prenatal genetic testing, the legality of abortion and the risks to women as a result of unsafe abortion practices. WHO consultants have stated that:

> Optimum reproductive counselling can take place only in the context of available and affordable contraception and abortion for congenital disorders, and available and affordable resources for caring for persons with disabilities (*267*).

The dialogue carried out between religious scholars, public policy officials and geneticists in the Islamic Republic of Iran in relation to abortion demonstrates the potential for constructive debate. In the Islamic Republic of Iran, religious scholars have determined a threshold for termination of fetuses with thalassaemia under 15 weeks, in accordance with religious opinion that a baby becomes ensouled at 120 days (*49*). See **Country example 4**.

Country example 4
Community engagement in thalassaemia screening in the Islamic Republic of Iran

The thalassaemia screening programme in the Islamic Republic of Iran is widely acknowledged as one of the best examples of genetic screening in a developing country. There are an estimated 25 000 thalassaemia patients in the Islamic Republic of Iran, accounting for about 0.04% of the population; and an estimated 4–5% of the population are carriers. This results in about 8000 at-risk pregnancies per year (*87*), approximately one quarter of which are affected by thalassaemia.

The programme was initiated in 1996 and within five years 2.7 million couples had undergone premarital screening. The 10 000 couples who were both found to be carriers were offered genetic counselling. A summary of the programme from 1997 to 2001 showed that on average 53% of carrier couples still chose to marry despite the genetic reproductive risk (*212*). At-risk couples wanted access to prenatal diagnosis and the option of selective termination of affected fetuses. This increased demand for termination services sparked debate among the public, religious leaders and policy-makers. In 2001, the law was amended to allow selective termination of fetuses at less than 15 weeks gestation for thalassaemia. It is anticipated that the option of selective termination will subsequently be extended to other serious congenital disorders (*49*).

Governments must take action to address unsafe abortion, which is a serious threat to women and women's health. In countries where abortion for fetal abnormalities is restricted or illegal, further

debate is required at the academic and policy level regarding the ethical acceptability of introducing prenatal genetic testing in the absence of safe abortion services for medical purposes. Evidence demonstrates that a significant proportion of couples will choose to abort fetuses affected by a serious genetic condition. In the absence of safe abortion services, some women will resort to unsafe abortion, thereby exposing themselves to the associated medical, financial, social and legal risks.

The success of the Iranian screening programme resulted from the holistic way in which the services were developed. The programme was supported by widespread public education and public health surveillance. The programme proved to be sensitive to the needs of the affected population, capable of engaging diverse sections of the community in debate and of reaching a consensus viewpoint by integrating the views of religious scholars and affected families, thus establishing a workable solution to the issue of termination of affected pregnancies.

4.3.4 Gender

There are a range of gender-related issues associated with the implementation of genetic testing services in developing countries. A consistent concern is the potential for stigmatization of, and discrimination against, vulnerable sections of the community. In communities where the social system does not treat men and women equally and where strict gender roles exist, the scope for discrimination against, and ill treatment of, women is greater. In cultures where marriages are traditionally arranged, there is potential for discrimination against women who are found to be carriers of genetic diseases (see section 4.4.1). A further implication for not only women, but also society in general, is the practice of sex-selective abortion in communities where social and cultural structures strongly favour the birth of male children. The appropriation of medical genetic services, introduced to help patients and families affected by a genetic condition, for the purposes of non-medical sex selection is a serious concern. The following section will address the issue of sex selection and the impact of this practice on sex ratios. Stigmatization and discrimination against carriers of recessive genetic conditions will then be discussed in section 4.4.

Sex selection and sex ratios

The term 'sex selection' can cover a wide variety of practices, including selecting embryos for implantation in IVF, sperm sorting and selective abortion, and may be carried out for different purposes. Sex selection for medical reasons involves selection to avoid producing a child affected by a sex-linked genetic disease. Family balancing refers to the selection of a child of a particular sex to achieve a mix of male and female children within a family, in other words for social reasons. Many countries, such as Australia, Germany, the Netherlands, the United Kingdom, and the United States, are currently considering the ethical and social validity of sex selection for the purposes of family balancing *(60; 59).* In some countries, there is no clear preference for choosing a particular sex. For example, one study conducted in Germany questioned 1084 men and women aged 18–45 about their gender preferences and whether they would use sperm sorting to select for their child's sex. More than half those surveyed had no preference about the sex of their child, with 30% expressing a desire for a family with an equal number of male and female children. Only 4% would prefer more boys than girls, and 3% more girls than boys. A slight preference for boys as the firstborn child was also expressed, with 14.2% wishing for a firstborn son, as against 10.1% wanting their firstborn to be female. A mere 6%, however, said they would use sperm sorting to choose the sex of their children (*61*).

However, sex selection can also be used to create *imbalance* in the sex ratio in a family, typically in favour of sons. In the context of developing countries, sex selection almost exclusively involves the *abortion* of *female* fetuses. Unless otherwise specified, we use the term *sex selection* in this report to refer to the abortion of female fetuses for non-medical reasons.

Sophisticated genetic diagnostic services are not required to identify the sex of a fetus. Ultrasound machines, which are relatively inexpensive and easy to use, have been used worldwide to determine fetal sex for a number of decades, with the invasive procedures of CVS and amniocentesis also employed. In high resource settings, this technology is being supplemented with sperm sorting services and pre-implantation genetic diagnosis; however, these services are not readily available in developing countries.

Sex selection and bias against female children

Approximately 51.3% of live births are male, giving a live sex ratio of 1.06 (*52*). The national rates reported throughout Europe indicate the consistency of this ratio: Austria 51.39%, Belgium 51.27%, Denmark 51.38%, England and Wales 51.26%, France 51.18%, Germany 51.47%, Italy 51.35%, Netherlands 51.38%, Spain 51.44% (*90*). By contrast, the sex ratios in many developing countries are changing significantly. According to China's fifth national census in 2000, the live birth sex ratio had reached approximately 1.17, meaning that 53.92% of all births were male. In some regions of China, the ratio was as high as 1.43 or 58.85% (*76*).

One explanation for this shift in sex ratios is that the social bias in favour of male children in certain cultures provides an incentive for parents to select the sex of their child or children. Sex-selective termination has become common in many countries—particularly in China (including Taiwan Province) and the Republic of Korea (*130*), and also in Singapore, India and other South Asian states (*216*). This section examines examples of two of these countries—India and China—and their efforts to curb the practice of sex-selective abortion of female fetuses (see **country examples 5 and 6**).

Country example 5
Sex-selective abortions in India

Abortion was legalized in India in 1971 with the introduction of the *Medical Termination of Pregnancy Act*, for cases where "…the continuance of the pregnancy would involve a risk to the life of the pregnant women or a grave injury to her physical or mental health" or where "there is substantial risk that if the child were born, it would suffer from such physical or mental abnormalities as to be seriously handicapped" (*157*, §3).

Abortions are permitted up to the 20th week of gestation; however, many illegal abortions are performed by both qualified and unqualified people beyond this limit, and for reasons other than those endorsed in the Act (*124*). Pressure to have male children as a result of son preference, which in combination with the availability of services for fetal sex determination and abortion, and decreasing fertility, results in some couples seeking prenatal diagnosis for sex selection and then choosing to abort female fetuses (*124*). Due to the illegality of the practice, it is impossible to establish the rates of sex-selective abortions in India (*172*).

To take an individual example, a study was conducted in Punjab between 1990 and 1991 on 596 children. Fifty four of these children had had their sex identified by ultrasound before they were born; 49 of these 54 children were boys. Each of the 5 girls born after their sex had been identified prenatally had either been wrongly identified as a male or had a male twin (39). The striking feature of this study, despite the small sample size, is the fact that the data implies that none of the pregnancies *thought* to involve only a female fetus were carried to term. As a result the sex ratio of the children born is vastly distorted in relation to the natural sex ratio. The study also found a positive correlation between the use of sex selection and (a) mother's education and (b) an increase in mother's income (*39*). It is not clear whether higher education and wealth result in an increased desire to select the sex of the child, or an increase in access to sex selection services, or both.

To curb this practice, the Indian Government introduced the *Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act* in 1994. The Act limits the use of prenatal diagnosis to the detection of listed diseases, and prohibits the use of prenatal diagnosis to determine

...Country example 5

the sex of a fetus (*200*, §4). It also makes it illegal for any person "conducting prenatal diagnostic procedures [to] communicate to the pregnant woman concerned or her relatives or any other person the sex of the fetus by words, signs, or in any other manner" (*200*, §5). All genetic counselling centres, genetic laboratories and genetic clinics are banned from performing prenatal diagnosis to determine the sex of a fetus (*200*, §5(2)). Genetic counselling centres, genetic laboratories, and genetic clinics must prominently display a notice that disclosure of the sex of a fetus is prohibited by law (*201*, r17(1)). In 2002, the Act was amended to include further prohibitions on sex selection. The amendments made it an offence to conduct or aid in conducting "sex selection on a woman or a man or on both or on any tissue, embryo, conceptus, fluid or gametes derived from either or both of them" (*200*, 3A). Selling any equipment that could be used to detect the sex of a fetus to clinic, laboratory or person not registered under the Act was prohibited (200, §3B). Finally, all persons were banned from seeking or encouraging the conduct of any sex selection technique, and from causing or allowing to be caused the selection of sex before or after conception (*200*, §4(5), 6(c)).

However, according to Mudur, the Act is not enforced and critics have accused the medical profession in India of showing "gross indifference to this issue" through their inaction (*172*). In 1999, the Indian Medical Association and the Medical Council of India instructed doctors to stop performing ultrasounds and terminations for the purpose of sex selection (*172*). The Indian Medical Association has stated that it will launch independent investigations of suspected doctors, and has threatened to revoke the licences of doctors found guilty (*172*).

Sex selection and human rights

Sex selection is widely condemned in the literature. In its *Review of ethical issues in medical genetics*, WHO consultants argued that sex selection is oppressive (*267*). Governments in China and India, where sex selection is widespread, have introduced legislation banning the practice. Academics in countries where sex selection is not prevalent *(197; 74)*, and in countries where it is, *(205; 14; 46)* have condemned the practice.

The United Nations Convention on the Elimination of all forms of Discrimination Against Women (CEDAW) requires States Parties to take all appropriate measures:

> To modify the social and cultural patterns of conduct of men and women, with a view to achieving the elimination of prejudices and customary and all other practices which are based on the idea of the inferiority or the superiority of either of the sexes or on stereotyped roles for men and women (*228*, Art. 5(a)).

The CEDAW Committee has specifically addressed the issue of sex-selective abortion. In 1999, the Committee called on the Government of China to take all appropriate measures to modify and eliminate son preference, by expanding educational and employment opportunities for women in rural areas. It also called for the Government to enforce laws against sex-selective

abortion, female infanticide and other associated practices (*231*). In 2000, the Committee commended the Government of India for introducing legislation that has banned sex-selective abortions, but also called upon the Government to elicit the support of medical associations in enforcing professional ethics and preventing sex-selective abortions (*233*).

There is, however, a human rights argument in favour of tolerance of prenatal and pre-implantation sex diagnosis. This argument holds that individual women, who may already be oppressed by family and social structures they are powerless to change, should not be burdened by the continuation or initiation of pregnancies they do not want (in this case female pregnancies). Women are not the sole perpetrators of son preference or the devaluation of women in general, and therefore should not be compelled to continue unwanted pregnancies that may further increase the burden on women *(56; 66)*. WHO stated in the 2005 World Health Report:

> In societies where giving birth to sons defines women's status and rights as wives, daughters-in-law and mothers, sex determination and sex-selective abortion allow women to gain control over at least one aspect of their lives (*273*).

As indicated by the CEDAW statement to the Government of the People's Republic of China, the solution to sex-selective abortion is likely to lie in social measures that reduce son preference though the promotion of the status of women, such as increasing educational and employment opportunities for girls and women. **Country example 6** examines some of the reasons for sex selection in China and the country's attempts to curb this practice.

Country example 6
Sex-selective abortions in China

In 1999, the live birth sex ratio in China was 117 males for 100 females or 53.92%, a significant increase from the 1980 pre-policy rate of 51.69% (*76*; *147*). The 2000 national census counted approximately 12.8 million fewer females born between 1980 and 2000 than would be expected based on normal sex ratios (*43*). There is a strong cultural preference for sons in China and son preference is viewed as the fundamental factor influencing the sex ratios.

There are three potential explanations for the high ratio: (a) parents are underreporting female births and female children to official authorities; (b) female fetuses are selectively aborted; (c) female babies are the victims of infanticide *(116)*. Hypothesis (a) challenges the accuracy of the official sex ratio, while explanations (b) and (c) accept the ratio. Zeng et al. argue that data from a range of national and local sources demonstrate that underreporting and sex-selective abortion of female fetuses can explain almost the entire increase in the reported sex ratio, essentially ruling out infanticide and infant abandonment as a main contributing factor *(278)*.

In 1979, China introduced a One-Child policy in an effort to curb its exponential population growth. Although the policy is widely referred to as the 'One-Child' policy, it is important to note that its implementation has not been uniform and varies significantly between provinces. Important exceptions to the One-Child rule include the following justifications for a second child: (a) the first child is a girl; (b) the first child is disabled; (c) both parents are themselves only children; and (d) the parents have certain occupations. Exceptions are more common in rural areas. An estimated 25% of all communities allow all couples to have two children and another 30% of communities allow couples with a girl to have a second child *(147)*.

For the purpose of this report, we are specifically interested in the magnitude of sex-selective female abortions, and the role of genetic testing and screening services. The availability of sex-determination technology, based on CVS, amniocentesis and ultrasound, is viewed by some as a major factor in the increased Chinese sex ratio (*116*; *186*). Evidence in favour of the influence of sex-selective technology on the increasing sex ratio is

...Country example 6

the fact that although the One-Child policy was implemented in 1979, sex ratios did not start to rise until about five years later, shortly after sex-selective technology became more widely available (*147*). Coale and Banister argue that the commonality of decreasing fertility and availability of technology for prenatal sex determination are features in both China and the Republic of Korea, and that these factors explain the rising sex ratios:

> **Sex-selective abortion also has emerged in Korea..., which enjoys many forms of advanced technology and where the demand for sex identification is very high because the preference for males is much like that in China. No coercive one-child policy exists on Korea, but through voluntary use of contraception and abortion, the total fertility rate in Korea has fallen to about 1.5 births per woman. In both the People's Republic of China and South Korea (Republic of Korea), couples strongly desire more sons than daughters, on average. As prenatal sex determination has become available, parents in both countries have evidently used it (52).**

The One-Child policy, and in particular the monetary penalty for exceeding the designated limits, is widely believed to be a contributing factor in the rising sex ratio (147); however, it is difficult to disassociate this influence from the other factors discussed above. For example, Shanghai and Beijing, where the One-Child policy has been most effective, have relatively normal sex ratios (*147*).

Irrespective of the specific causes of sex-selective abortion, it must be acknowledged that the practice reflects morally unacceptable social discrimination against females. Anti-female sex selection contravenes the principle of gender equality; female infanticide and abandonment are a serious violation of the fundamental human rights of women and children (*278*).

The Chinese Government has tried a number of methods to reverse the sex ratio. In 1994 China prohibited the use of ultrasounds or other technical means to detect the sex of an unborn fetus, except where necessary on medical grounds (*154*, Art.32). As of 2003, sex-selective abortions were also prohibited, although some provinces such as the Shandong province had already passed local prohibitions on such abortions (see, e.g. *206; 171)*. However, these legal measures are hard to enforce, and seem to have had little effect. To redress the problem, China's political leadership has set the goal of reversing the rising sex ratio over the next few years: "With the strengthening of the responsibility system, with the joint evaluation of indicators of population quantity and population sex ratios, we aim in three years to bring the trend of rising sex ratios under control" (*115*).

The driving motivational force behind sex selection in China is son preference, especially in rural areas. Research indicates that an increase in mothers' education decreases the sex ratio, presumably by reducing son preference (*147*). This helps to explain why both Shanghai and Beijing, with relatively high average levels of education among mothers, have not experienced rising sex ratios despite decreasing fertility. Mothers' education is also associated with higher levels of development and higher family income (*147*). Gu and Roy observed in 1995, that provinces in China with normal sex ratios were those with: (a) the highest level of development (and lower fertility), or (b) the lowest levels of development (with high fertility) (*95*). High fertility results in larger families and therefore a higher likelihood that families will naturally include a son. In order to reverse the sex ratios, while maintaining small families, son preference must be addressed. It therefore seems that increasing mothers' education is a promising strategy for reversing an imbalanced sex ratio (*147*).

Conclusion

Clearly, sex-selective abortion often occurs due to considerable social pressures, and simple legal prohibitions on such abortions are likely to fail if these social pressures remain strong. Thus, it seems likely that adjusting social incentives will be a more effective strategy in combating the practice of sex selection than legislative prohibitions alone. Given the apparent high correlation between mothers' education and the prevalence of normal sex ratios, prioritizing girls' and women's education seems to be a promising strategy.

On this issue, the United Nations Population Fund has stated that:

> Overall, the value of girl children to both their family and society must be expanded beyond their definition as potential child-bearers and caretakers and reinforced through the adoption and implementation of educational and social policies that encourage their full participation in the development of the societies in which they live. Leaders at all levels of the society must speak out and act forcefully against patterns of gender discrimination within the family, based on preference for sons. One of the aims should be to eliminate excess mortality of girls, wherever such a pattern exists. Special education and public information efforts are needed to promote equal treatment of girls and boys with respect to nutrition, health care, education and social, economic and political activity, as well as equitable inheritance rights. Governments are urged to take the necessary measures to prevent infanticide, prenatal sex selection (*240*, paras 4.17, 4.23).

One example of a country that has successfully reversed the rise in sex ratios is the Republic of Korea. In the mid-1990s, sex ratios at birth for the third and fourth child had increased dramatically, peaking at their highest level above 200 (reaching as high as 240 for the fourth child in 1993). The live birth sex ratio for third and fourth children decreased to approximately 150 in 2003 as a result of the following government initiatives:

Legal and policy measures: These included legal prohibitions on sex determination and strong policy measures to prevent sex-selective abortion, implemented through medical guidelines, norms and codes. These have been enforced since 1992; doctors found guilty of conducting sex-selective abortions are de-licensed.

Mass media campaigns: Media campaigns were initiated in 1991 encouraging couples to change their attitudes to sex-selective abortion.

Social policies: The initiatives included a range of policies to bring about changes in gender norms, values and attitudes in addition to specific policies to improve the status of women by increasing education and employment opportunities (*130*).

4.4 Discrimination and stigmatization

The issues central to debates concerning HIV testing—such as discrimination, psychological trauma, and stigmatization—reverberates in discussion surrounding genetic testing (*176*).

As has been seen with the HIV/AIDS epidemic, the combination of lack of treatment, low levels of public education about the disease and fear of stigmatization can create informal barriers to people seeking testing. For the 40 million people living with HIV/AIDS, particularly those in developing countries, stigmatization and discrimination discourage many individuals from seeking treatment for, and information about, the disease. As the United Nations Educational, Scientific and Cultural Organization (UNESCO) has stated, "Many are even afraid to take the AIDS test because of the shame associated with the pandemic" (*238*). This same pattern of stigmatization and fear has been observed in response to some genetic testing and screening programmes. The informal barriers arising as a result of systemic stigmatization and discrimination of those affected by genetic conditions breach the principle of distributive justice, because while services may be available within a community, some people have their access to those services unjustifiably and unfairly restricted.

The potential for discrimination and stigmatization as a result of genetic testing has been a primary focus of debates regarding ethics, regulation and

legislation in developed countries. However, in these countries, the focus has generally been on discrimination in relation to insurance or employment. While these are also relevant concerns in many developing countries, there is the additional concern of discrimination in relation to marriage, and this is a burden that is expected to fall disproportionately on women.

4.4.1 Arranged marriage

Arranged marriages and arranged introductions are common in communities throughout India, Pakistan, Sri Lanka, the Middle East, and parts of Africa, as well as in certain communities living in other regions, such as the Orthodox Jewish community. Many cultures that favour arranged marriages also favour consanguineous and endogamous marriages.

The formal process of arranging marriages or introductions can provide a window for genetic screening services to be offered to the population in question. Premarital screening can provide individuals and couples with greater reproductive choice. If genetic screening is conducted prior to partner selection, available reproductive choices include (a) the decision to change reproductive partner; (b) the decision not to have children or to adopt; (c) the decision to request pre-implantation diagnosis or prenatal diagnosis; or (d) if prenatal diagnosis identifies an affected fetus the parents can choose to prepare for the management of the disorder or to terminate the affected pregnancy.

Throughout the report we argue that sensitivity to the local socio-cultural context can improve the efficiency of genetic testing and screening programmes. However, it is important to point out that the process of *non-voluntary* arranged marriage contravenes the human rights principle of free and full consent in marriage. The *Universal Declaration of Human Rights* states that "Marriage shall be entered into only with the free and full consent of the intending spouses" (*225*, Art. 16(2)). Although the report discusses strategies for minimizing discrimination as a result of genetic testing and screening programmes in communities where arranged marriages are popular, we recognize that *non-voluntary* arranged marriage breaches human rights and do not endorse this practice. However, it should also be noted that many arranged marriages are voluntarily entered into.

Empirical evidence suggests that premarital screening and discovery of mutual carrier status for a particular disorder often does not lead couples to separate and choose other partners. For example, in the Islamic Republic of Iran, where many marriages are arranged, more than 50% of couples who discover they are at risk of passing on a recessive genetic disease to their children still marry, and then utilize prenatal diagnostic services (*16*).

Arranged marriages and the stigmatization of female carriers of genetic diseases

While premarital screening can increase reproductive choice, it can also lead to physiological and emotional stress and strain within the relationship, in addition to social discrimination and stigmatization. These negative repercussions need to be acknowledged and minimized. Where marriages are arranged, families may be less inclined to match their children with a person who is known to be a carrier for a genetic disease. In some communities, this may lead to stigmatization of carrier individuals. In societies where women are not treated as equal to men, the burden of stigmatization and discrimination due to carrier status for genetic diseases can disproportionately affect women.

One effect of this discrimination is that in communities favouring arranged marriage or introductions, women identified as carriers of a genetic disorder may be unable to find a husband.[5] In research concerning the screening of extended families for haemoglobin diseases in Pakistan, a country where arranged marriages are common, Ahmed et al. found that the parents of women found to be carriers preferred to postpone testing of the partner until after marriage and then to use prenatal diagnosis. This option is obviously more suited to

communities, such as Pakistan, that permit abortion of affected fetuses (*4*).

Concerns regarding the eligibility of female carriers can also arise in developed countries. Some conservative subsections of the Ashkenazi Jewish communities continue to favour arranged introductions. In addition, this community experiences a high prevalence of a number of recessive genetic diseases. Therefore fears have been expressed that carrier screening could lead to the discrimination of female carriers by creating "a class of unmarriageable women" (*219*).

The potential for discrimination against carriers, particularly women, is a significant threat to the equitable and fair integration of genetic carrier screening in developing, as well as developed, countries.

Responses

There are a number of responses to this potential form of discrimination. The Dor Yeshorim genetic screening model described below (**Community example**) offers an example of a response to this concern in developed countries. The student screening programme for genetic blood diseases in the Kingdom of Bahrain (section 4.7.1) presents a different approach based on community education (*27*).

Community example
"Dor Yeshorim" as a response to the specific cultural needs of the Ashkenazi Jewish population

A range of specific genetic diseases occur at higher prevalence in the Ashkenazi Jewish population. One example is Tay Sachs disease, a degenerative neurological disorder that follows an autosomal recessive inheritance pattern. One in 25 Ashkenazi Jews are carriers for the disease, and screening for the mutation is well established. The strict Orthodox Jewish community has specific social and cultural requirements for a successful genetic screening programme because they do not endorse prenatal diagnosis or abortion. In this community, marriage often arises as a result of an arranged introduction undertaken by parents, with the support of a professional matchmaker (*70*).

In response to demand for carrier screening, a private international organization called Dor Yeshorim was established in the United States in the late 1980s to provide pre-introduction screening of teenagers for Tay Sachs disease (*150*). The service now includes carrier testing for up to 10 genetic diseases.* In the United Kingdom in 2004, the set of tests cost £150.

One major concern raised in relation to the screening programme was the potential stigma that detected carriers, particularly women, could suffer and how this might affect their chances of being introduced to potential partners. The programme developed an innovative solution to minimize stigmatization and discrimination of identified carriers: test results remain confidential, even to the individual and their family (*84*). Each blood sample is given a code number and the results are stored in an international database only under the code, which is given to individuals and their parents. Prior to an introduction, the codes of both potential partners will be given to the professional matchmakers who will submit them to Dor Yeshorim for analysis. The matchmaker, and subsequently the families, will receive one of two responses: *compatible* or *incompatible*. If the result is *incompatible,* the introduction will not occur but neither family will know for which of the 10 diseases their child is a carrier.

* Including Tay Sachs Disease, cystic fibrosis, Canavan Disease, Fanconia Anemia Familial Dysautonomia (Riley-Day Syndrome), Glycogen Storage (Type 1a) / Von Gierke Disease, Bloom Syndrome, Gaucher Disease (on demand only).

See Chicago Centre for Jewish Genetic Disorders, *Dor Yeshorim*, http://www.jewishgeneticscenter.org/genetic/doryeshorim/ (accessed 15 April 2005).

The Dor Yeshorim service has successfully reduced the birth of children affected with the recessive genetic disorders it screens for, and provides an innovative example of the way in which genetic services can be adapted to the cultural and social requirements of different communities. There are, however, valid concerns with this approach. Keeping the test results confidential does not tackle and may, in fact, perpetuate, the underlying stigma associated with genetic disease. Furthermore, the strict rules regarding confidentiality run contrary to the principle of autonomy because patients are not allowed access to the results even if they request them. In the absence of viable alternatives—except to undergo testing for each disorder independently, which can often be restrictively expensive and time consuming—the confidentiality clause can seriously impede individuals' autonomy. This limitation can be very frustrating for individuals who wish to know their carrier status. Some have argued for the availability of publicly funded alternatives to the Dor Yeshorim model to increase choice among the Ashkenazi Jewish population (*144*).

By contrast, the student screening programme for genetic blood diseases in the Kingdom of Bahrain (see Case study 5) represents a different response to the potential discrimination of carriers in marriage. It relies on a system of comprehensive community education to address stigmatization and discrimination, rather than strict confidentiality of test results. This approach has been very important in addressing the initial public resistance to the screening programme because of concerns that girls found to be carriers would not be able to find husbands. The programme includes an education campaign targeted at teachers, parents and children, which emphasizes that (a) all people carry some defective genes; (b) if a carrier married a non-carrier they would be able to avoid the heightened risk of giving birth to an affected child; (c) that although carriers were *advised* to marry non-carriers instead, they were not *prevented* from marrying other carriers.

By relying on a comprehensive education programme to reduce stigma and discrimination of carriers, public understanding about genetic disease—how it is passed on and how it can be treated or prevented—is likely to increase.

Some research suggests that the potential for discrimination may be lower in communities that favour consanguineous marriage, such as the Kingdom of Bahrain, because of the highly cohesive and mutually supportive nature of family and community structures. A study of South Indian families at risk of familial adenomatous polyposis concluded that this tight knit, supportive social structure might result in less stigmatization of affected and carrier individuals (*214*:59–60).[6]

4.4.2 Regulation

Anti-discrimination regulations in countries are founded on the principles of fundamental human rights, which are enshrined in regional (see, e.g. *57; 181; 182*) and international instruments (see, e.g. *225; 226; 227; 229; 228*). Countries that have ratified international human rights treaties have taken on an obligation to give effect to the rights contained within these documents through their national legal systems. Several international human rights documents address the issue of genetic discrimination. The UNESCO 2003 *International Declaration of Human Genetic Data* asserts that every effort should be made to ensure human genetic data are not used for purposes intending or having the effect of infringing upon human rights, fundamental freedoms or the human dignity of an individual (*236*, Art. 7(a); *237*, Art. 6). The Council of Europe also addresses genetic information in the *Convention on Human Rights and Biomedicine;* however, it uses the more general wording "[a]ny form of discrimination against a person on grounds of his or her genetic heritage is prohibited (*57*, Art. 11)".

A number of developing countries have introduced legislative measures to discourage or prohibit discrimination and stigmatization, some of which focus on discrimination specifically related to medical conditions or genetic disease. In Georgia, for example, discrimination on the grounds of genetic heritage is prohibited (see section 4.5.1 for further details) (*140*, §31).

Other countries have enacted more general prohibitions of discrimination on the grounds of health status. Under the law of Peru, individuals have the right not to be discriminated against for suffering a disease or disorder (*82*, r15). The Fijian Constitution prohibits discrimination on the basis of disability, which could include genetic disease (*54*, §38). Similarly, the Constitution of Ghana guarantees freedom from discrimination (*55*, §17).

4.5 Privacy and confidentiality

As noted in the previous section, there are genuine concerns that people who are affected by a genetic disease, or are disease carriers, may suffer stigmatization and discrimination. As an example, the previous section discussed the potential for discrimination against women in countries that favour arranged marriage, and the stigmatization suffered by thalassaemia patients in Sri Lanka is discussed in Case study 3.

Privacy and confidentiality standards are a vital tool for protecting individuals from possible discrimination and stigmatization on the basis of a genetic disorder. Both the right to privacy and the right to confidentiality can be derived from the principle of autonomy. Autonomy, broadly understood, is the capacity of self-determination: based on the idea of a region of sovereignty for the self and the right to protect it by restricting access (see also Autonomy 4.6.1) (*24*). Protecting privacy is one aspect of protecting the realm of personal space (*75*). Privacy, fully conceived, can include all things that fall within this personal space—bodily integrity, mental space, personal relationships, and personal information. Privacy is often defined, more narrowly, as relating exclusively to information about a person. For the purposes of the following discussion, we are interested in this narrower definition, though in the context of genetic testing, privacy and confidentiality rights can extend to the right not to disclose information to third parties and the right not to undergo testing.

Privacy and confidentially are two related, overlapping, but distinct concepts. The difference is:

An infringement of X's right to confidentiality occurs only if the person to whom X disclosed the information in confidence fails to protect the information or deliberately discloses it to someone without X's consent. By contrast, a person who without authorization enters a hospital record room or computer databank violates rights of privacy rather than rights of confidentiality (*24*).

Privacy and confidentiality may be particularly important in countries where genetic diseases are not well understood and where widespread knowledge of an individual's genetic status (such as the fact that a woman is a carrier for a disorder) may affect them socially.

The limit of an individual's right to confidentiality of genetic test results is a question that generates controversy. In Australia, Canada, New Zealand, the United Kingdom, the United States, and many European countries confidentiality is currently considered to be paramount, and full consent must be received before any information is disclosed to third parties *(175; 110; 107; 106; 109).* However, because genetic information may affect an entire family, rather than only the individual, the information revealed by genetic testing may be relevant to the health of people beyond the patient themselves. In many cultures, especially in highly endogamous or consanguineous communities, and where arranged marriage is the norm, a genetic disease may influence, not only the marriage prospects of the affected individual, but potentially all members of the extended family. Under such circumstances, it may be necessary to balance respect for patient confidentiality against the needs and considerations of other family members for whom information about genetic risk could influence decision-making about their own health or reproduction. Achieving this balance is a challenging task and is rightly the responsibility

of national governments, who should consider the risk of discrimination to the patient and the potential harm to other family members within that local context.[7]

4.5.1 Regulation

International human rights documents state that individuals should be protected from unauthorized disclosure of genetic information (*236*, Art. 14(a), (c)–(e); *237*, Art. 7; *57*, Arts. 4, 10(1)) and assert a patient's right to be informed of genetic test results (*236*, Art. 10; *237*, Art. 5(c); *57*, Art. 10(2)). Also addressed are issues of authorized disclosure, and unauthorized disclosure to third parties for public interest reasons (*236*, Art. 14(b); *237*, Art. 9; *57*, Art. 10(3)).

Legislative measures in this area seek to ensure that medical practitioners and people with access to sensitive medical and genetic information are prevented from disseminating that information to other family members or more widely. Legislation may also provide sanctions to encourage compliance. One example of a developing country that has introduced such protection is Georgia, which has passed laws to protect citizens' health care rights and to ensure the inviolability of citizens' dignity and privacy (*140*, §1). These are outlined in **Country example 7**.

Country example 7
Patient rights in Georgia

Since 2000, Georgian citizens have enjoyed the right to information about proposed procedures, the results of medical examinations, alternative treatments, diagnosis and prognosis and the right to determine with whom this information may be shared (*140*, §18, 21). Health care providers are also required to maintain a patient's confidentiality (*140*, §27).

In Georgia, informed consent is required for the lawful provision of a medical service, which would most likely include a genetic test (*140*, §22). Genetic testing to identify a genetic disorder or predisposition to a disorder may be carried out only for the purposes of the patient's health care or for health-related scientific research (*140*, §32). Together, these two provisions work to ensure that only necessary, voluntary genetic testing will occur.

Other countries, for instance Peru (*82*, r15) and Argentina (*138*, r2(f)) have passed more generic privacy and confidentiality laws that do not focus on genetic information specifically, but which may cover it. As an example, Peruvian law states that all users of health services shall have the right to respect for his or her person, dignity and privacy and to demand confidentiality of his or her medical information (*82*, r15). Turkish law holds that "the patient may request that data concerning his state of health are not communicated to himself, to his family, or his associates" (*207*, §20) and that "[r]espect for a patient's privacy is a fundamental principle". The law further states that "[e]very medical procedure shall be carried out in such a way that the patient's privacy is respected" (*207*, §21).

The implementation of the privacy legislation and regulations discussed above is commendable; however, it should be acknowledged that there is the potential for discrepancies between law, policy and practice. Enforcement can often depend on a number of factors relating to the status of the individual whose rights have been breached (including socioeconomic, ethnic or other status). In settings where female carriers are stigmatized and where there are social repercussions for the reputation of the family, any further publicity of test results is likely to serve as a significant disincentive to people bringing cases to court or even reporting a breach of confidentiality or privacy. Women may be especially disadvantaged in this respect as they may be unable to access mechanisms for remedying discrimination on the basis of gender. For example, in some countries women may lack legal standing to bring complaints or face bias within the legal system. They may also be unable to access mechanisms to report and remedy discrimination due to restrictions on their access to public spaces or illiteracy (*239*).

4.6 Facilitating patient decision-making

The WHO *Genomics and World Health* report states that the importance of developing genetic services worldwide, including public education and genetic counselling, cannot be overemphasized (*268*). The report warns against introducing medical genetic services in the absence of public education and without the support of genetic counsellors (*268*). In 1993, a WHO scientific group endorsed the following principles of genetic counselling: (a) the autonomy of the individual or couple, (b) their right to full information, and (c) strict confidentiality of genetic test results (*276*).[8]

4.6.1 Autonomy

Individual autonomy refers to the capacity to be one's own person; to live one's life according to reasons and motives that are one's own and not the product of manipulative or distorting external forces (*50*). Autonomy is also described as a second-order capacity of persons to reflect critically on their first order preferences, desires and wishes, and the capacity to accept or to attempt to change them. By exercising such a capacity, persons define their nature, give meaning and coherence to their lives, and take responsibility for the kind of person they are (*69*). The principle of autonomy in the context of health care draws attention to the fact that each individual has personal beliefs and values, and their own life plan; it states therefore that competent individuals are in the best position to make decisions regarding potential medical interventions. The value of autonomy is ultimately based on respect for persons, and the preservation of their dignity.

In health care, respect for autonomy is typically contrasted with paternalism. Paternalism is "…the intentional overriding of one person's known preferences or actions by another person, where the person who overrides justifies the action by the goal of benefiting or avoiding harm to the person whose will is overridden" (*24*). While in many cultures doctors have traditionally played this role in relation to their patients (*211*), autonomy is now widely accepted as a core ethical principle of medicine. Respect for autonomy emphasizes the value of a competent individual's informed and voluntary decisions (*47*). However, as noted earlier, the gap between policy and practice can be wide, and in many countries paternalistic medical structures persist. Women may be especially vulnerable to paternalism in medicine, particularly if they are illiterate or have had limited access to education, and/or live in societies where gender norms constrain women's autonomous decision-making and encourage women to defer to authority, particularly male authority.

A requirement of autonomy is the practical ability to act on decisions. In practice, autonomous choice depends on the availability of economically, socially and legally viable alternatives. Limited resources—both material and human/personal and societal—can significantly limit the scope of autonomy. Further, social expectations based on sex, class and ethnicity can affect the availability of viable alternatives.

4.6.2 Informed consent

The principles of informed consent in the context of genetic testing are upheld in several human rights instruments (*237*, Art. 5; 236, Art. 6(d)). Obtaining informed consent to genetic testing and screening is essential to promote individual autonomy in medical decision-making.[9] The process of gaining informed consent aims to ensure that the individual understands the relevant information (medical, social and/or legal) and that their decision to undergo any medical intervention is made voluntarily. Valid informed consent for genetic testing requires a bilateral process involving a dialogue of questions and answers between the individual considering testing and the person obtaining informed consent (often a health care professional). This dialogue requires the person obtaining informed consent to gauge the appropriate level of language and technical detail suitable for the individual's understanding.

See **Box 5**.

Box 5
Recommendations for gaining informed consent for genetic testing

1. Preconditions

The person considering testing should be:

- **competent** to make autonomous decisions (for example, children and persons with mental impairment may or may not be considered competent; local laws and regulations often provide further guidance on the requirements for competency);
- aware that the decision to undergo testing is **voluntary;** and
- substantially **free from control** by others (for example, there should be no coercion, subordination and undue influence).

2. Information and understanding

2.1 Disclosure of information relevant to the individual's decision-making. This will differ according to the needs of each individual but should contain an explanation of the following elements:

a) The purpose of the test, including an explanation of the condition(s) to be tested for: invite the individual to explain any previous experience they have had with the condition (personally, or through family and friends).

b) The clinical validity of the test: the capacity of the test to predict a particular clinical outcome.

c) The clinical utility of the test: if the test is positive, the potential treatment options for the tested person.

d) The logistics of testing: including (a) whether fees will be charged; (b) where, and how testing will be done; and (c) the appropriate window for testing; how long does the individual have to decide whether to undergo testing?

e) The medical implications of the test results for the individual and family.

f) The potential benefits and risks: including social and psychological factors associated with (a) taking the test; and (b) declining the test.

g) Discussion of the alternatives to genetic testing.

h) Discussion of confidentiality: who will have access to test results and where will results be stored?

i) Discussion of the issue of non-paternity: if there is a possibility that the test will uncover non-paternity, an explanation is given of how non-paternity issues will be handled.

j) Statement that social risks may include discrimination by insurers and employers (even though this may be illegal). Explanation of the relevant laws and regulations currently in place.

k) Statement that whatever decision individuals and families make, their care will not be jeopardized.

The above information should be presented in an unbiased manner (as far as possible).

2.2 Understanding. This ensures that the individual has understood the information outlined in 2.1. This will require a two-way dialogue between the person considering testing and the person gaining informed consent. The person obtaining consent should do the following:

a) Question the individual to assess whether they have understood this information; if not repeat 2.1 and 2.2 until understanding is achieved.

b) Ask the individual whether they have any questions and provide answers to the individual's questions or refer them to someone who can.

c) Offer to provide relevant written material (*ideally* written information should always be available).

3. Consent

3.1 Decision. The individual makes an autonomous decision to undergo or refuse testing. Individuals may choose not to make an immediate decision or may subsequently change their mind; even after the test has been performed individuals may chose not to receive the test results.

3.2 Authorization. This is the formal process of recording the individual's informed consent to undergo testing, usually in writing. Specific authorization forms differ between institutions; however, it is good practice for these forms to include a record of the issues discussed prior to consent.

...Box 5

Sources: Some elements of this list are taken from the following references. Beauchamp TL, Childress JF (1994). P*rinciples of biomedical ethics*, 4th ed. Oxford, Oxford University Press. World Health Organization Human Genetics Programme (2001). *Review of ethical issues in medical genetics: report of consultants to WHO by Professors DC Wertz, JC Fletcher, K Berg.* Geneva, World Health Organization (WHO/HGN/ETH/00.4):44. McKinnon W et al. (1997). Predisposition genetic testing for late-onset disorders in adults: a position paper of the National Society of Genetic Counsellors. *JAMA: Journal of the American Medical Association,* 278(15):1217–1220.

The model in **Box 5** is generic, and specific practices may need to be altered to suit the local circumstances. For example, some individuals presenting for testing may be illiterate, in which case information will need to be provided in a way that they can understand (for example, pictorial representations and diagrams), and authorization may be satisfied by means other than a signature, such as a thumbprint. While specific practices like these may vary, the fundamental principles underlying this model should be adhered to. For example, illiteracy is not an excuse for doing away with authorization.

Informed consent in developing countries

Most developed and some developing countries have enacted legislation requiring that informed consent is obtained for medical procedures, including genetic testing.

Under Peruvian law, consent is required for medical treatment, except in the event of an emergency (*82*, §4). Each person must be given all information necessary to give informed consent or refusal prior to any treatment. This includes the right to receive comprehensive and comprehensible information about his or her condition, including diagnosis, prognosis, alternative treatments and the risks associated with treatments prescribed and administered (*82*, r15). Individuals also have the right not to be subjected to non-consensual examination or treatment (*82*, r15).

The Public Health Code of Guinea requires that individual autonomy and the right to self-determination of all people be respected in relation to health care (*139*, §238). Turkish law contains various provisions designed to promote autonomous choice in medical treatment (*207*, §5, 7, 8, 9, 12). The Fijian Constitution holds:

> that every person has the right to freedom from scientific or medical treatment or procedures without his or her informed consent, or, if he or she is incapable of giving informed consent, without the informed consent of a lawful guardian (*54*, §25).[10]

4.6.3 Counselling

The place of genetic counselling in medical genetic services is discussed in section 3.4.1. Genetic counselling is the process by which individuals at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and the ways in which this may be prevented, avoided or ameliorated (*99*). It is an acknowledged standard of practice that this be done in a respectful, non-directive and confidential manner (*236*, Art. 6(d); 175). Genetic counselling is a service which aims to respect, protect and foster individual autonomy when decisions are made regarding the use of medical genetic services, for example genetic testing. The primary role of genetic counsellors is to facilitate autonomous decision-making.

Many developed countries have established training programmes to generate specialized genetic counsellors to work alongside clinical geneticists in providing tertiary-level genetic services. In these specialist tertiary care settings, a genetic counsellor works within a multidisciplinary team and acts as the primary liaison between the

patient and other medical professionals. Genetic counsellors can also act as a knowledge resource and educator for other health professionals, as well as the general public.

In most developed and developing countries there is a severe shortage of genetic counsellors. Inequities in access to genetic counselling should be tackled with proper funding and training of different kinds of health professionals at the primary health care level. Case study 3 illustrates the crucial role played by genetic counselling and individual and family education in improving the quality of life of thalassaemia patients in Sri Lanka.

Case study 3
Social and ethical issues posed by thalassaemia in Sri Lanka

Background

In the late 1990s, with the help of outside funding and collaboration between Oxford University and the University of Toronto, a national thalassaemia treatment centre was built in Kurunegala, Sri Lanka, and a central diagnostic laboratory was established at Ragama. This site was selected because, although thalassaemia occurs in many communities throughout Sri Lanka, by far the largest number attend the government hospital at Kurunegala, where close on 500 patients are registered. After a preliminary study to assess the frequency of thalassaemia throughout the country, patients attending the main centres were fully genotyped. It was found that between 10 and 30% of the patients had Hb E-â-thalassaemia while the rest had transfusion-dependent â-thalassaemia major. Blood is available for transfusion and the government supplies desferrioxamine,* although there has been a shortage of the drug at times and an even greater shortage of pumps to administer it. The quality of clinical care and documentation in Kurunegala is now quite high, although there is much work to be done in the other centres in the country.

As the programme evolved, it became clear that counselling and support for the families of thalassaemic children would be critical and that the Sri Lankan doctors looking after these patients would have very limited time for this purpose. For these reasons, it was decided to try to conduct a pilot programme to examine the social consequences and related ethical issues affecting the thalassaemia population in Kurunegala.

There are very few trained counsellors, and even fewer genetic counsellors, in Sri Lanka. However, the centre became aware of the work of the Reverend Father Anthony Fernando, who obtained his PhD in psychology in the United States. Father Anthony runs a 12-month formal course in counselling, though not specifically genetic counselling, at the University of Peradeniya. One of the students on this course, Mr H.G. Sampath, joined the National Thalassaemia Centre in Kurunegala, first on a voluntary basis, and then with some small financial help from the local Parents' Thalassaemia Association. He sees all the patients and their families in the clinic and has been able to make a number of home visits. The latter is extremely difficult because many of the patients live long distances from the hospital in villages that can only be reached by bus.

Initial report on pilot programme

Some of the major findings of a preliminary report by Mr Sampath, written three years later, are summarized in the following sections.

Patients: Thalassaemic patients are sometimes isolated in society and, in the past, when blood for their transfusions had to come from their family members, they were labelled 'blood suckers'. As a result of adverse public responses to their disease, a proportion of the children do not attend school and adolescent patients tend to drop out of school and disengage with society. This is exacerbated by the schools' tendency not to allow the thalassaemic children to take part in extra-curricular activities. The preliminary report notes that there is also a tendency for the children to despise their parents as they get older, and many blame them for their disease. Particular stresses occur among children who are born into families with unaffected children as this seems to add further to their exclusion from family life. In families with multiple affected children, the death of one causes severe psychological trauma to the remaining child(ren).

Parents: Preliminary counselling in the hospital has clearly done little to increase understanding of thalassaemia among many of the parents and families. Husbands tend to blame their wives for the disease in their child. There are misconceptions about the cause of thalassaemia and it is widely believed that it results from drugs administered during pregnancy. A considerable number of the parents have resorted to local healers and there is an increasingly high frequency of depressive illness with several suicides among the mothers. These problems have been exacerbated by other family strains including the diversion of the mother's attention to the chil-

...Case study 3

dren at the expense of the husband, and a decrease in the wife's sexual responses due to stress or fear of bearing another thalassaemic child.

Challenges

It is clear that the initial time-consuming explanation of the nature of genetic disease, and the patterns of its inheritance are still very difficult for much of the population to understand. It is also extremely difficult to persuade people found to be carriers that the heterozygous state is not a 'disease'. Women feel particularly isolated when they are found to be carriers because in a society with a large number of arranged marriages, they feel they may never marry. There have been preliminary debates on the possibility of developing prenatal diagnosis programmes but termination of pregnancy is illegal in Sri Lanka (even though a very large number of terminations occur annually). Despite these concerns and the pressures on the clinics, disease management is improving, as is the morale of patients in Kurunegala.

There is an urgent need to train counsellors in developing countries. A counselling course has been developed in Sri Lanka, by the Department of Clinical Genetics in Colombo, and it is planned to try to obtain at least one fully trained counsellor for each centre on the island. A great deal more research needs to be undertaken into the best ways of educating populations, particularly those with little formal education, about the complexities of genetic disease. This work needs to be followed up by an equally careful assessment of the outcomes. Above all, it is clear that because of the complex social structures of different societies in developing countries, it cannot be assumed that methods that are used in high resource settings will be applicable. At least from the very preliminary observations in Sri Lanka, it appears that the social and ethical problems raised by the thalassaemias, and their effects on families, have been grossly underestimated in our thinking about the development of thalassaemia services.

* Desferrioxamine is a medicine that binds to excess iron in the body and allows it to be excreted, therefore avoiding excess iron build-up in the body which results from regular blood transfusions.

...Case study 3

This study of a pilot assessment is based on information provided by Professor Sir David Weatherall, University of Oxford, UK, in collaboration with: Professor Nancy Olivieri, University of Toronto, Canada; Dr Shanthimala de Silva, Colombo, Sri Lanka; Dr A Premawardhena, Ragama, Sri Lanka; and Mr HG Asanka Sampath, Kurunegala, Sri Lanka (reference: 65)

As highlighted in Case study 3, there is not only a serious shortage of clinical geneticists in many developing counties, but also a lack of trained genetic counsellors. In developing countries it is often primary care community health workers, nurses or relevant specialists (often without training in genetic counselling) who take on the role of genetic counselling. Genetic counselling has been a commonly identified challenge in developing countries, despite acknowledgement that it is an essential component of genetic testing and screening programmes *(3; 161)*. Although a challenge, Christianson and Modell argue that basic genetic counselling remains both "feasible and increasingly necessary in primary health care" (*48*:239). Research has revealed gender differences in counselling which suggest that individuals and families should *ideally* be offered the opportunity to meet with counsellors of both genders in order to cancel out possible gender biases (*254*). In countries with a significant shortage of trained genetic counsellors this will not be an immediately realizable goal, therefore training programmes should actively try to recruit both men and women. Country example 8 provides an example of a developing country's attempt to upscale capacity for genetic counselling.

Country example 8
Scaling up genetic counselling capacity in Saudi Arabia

Premarital screening for sickle cell disease and ß-thalassaemia is now compulsory in the Kingdom of Saudi Arabia (*161*).* This screening programme has apparently been well-received by the community because it allows couples to make informed decisions about marriage with knowledge of the reproductive risks and prenatal options, and it has not been linked to enforced prevention of genetically at-risk marriages.

However, the current lack of genetic counsellors in the Kingdom of Saudi Arabia poses an immediate problem for preventive programmes designed to reduce the occurrence of genetic diseases (*161*). As an interim solution, short intensive training programmes for medical and health science professionals are being established (*161*). These are typically conducted at major hospitals on an *ad hoc* basis, although a national training programme for genetic counsellors is under consideration. The Medical Genetics Department at the King Faisal Specialist Hospital Research Centre is establishing a short generic genetics training programme; the Diabetes Centre at the King Abdul Aziz University Hospital in Riyadh runs an intense diabetic educators' programme for individuals working in diabetic care. Both of these courses specifically address genetic counselling and include presentations by qualified genetic counsellors. Health professionals involved in the compulsory premarital screening programme for sickle cell disease and thalassaemia receive instruction in the genetics of these diseases (*160*). It is envisaged that professionals who receive training in these programmes will work alongside qualified medical professionals to provide basic genetic counselling (*161*).

* However, we argue in this report that participation in genetic testing and screening programmes should be voluntary (see also *267*:38–9; *224; 51)*.

Directive counselling

As noted above, a well accepted goal of genetic counselling is the promotion of autonomy and human dignity by assisting people to make independent and voluntary decisions (see, e.g. *175*, Section II).

However, in practice pure non-directiveness can be difficult if not impossible to achieve. Both counsellors' unavoidable personal views and biases, and patients' expectations that their physician will offer advice, can present challenges to the principle of non-directiveness. It is therefore important to distinguish between (1) medical knowledge, experience and advice, on the one hand; and (2) personal values, life plans and autonomous decisions, on the other. Physicians can and should offer *medical* advice, and this guidance may be very helpful for the individual or couple. In offering this advice physicians should be aware of their own biases and should not attempt to manipulate the values or the decision of the couple.

Decisions are made, not only on the basis of knowledge, in this case medical knowledge, but also personal values. It is for this reason that the individual should make the final decision about the appropriate course of action for them. There may be a role for physicians to challenge the couple's decision to ensure that it is autonomous and that they have deliberated sufficiently about the available choice. Despite ongoing debate about the precise standards of non-directiveness, the essential point is that counsellors and physicians should present information in as unbiased a manner as possible; should not attempt to manipulate the individual's or couple's decision-making process; and should respect the autonomous decision of the individual or couple.

Directive genetic counselling is thought to be a widespread problem, occurring not only in countries that appear to endorse this approach but also those that formally discourage or even ban this practice. The directive nature of genetic counselling in China has attracted attention. In 1995, the Chinese Law on Maternal and Child Health Care came into effect. International concern focused on articles 10 and 18. Article 10 states that after providing a premarital physical check-up, physicians should inform the couple if they have been diagnosed with a genetic disease that is "considered inappropriate for child bearing from a medical point of view" (*154*, Art. 10). The

couple may then be married only if they (a) agree to long-term contraception or (b) undergo a tubal ligation, hysterectomy, or vasectomy.[11]

In addition, Article 18 of the Maternal and Child Health Law states that the physician shall give the couple "medical advice for termination of pregnancy" if (1) the fetus is suffering from a genetic disease of a serious nature; (2) the fetus is found to have a defect of a serious nature; or (3) the continuation of pregnancy seriously endangers the life of the mother (*154*, Art. 18). However, it should be noted that there are no enforcement mechanisms in place for this law, and it is viewed more as a standard of care (*202*; *267*).

This approach to counselling appears to be directive. The language used—at least in the translations accessed by WHO (see, e.g. *153*; *141*)—is not restricted to informing, warning, or supporting the couple to make an independent choice but extends to offering specific advice to terminate the pregnancy. Whether in practice, this results in directive counselling, depends on whether the advice is limited to unbiased medical information or extends to trying to influence the couple's values and their decisions regarding abortion.

One possible motivation for this approach to counselling is the public benefit of reducing the health burden of congenital diseases (*220*). For example, Chinese Minister of Public Health Chen Minzhang has stressed that "the cost of looking after those with hereditary handicaps was enormous, imposing a heavy burden both on the state and on millions of families" (*247*). In developed, high-income countries with good public health infrastructure, the cost of caring for a child born with a genetic disorder is often carried, partly or fully, by the state. However, in many developing countries neither families nor governments have the financial resources to care for and support a significant number of children with severe genetic disorders. In India, for example, prenatal diagnosis (PND) is seen as an important preventive measure to reduce the burden of ß-thalassaemia (*79*). It has been reported that after PND parents are counselled to continue the pregnancy only in the case of unaffected fetuses *(2)*.

Prevention is indeed an essential part of comprehensive medical genetic services, but this perceived tension between care and prevention represents a false dichotomy (see 3.4). As programmes in Cuba, Cyprus, the Islamic Republic of Iran and Thailand demonstrate, prevention of the occurrence of genetic disease and care of those affected go hand in hand *(264; 191; 48)*. Appropriate care for affected individuals reduces stigma and increases trust in the public health system, thereby improving the effectiveness of prevention programmes; while effective prevention programmes free resources for the care of individuals with the disease. Furthermore, evidence suggests that a high proportion of couples will voluntarily choose to terminate pregnancies that are affected by a severe genetic condition when safe abortion services are available *(4)*.

Another possible reason for the use of directive counselling in developing countries may be the pervasive tradition of paternalism in medicine. For example, where there are high rates of illiteracy among the general public, many physicians take a paternalistic stance that it is their duty to direct a less-educated population (*255*). Some individuals expect to be told what to do by their doctors (*211*:774), and so do not question this directive approach. There is an important distinction, however, between making an autonomous choice to accept medical advice from a physician, and a prima facie assumption that it is the physician's role and responsibility to decide what interventions are in their patients' best interests. Sub-populations with lower rates of literacy, typically women and those of a lower socioeconomic strata, are more likely to experience medical paternalism. Despite the pervasiveness of the paternalistic approach to health care in many countries it is important to re-emphasize the value of autonomy.

Decisions regarding health and reproduction are deeply personal and are typically made based on both information and values. While health care professionals should offer advice regarding the

known health consequences of specific interventions, patients themselves are in the best position to know their own personal values. It is important that once health care professionals have discussed the medical implications of potential treatment options with the patient, the patients are then encouraged to make autonomous decisions.

4.6.4 Patient support organizations

Support organizations worldwide provide valuable resources for both patients and health care providers. Support groups often have the most up-to-date information on genetic research and available tests and treatments, particularly for rare genetic diseases. Such groups are valuable in providing long-term support for affected persons, and can be very effective when working alongside regional genetic services. They can provide a good network for collecting and coordinating funds for research and other resources. For example, the local Parents' Thalassaemia Association in Kurunegala, Sri Lanka, raised funds for a counsellor to be employed for the patients and families receiving treatment at the National Thalassaemia Centre in Kurunegala (see **Case study 3**). Support organizations can also act as a platform for communication with affected communities, especially those that have difficulty accessing genetic services. They can facilitate the recruitment of research subjects, contact large family groups and disseminate new information.

Even developed countries have a shortage of specialized genetic counsellors, and therefore such services are often supplemented by patient support organizations. For example, the majority of public education about Tay Sachs disease in the United Kingdom is conducted by volunteers from the charitable organization Jewish Care. While the organization currently seems to be able to fulfil the education needs of those affected by the disease, the situation does raise the question of whether governments and public health systems should be relying on a charity or volunteer organization to provide disease education and counselling for affected families and their communities (*144*).

Parents' associations have played a fundamental role in improving ß-thalassaemia treatment and population screening in many Mediterranean countries over the last 25 years. The thalassaemia prevention strategy in Cyprus consists of four interdependent techniques: (1) public education, (2) population screening, (3) genetic counselling and (4) PND (*18*). The programme is extremely successful, and cases of thalassaemia declined by 97% between 1975 and 1984 (*44*). Part of the success of the programme has been attributed to the very active parents' association and the supportive role of the Orthodox Church (*44*). The Cyprus Parents' Association argued strongly in favour of a premarital thalassaemia certificate. In 1983, the Orthodox Church, although it does not support termination of affected pregnancies, agreed to the prerequisite that all couples undergo carrier screening for thalassaemia and receive genetic counselling prior to marriage. Carrier–carrier couples are not prevented from marrying *(96; 44)*.

The Thalassaemia International Federation (TIF) was established in 1986, by a small group of thalassaemia patients and parents from Cyprus, Italy, the United Kingdom and the United States. TIF works to improve awareness and support prevention of thalassaemia and promote clinical management of affected patients. TIF also collaborates with governments and official health bodies, such as WHO. TIF runs regional and national workshops on the treatment and prevention of thalassaemias, including genetic counselling; produces education material for patients, families and physicians around the world (which is distributed free of charge); and provides networks for health professionals involved with thalassaemia care, among other activities.

Case study 4 illustrates the essential role that patient support organizations can play in low-resource settings.

Case study 4

Role of a patient support organization in sickle cell disease diagnosis and treatment in Nigeria

Nigeria 2001–2003

Background

Sickle cell disease is a widespread problem in Africa. Its prevalence is partly due to the fact that carriers may be protected against some forms of malaria. In Africa an estimated 7.4/1000 children are born affected with sickle cell disease, and this figure reaches as high as 14.8/1000 in West Africa. Sickle cell disease is thought to be responsible for 4% of under 5 mortality in West and Middle Africa (*48*).

In Nigeria, sickle cell disease is stigmatized, largely due to the almost complete lack of appropriate or affordable services. For this reason, virtually all Nigerian couples with affected fetuses opt for termination of pregnancy.

In the absence of genetic services for sickle cell disease, patient support and advocacy groups, such as the Sickle Cell Club (SCC), play a significant role (*218*). The SCC is a nongovernmental organization present in a few centres in Nigeria and run by volunteers. Membership of the SCC comprises a disproportionate number of the poorer members of society as the more affluent families are deterred by the stigma associated with sickle cell disease. The SCC runs a PND service by CVS, with samples sent to their collaborating Perinatal Unit in London for molecular diagnosis.

Prenatal genetic testing is still beyond the financial means of the vast majority of Nigerians, partly because test samples must be sent abroad for analysis. The service costs US$ 400, of which US$ 265 is transferred to the perinatal unit in London. Sending the samples abroad can also result in delays in receiving results. Meeting the potential demand for prenatal genetic testing requires that molecular diagnosis be available locally.

It should be noted that molecular testing is not necessary to determine *carrier* status for sickle cell disease, which can be determined by a phenotypic test, using a simple haemoglobin electrophoresis.

Case description

Mr and Mrs A married in 2001. Before then, their families had insisted on determining their genotypes in order to ensure that they did not bear children with sickle cell disease. This was principally because Mr A's elder brother had lost a number of children to sickle cell disease. Mr A already knew that he was a carrier. When Mrs A took the genetic test, offered by a commercial testing company, she was told she was not a carrier, so they married.

During Mrs A's first pregnancy, she went to a hospital for antenatal care. She was informed by a visiting obstetrician that a routine test had shown her to be a carrier for sickle cell disease. She questioned the result, but it was subsequently confirmed. Mrs A enquired about PND but was informed by her physician that at six months the pregnancy was too advanced. The child was a carrier and has remained healthy.

She delivered her second child without the benefit of prenatal diagnosis. At 9 months, he was diagnosed with sickle cell disease, and at 18 months, his symptoms were treated with blood transfusion, antibiotics and antimalarial drugs. He recovered and is receiving daily prophylactic treatment, folic acid and vitamin B complex tablets. The SCC provided advice regarding the medical management of his disorder and arranged to enrol him in a well run and highly subsidized clinic. The family remain anxious about his health and their ability to cope with the cost of frequent illness.

Their third child was also born without PND. He died of an undiagnosed illness at 4 months. The child's genotype had not been determined but the parents feared that he might have been affected by sickle cell disease. Both parents were understandably shocked and upset and Mrs A felt guilty that her inaccurate genetic test result encouraged their marriage.

Mrs A reported her fourth pregnancy early because she was, by that stage, eager to have PND. Mr and Mrs A were not able to afford the US$ 400 fee for the test, so the SCC raised sufficient funds through private donations from members to cover the cost. The couple were counselled prior to the CVS. The fetus was found to have sickle cell disease, and the couple opted for termination of pregnancy. The SCC was again able to contribute part of the fee for termination. Mrs A expressed a desire to have more children but the couple did not believe that they would be able to afford future PND or terminations.

continued...

...Case study 4

Ethical, legal and social issues

Both Mr and Mrs A were certain that the marriage would not have been contracted if they had known the carrier status of Mrs A. The couple are both Nigerians of Igbo descent and are Roman Catholics, neither of which supports divorce. Some churches in Nigeria refuse to marry carrier couples, which can have the unintended consequence of increasing stigmatization and falsification of test results.

Genetic services and PND are financially inaccessible to the majority of the population. The service is only available in Lagos and is not subsidized by the government. The absence of well regulated laboratories has also allowed for the growth of commercial laboratories, some of which are suspected of issuing inaccurate results.

The SCC was a valuable resource for this family in terms of coordinating funds for PND and the abortion, as well as coordinating care for their affected son, particularly as there were no alternative services available in the public health system. A publicly available genetic testing service, with appropriate quality assurance standards, informed consent guidelines and genetic counselling would have reduced the emotional and financial stress placed on this family.s

This case study illustrates a few of the many problems arising from the neglect of sickle cell disease in sub-Saharan Africa. The Sickle Cell Foundation Nigeria is developing a National Sickle Cell Centre, which will introduce genetic services and continue to advocate for their integration into primary health care.

This study is based on information provided by Dr Olu Akinyanju, founder and Chairman of the Sickle Cell Foundation, Nigeria.

Assisting the development of patient support organizations in developing countries

One programme in place that could act as a model for measures to establish, support and coordinate patient support groups in developing countries is the World Federation of Haemophilia (WFH). The WFH is an umbrella organization that represents haemophilia patient support groups globally (*262*). It runs a twinning programme, where genetics clinics in developing nations are paired with clinics in developed countries for training and workshops (*261*). This allows for sharing of information about the disease, safety of treatments, care options, counselling and prevention options. Cystic Fibrosis Worldwide (CFW) is another international non-profit organization (based in the United States) dedicated to improving the quality of care and education for those individuals living with cystic fibrosis in developing countries. Recently, CFW has commenced a project in the Republic of Georgia to develop sustainable delivery of clinical care, access to medicine and to facilitate the spread of education in the treatment of CF (108). CFW also works to promote and improve knowledge of CF among medical professionals and governments worldwide by serving as an international platform for the exchange of information. In Brazil, the CF Brazilian Association has been influential in the development of, and active in supporting the implementation of, the National Newborn Screening Programme (see Case study 1).

Despite the positive example provided by the SCC, and other patient/parent organizations highlighted throughout the report, patient support groups should not be seen as an alternative to the services provided by a genetic counsellor. Genetic counselling is a medical specialization that requires specific training, for example in the skills required to facilitate individual's decision-making in a non-directive manner. However, a severe lack of genetic counsellors in developing countries, even those nations with more advanced genetic services in place such as Brazil and India, means that patient support groups and untrained medical staff are often called upon as the only available resource to provide genetic counselling. Further, the weakness of the health care infrastructure and the lack of recognition of genetic diseases in many developing countries results in the burden of genetic counselling falling on support organizations, as they have both the experience and the motivation to assist other affected families. Ideally, patient support groups would work in conjunction with a medical team, including a genetic counsellor, to

provide the patient and family with the full spectrum of medical genetic services.

Conclusion

Genetic counselling is a specialist service that aims to foster individual autonomy during the decision-making process about the use of medical genetic services. Patients' informed and voluntary consent is a prerequisite to medical intervention, and genetic counsellors help to ensure that patients understand the relevant information, including potential risks and benefits, before making a decision to undergo genetic testing. If testing is carried out, counsellors are responsible for explaining to patients the results of tests and facilitating, in a non-directive manner, decision-making about the appropriate course of action for the specific patient. There are an insufficient number of genetic counsellors worldwide, but particularly in developing countries. The rapid rise in availability of genetic tests has restricted access to genetic counselling, in many instances, to cases where genetic tests are ordered through a physician or health care provider. Some countries such as Saudi Arabia are implementing interim measures to provide health care professionals and geneticists with short courses in counselling. In both developed and developing countries, patient support organizations play an important role in educating and supporting patients and affected families. This valuable resource should be acknowledged and support groups should be encouraged to work alongside medical professionals and genetic counsellors; however, support organizations should not be viewed as an alternative to genetic counselling, which involves specialist skills and specific training.

4.7 Education

Both developed and developing countries need to improve community awareness of, and knowledge about, genetics, the relationship between genotype and phenotype, the process of genetic inheritance and the implications of carrier status for reproductive decisions. A good education of the public supports the effectiveness of genetic services, can increase the reproductive choices available to the community, and helps to prevent discrimination and stigmatization. Knowledge within a community typically varies according to class, gender and profession, among others, as a result of differences in literacy, education and social mobility. Public education campaigns need to be cognizant of the different levels of, and barriers to, education among sub-populations within a community.

In developed countries, particularly the United Kingdom, the assumption that the public's technical knowledge of science is *inadequate* and needs to be addressed through *unidirectional* education by scientists, has become known as the 'deficit model' of public understanding. In response, social scientists have sought to legitimize the relevance of lay perspectives and values and to replace the deficit model with a bidirectional 'dialogue model'. Throughout the report we highlight the importance of inter-sectoral communications and dialogue as the basis for effective *public policy*. Cultural and religious views about genetics and inheritance should be taken into account when developing public policy, so that it is relevant and specific to the needs of a particular society.

However, the following discussion about public, patient and physician understanding of genetics in developing countries focuses on the implications of genetic knowledge for clinical and reproductive decision-making rather than policy development. Education is an important tool for combating discrimination and stigmatization of genetic conditions and empowering vulnerable sections of the community. The aim of public education in genetics, in this context, is to empower people to make their own decisions in ways that maximize their well-being and health (*264*).

4.7.1 Public understanding of genetics and inheritance

The lack of general education about genetics in developing countries presents a barrier to the successful implementation of genetic services. Studies conducted in some developing countries demonstrate that the level of community knowledge and understanding about genetics is low (*189*). As a result, misconceptions about genetic testing services and genetic diseases are common in these populations (*191*). For programmes that diagnose and treat genetic disorders to be effective, the community in which they operate must be educated about the nature of genetic diseases and how to access testing and treatment services (*264*; *191*). Without such knowledge, many people may fail to receive treatment for diseases or to undergo testing for carrier status prior to reproducing, because they are not aware that they may be at risk of passing a genetic disease on to their children or do not know where to seek medical advice.

Further, people may fail to seek *appropriate* treatment as a consequence of limited knowledge of genetic diseases. For example, it has been reported that in Ecuador some people seek treatment from shamans not only because they have little understanding of genetic diseases, but also because they are unaware of where to seek information or counselling in relation to the disorders (*189*). The example of screening programmes in the Kingdom of Bahrain (Case study 5) demonstrates how effective education campaigns can be in raising education levels and avoiding some of these problems.

Even when people are aware that services are available, "low education levels in some developing countries and limited familiarity with genetic medicine … present special obstacles to obtaining truly informed consent" (*268*). As genetic services become available in developing countries it is important to ensure that the community's level of knowledge of genetics is sufficient to enable people to make informed autonomous decisions about their health. Education should also seek to overcome the socio-cultural barriers that affect women's ability to access medical genetic services, even when they know they exist.

Public education

Public education about genetics is an indispensable platform upon which to introduce widespread genetic testing and screening. Such programmes should be culturally sensitive and provide information in a manner that takes account of religious and traditional beliefs and attitudes to medical care, in order to effectively target information towards different sectors of the community in a way that will maximize accessibility (*191*). WHO experts have recommended that genetic education programmes should target the general public, using courses and workshops; such education programmes should be implemented in schools and community organizations (*263, 264*).

If there are social barriers preventing women, or other groups, from entering these public spaces and actively engaging in these activities, material will need to be delivered through other channels. Education programmes should start with an initial assessment of the educational requirements of different groups and the best methods for reaching target audiences. These programmes should encompass the ELSI of genetics, as well as providing a good understanding of the basic science of genetics and inherited disorders (*271*; *264*). Dissemination approaches should take into account local literacy levels. The information should be easy to understand and it also should be free from "derogatory, guilt-provoking, or discriminatory overtones" (*264*). Information should also actively redress assumptions and beliefs leading to the stigmatization and discrimination of certain groups, for example the assumption that women are to blame for the occurrence of genetic diseases in their children (see Case study 3).

Major barriers to public education about genetic information are high rates of illiteracy and low standards of education, which make it difficult to communicate complex genetic concepts. These barriers typically affect women more significantly

because they often have lower rates of literacy than males.[12] There is stigma attached to carrier status and to some medical services associated with genetic testing, like selective abortion of affected fetuses. Such stigma can make the subject of genetic testing and screening taboo, resulting in a reluctance to initiate discussion about genetic disease. A lack of understanding about the relationship between individuals who have genetic diseases and those who carry the relevant allele can similarly present a barrier to effective control of genetic diseases. As with other autosomal recessive disorders, ß-thalassaemia presents challenges for genetic counselling and public education because carriers express the ß-thalassaemia trait, but are apparently healthy (*79*). Carriers can therefore be in denial about the implications of their carrier status for the health of their children.

Countries with decentralized rural populations also face geographical barriers regarding how and where to target education programmes and resources. Schools are a common choice for education about early onset childhood diseases, but the proportion of children who actually attend school must also be taken into account. Hospitals are another common choice, since many women will access a hospital at some point during a pregnancy. However, this rules out preconception intervention, and women in rural communities may still not have access to prenatal health care services. Outreach clinics and organizations will be critical in such areas. Targeting education to patient support groups can be effective, as significant sections of the target population will have already been identified and have an established communication network (see section 4.6.4).

Public education programmes, in the context of genetic screening for common recessive diseases, have been successfully implemented in Cuba (sickle cell disease) and Cyprus (ß-thalassaemia), with decreases in the prevalence of each disease of 30% and 97% respectively (*91*; *44*). In Cuba, public education was achieved through the mass media, and was also targeted at women attending hospital for antenatal care (*91*). Similarly, Cyprus used the mass media (TV, radio) to improve public education, along with talks targeted to smaller groups, school education, an information booklet and the initiation of a thalassaemia awareness week. Much of the programme's success is attributed to the small population of Cyprus; in such small communities many members of the public are in contact with an affected person, and there is therefore a good base of general awareness upon which to build education campaigns (*96*; *18*). International patient organizations such as CFW, TIF and WFH have played a key role in providing public education resources, particularly in developing countries.

Case study 5 provides a more detailed example of the role of education in the success of a national screening programme. Interestingly, the Kingdom of Bahrain, like Cyprus, is an island with a small population, many of whom have known an affected individual or family, and it seems likely that this geographical context plays an important role in successful implementation of such programmes.

Case study 5
Student screening and public education in the Kingdom of Bahrain

Ministry of Health, Kingdom of Bahrain, 1999—ongoing

Background

A newborn screening study conducted between 1984 and 1985 in the Kingdom of Bahrain showed that 2.1% of newborns had sickle cell disease, 11.2% were carriers of the abnormal allele for sickle cell disease, and 20% were born with glucose 6-phosphate dehydrogenase deficiency (G6PD). A 1994 premarital counselling study further revealed that 2–4% of people screened were carriers for ß-thalassaemia.

Description of the project

The National Student Screening Project (NSSP) was designed to (a) gather epidemiological data about prevalence rates of carriers of sickle cell disease, thalassaemia and G6PD in the community; and (b) provide teenagers and their families with the opportunity to discover their carrier status for these disorders prior to making decisions about marriage and reproduction.

The NSSP also aimed to:

- raise awareness among young people about these diseases through a comprehensive education campaign, thereby empowering them to make informed reproductive decisions in the future;
- establish a database registry for all screened affected students;
- identify the geographic distribution of carriers of these disorders; and
- identify the frequency of rare abnormal haemoglobin variants.

In order to ensure equitable access to the genetic screening service, testing is offered to all students in the 11th grade of secondary school, in both public and private schools, with 7000–8000 students targeted every year. The Ministry of Health has provided training sessions for teachers, in addition to school nurses and doctors, who are then responsible for educating the students about these diseases through educational sessions. Students and families are also supplied with information leaflets and booklets.

Testing is voluntary and permission for screening is taken from parents, or directly from students if they are 18 years or older. The informed consent forms contain general information about the project and a description of the benefits of the project for students. So far, approximately 80–85% of parents or students have voluntarily agreed to be tested each year. Test results are returned to students on a standardized official medical report card, and are delivered via their school in a sealed envelope, with students encouraged to open their envelopes at home with their families. In order to protect privacy and confidentiality, all samples stored in the central database are anonymously coded. Each school receives reports on the prevalence of the three diseases in their student body. The project takes six months on average every year for planning, education sessions, blood collection, laboratory testing, data processing, the distribution of report cards, data analysis and delivery of results. The estimated cost per student is US$ 6–7 which covers laboratory costs, human resources and educational materials *(9)*.

Challenges

The public was initially resistant to the screening programme because they feared that girls identified as carriers would not be able to find a husband. The education campaigns therefore stressed that (a) all people carry some defective genes; (b) carriers could avoid the risk of giving birth to an affected child if they married a non-carrier; and (c) no one, including carrier–carrier couples, would be prevented from marrying. Broad-based public campaigns were also required to encourage parents and students to agree to screening.

The Ministries of Health and Education were initially reluctant to prioritize genetic screening over other public health demands. However, they were convinced by epidemiological data demonstrating the high birth prevalence of the three disorders. Since its inception in 1999, the project has significantly increased awareness of the three disorders and more than 35 000 students have been screened.

This study of student screening for genetic blood diseases in the Kingdom of Bahrain is based on information provided by Dr Shaikha Al Arrayed, Head of the National Committee for the Prevention of Genetic Diseases (reference: 10).

The Bahrain premarital screening programme (mentioned in section 4.3.1) and the above student screening programme, both of which included comprehensive public education programmes, have, in combination, been highly effective. The rate at birth of sickle cell disease has decreased from 2.1% in 1984–1985 to 0.9% in 2005, a decrease of 60% *(8)*.

4.7.2 Health-care providers' knowledge about genetic services

Education levels among health care providers also present a challenge to effective public education. Primary health care providers (general practitioners, clinic nurses) are often poorly informed about genetic disorders and available genetic services and so are often unable to pass relevant information on to their patients. This is a problem in developed nations as well, where many general practitioners do not consistently assess genetic risk, do not refer at-risk patients to genetic services, and are not aware which services are available *(42; 250; 198)*. Education of health professionals at a local level must go hand in hand with public education in both developed and developing nations. In addition to general knowledge about genetics, health professionals' training should include the basic principles of genetic counselling, and the primary ethical, legal and social issues associated with medical genetic services.

The WHO report *Genomics and world health* noted that the information generated by genomics will, over time, aid in the treatment and prevention, not only of single-gene disorders, but also of other common killers and causes of chronic disease involving significant genetic predispositions, such as cancer, cardiovascular disease, diabetes and mental health (*268*). It is therefore important to stress the importance of ensuring that general medical staff have training which enables them to competently discuss with patients, genetic information relevant to a wide range of pathologies. To this end, governments should ensure firstly that genetics is a component of all medical training, and secondly that health professionals have regular opportunities to access continuing education to update their knowledge of genetics (*155*).

4.8 Patient well-being: quality assurance and patient safety

Patient well-being is an overarching concern that encompasses many of the issues already discussed. Arguments for comprehensive treatment and prevention services are essentially about fostering patient and family well-being. In this section, we discuss two issues that are not always thought of as components of patient well-being: quality assurance standards and commercial testing.

Genetic testing and screening raise particular issues in relation to quality assurance and patient safety, in part due to how a community and its members understand the meaning of genetic information. While there is a common perception that genetic information differs in some ways from other medical information, there is substantial debate about the nature and degree of this difference. The knowledge that one is a carrier of a genetic disease can have implications for potential reproductive partners and future children. Genetic information can indicate that a person will develop a disorder in the future, despite being currently well, as in the case of late onset diseases such as Huntington disease. Genetic information may also indicate that a person is predisposed to developing a disorder but, because of the complex multifactorial factors involved in disease development, geneticists cannot convert this knowledge into a precise outcome, only a more general risk value. Genetic information about one individual can also reveal information about his or her wider family. The view that genetic information is sufficiently different from other health care information to raise *unique* social issues has been referred to as genetic exceptionalism. This view supports the establishment of separate regulations for managing and protecting genetic information.

On the other hand, others have argued that the exceptionalism of genetic information has been

exaggerated *(92; 89)*. Supporters of this position argue that almost everything relevant to human health has *some* measure of influence by genetic factors and at the same time, very little about our health is determined *only* by our genome, much less by one gene. On this view, the dualism created between genetic and other medical information is unjustified and misleading. Furthermore, there are multiple examples of medical 'tests', such as those measuring blood pressure, cholesterol level and bone density, that provide insight into individual and familial risk of disease but have traditionally not been subject to requirements for genetic counselling or genetically-oriented informed consent processes.

Despite this controversy, it is clear that many people *believe* that genetic information, because of its heritable nature, is different to other medical information and therefore find genetic information (particularly that relating to predispositions and information that affects other family members) more upsetting and challenging than other medical information. Countries should determine, on an individual basis, the degree to which they believe it is necessary to introduce *specific* regulations relating to genetic information in order to protect patients from the harm associated with unnecessary or inaccurate genetic testing (see e.g. **Case study 4**).

4.8.1 Quality and safety

Quality and safety standards for genetic testing aim to ensure accuracy of results and to protect patients from the range of possible risks associated with testing. Accuracy of results is particularly important given the emotional and psychological effect that testing may have on patients and their families. Despite this, some countries do not have adequate systems in place to regulate and standardize laboratory practices. As a result, insufficient or incorrect information may be provided to patients (see e.g. Case study 4). Information may also not be provided in a timeframe that allows for a full range of options, interventions or treatments. In the case of misplaced, misidentified or mistreated samples, information may not be provided at all.

Quality assurance

Quality assurance covers a range of aspects of testing, including the decision to test, the accuracy of results, the delivery of results and support following that delivery. At the testing stage, protocols should regulate handling and labelling of samples, testing procedures and interpretation and recording of results, in addition to laboratory accreditation.

Standards should address the analytical validity, clinical validity and clinical utility of a test. As noted in the Primer of medical genetics and genetic services, analytical validity is the test's ability to detect the trait it seeks to measure. Clinical validity refers to the test's capacity to predict a particular clinical outcome, which gives the test meaning. Clinical utility refers to whether the test can provide some guidance on how to treat the disorder. For example, tests that reveal a patient has an incurable or untreatable disorder have relatively low clinical utility. Where treatment options exist, a test will have high clinical utility.

Once testing is completed, the results should be delivered to patients again in the context of non-directive genetic counselling. Patients should be assisted to select a course of treatment appropriate for them and be made aware of their reproductive options. If the test indicates that the individual is affected by the disease, he or she should be informed of the support and management structures in place for patients with the disorder.

Developing quality assurance standards and mechanisms

Quality assurance standards and mechanisms are generally developed and implemented at the national level. They often work as a coordinated system, where national governments establish and enforce standards, while private or professional bodies conduct external quality assurance schemes

in line with these standards. However the Organization for Economic Development and Cooperation (OECD) and WHO have also been working together to establish international standards and best practices (*277*). In large part, such standards are developed in, or directed at, more developed nations. The urgent need for the introduction of mandatory quality assurance programmes for diagnostic laboratories was identified as a priority issue in a recent transnational genetics workshop held in the People's Republic of China (*155*).

Quality assurance measures in place in developing countries

Some developing countries have begun to develop mechanisms to promote quality assurance and patient safety. Turkish law regulates the establishment of genetic screening centres. Authorizations and licences are issued to establish and open genetic screening centres, and there is a range of requirements relating to methods, equipment and personnel (*208*). Indian law prescribes minimum requirements for equipment and premises of genetic laboratories, genetic clinics and genetic counselling centres, and also establishes a licensing and registration scheme for these centres, which includes requirements for obtaining informed consent (*200*; *201*).

Some developing countries have also laid down requirements for the licensing and training of medical practitioners and others involved in genetic testing and screening services. For example, Indian law lays down minimum qualifications of employees of genetic counselling centres, genetic laboratories and genetic clinics that provide prenatal diagnostic services (*200*, §3(2); *201*, r3). See **Country example 9**.

It should be acknowledged that the development of quality and safety standards is often difficult for developing countries with limited resources. Countries struggling to provide sufficient genetic testing and screening services may be reluctant to fund organizations to monitor and enforce quality standards or to license laboratories. Further, many developing countries lack sufficient legal specialists with skills in drafting legislation.

Nevertheless, appropriate legislative and regulatory frameworks are necessary to ensure those testing and screening programmes that are introduced function effectively and with maximum efficiency. Investing in suitable legislation can prevent the waste of resources arising as a result of

Country example 9
Prenatal diagnosis regulation in India

India has enacted laws regulating the use of prenatal diagnosis *(200; 201)*. These laws permit prenatal testing only to detect chromosomal abnormalities, genetic metabolic diseases, haemoglobin diseases, sex-linked genetic diseases, congenital anomalies, and any other abnormalities or diseases as may be specified by the Central Supervisory Board *(200,* §4(2)). Prenatal testing is also only permitted if one of the following conditions is present: (i) the age of the pregnant woman is above 35 years; (ii) the pregnant woman has undergone two or more spontaneous abortions or fetal losses; (iii) the pregnant woman had been exposed to potentially teratogenic agents, such as drugs, radiation, infection or chemicals; (iv) the pregnant woman or her spouse has a family history of mental retardation or physical deformities, such as spasticity or any other genetic disease; or (v) there is a family history of any other condition as may be specified by the Central Supervisory Board (*200*, §4(3)).

The regulations also include requirements that informed consent be obtained from the mother prior to testing (*201*, r10). Sanctions are provided for violation of these regulations (*200*, §23–27). Genetic laboratories are prohibited from accepting for analysis or testing any samples unless referred to them by a genetic clinic (*201*, r14). These legislative requirements are also augmented by ethical guidelines issued by the National Bioethics Committee of the Indian Department of Biotechnology (*174*, Genetic testing and counselling, paras 1–3).

unregulated laboratories and the unnecessary use of genetic tests. Anti-discrimination legislation also protects vulnerable members of the community by removing the informal barriers to genetic testing that result from fear of stigmatization. Such fears limit the ability of programmes to reach their target populations and therefore decrease the efficiency of screening programmes. As regulation and legislation are a necessary component of effective testing and screening services, the international community should consider ways of encouraging capacity building and technology transfer in relevant public policy and legislation drafting skills.

4.8.2 Commercial testing

Commercial genetic testing services pose problems in both developed and developing countries, although the nature and scope of these problems may vary between the two. In general, the provision of testing services through the private sector raises concerns about the proper regulation of testing processes to ensure results are accurate and that tests have sufficient utility. Specific concerns relate to: the quality of informed consent; the inequality of access to genetic services within the community; the accessibility of genetic counselling; and the unnecessary use of tests in a commercial environment.

Lower levels of general education and lack of regulation make private sector genetic testing in the absence of fully informed consent more acute in developing countries. In some countries, private sector testing may also lead to direct marketing of tests to the public, through the internet, for example, where individuals decide, in the absence of professional health care advice and support, to undergo genetic testing.

In developing countries, the establishment of commercial testing facilities raises concerns about inequality of access to genetic services. Commercial genetic testing services are available in a number of developing countries, including India, Brazil, Chile, Colombia, Ecuador and other Latin American countries (see, e.g. *30; 271*; *221*; *88*). In some, the private sector is relatively well developed and provides services broadly. For example, in Colombia, the majority of prenatal screening is carried out in private laboratories (*88*). In other countries, however, only very limited genetic testing services are provided by either the public or private sectors. For example, in Paraguay, prenatal diagnosis by amniocentesis is only available in the private sector and access is limited to the wealthiest sections of the population (*20*).

Due to their cost, commercial genetic services are generally available to only a small minority (*271*). WHO experts have expressed concerns that the low priority placed on the provision of genetic services by governments in Latin America, and the high cost of private testing services, have resulted in inequitable access in this region (*271*). Access barriers due to cost are most acute where local public and private health insurance schemes do not cover the cost of testing, as is the case in Brazil, Colombia (*88*), Ecuador and Mexico City (*189*; *134*). Cost is not only a barrier to poor women, but to women whose access to family resources is restricted due to cultural norms.

Some commercial testing services are established locally or nationally; however, it appears that overseas companies have also shown an interest in setting up commercial testing facilities in some developing countries (*30*). In most cases, commercial genetic testing services emerge in developing countries because many such countries do not publicly fund comprehensive medical genetic services. The private sector begins to provide testing in response to demand from the wealthier sections of the communities (*264*:30). Service provision is driven by profit and so the more commercially profitable services, such as prenatal diagnosis, DNA paternity testing and chromosome analysis, are typically the first to be provided (*271*). For example, Penchaszadeh has noted that lack of regulation in Latin America has resulted in "the non-critical introduction of predictive genetic testing induced by commercial interests without clinical validation" (*193*).

Country example 10 considers the provision of commercial genetic services in Brazil.

Country example 10
Commercial genetic testing services in Brazil

In Brazil, 42% of medical institutions that have a genetic clinic are private, and 61% of clinical geneticists in that country work in private clinics either part time or full time (*151*). However, most comprehensive genetic services (services that encompass all or most aspects of testing, from referral for testing through to testing and post-test counselling and treatment) are located within tertiary care public university hospitals, which act as referral centres (*151*). Samples from both public and private centres are often sent to other hospitals or to other states for testing, without any proper formal controls (*112*).

One study of genetic services in Brazil reported that the private sector is well developed in some more affluent areas, "with services that include clinical evaluation and some laboratory studies, as well as prenatal diagnosis of chromosomal and monogenic conditions" (*151*). Cytogenetic and molecular testing is available in the private sector in some areas *(3)*. Prenatal ultrasound and amniocentesis services are also offered within the private sector in some states from the South and Southeast regions, including Minas Gerais, Paraná, Rio Grande do Sul and Rio de Janeiro, (*151*; *112*: *3*:, and it has been reported that genetic testing services in Rio de Janeiro are comparable in quality to those in developed countries (*112*).

The genetic testing services offered in Brazil are not generally comprehensive or accompanied by formal genetic counselling, and physicians with little or no training in genetics often deliver test results (*112*; *3*). Predictive genetic testing is also offered by some private laboratories, although again, genetic counselling is not routinely offered and tests may be carried out despite a lack of evidence that the test has clinical validity or utility (*3*). As most private health insurance plans in Brazil do not cover private sector genetic testing, access is limited to only the small proportion of Brazilians who can afford to pay for these services (*112*).

Private commercial genetic testing, including prenatal testing, is also often subject to few if any quality control measures (*191*). When services are not provided through public organizations, the absence of direct governmental responsibility means there is less incentive for governments to ensure these private services are well regulated. Some developing countries, however, have put in place measures to regulate private testing. For example, the regulations covering genetic testing services in India discussed in section 4.8.1 also cover commercial genetic testing services.

Finally, where genetic testing services are split between public and private organizations, these services may become fragmented and lack integration. For example, some private laboratories conduct newborn screening in Brazil (see Case study 1), but do not offer treatment or subsequent care (*3*). As WHO experts have noted, "genetics services cannot exist as stand alone vertical structures but should be integrated with related medical services" (*264*). Affected individuals, or parents of an affected child, require access to and guidance on the range of medical specialists who should be involved in managing the disorder (*264*). It is unlikely that a purely private genetic testing service will provide access to such coordinated care.

As a result of a WHO consultation on community genetic services in Latin America, a range of recommendations were made, some of which dealt specifically with concerns about commercial testing services (*271*). First, each country should develop systems to regulate the safety and effectiveness of privately provided testing. These systems should require that commercial genetic testing services establish mechanisms to protect the privacy and confidentiality of the genetic information they generate. They should also ensure that private testing occurs only once appropriate informed consent has been obtained, and should outline what constitutes informed consent. Finally, countries should require commercial laboratories to provide genetic counselling before and after testing, and this counselling should be sensitive to the cultural traditions and religious beliefs of the region.

The development of medical genetic services that are both publicly funded and administered is the preferred means of introducing genetic testing to a developing country because it promotes equitable access and facilitates regulation and oversight. In the absence of publicly funded genetic services, it is important for countries to regulate the conduct and standards of private testing services and laboratories.

5
Conclusion, principles and recommendations

Comprehensive and integrated treatment and prevention services are needed to effectively reduce the burden of congenital and genetic disorders. Yet, in many developing countries the level of genetic services is currently inadequate to meet population needs; frequently these services are available only to the wealthy, educated sectors of the community.

The provision of genetic services must be weighed responsibly and fairly against the competing health needs in each country. Available epidemiological data regarding the prevalence of congenital and genetic disorders, and the cost-effectiveness of control programmes, indicates that many developing countries would benefit from incorporating genetic approaches into their health services. While many options for controlling congenital and genetic disorders are cost-effective, they are currently underutilized in most developing countries as means of reducing the burden of disease. In addition, there is also a significant need to develop and expand the collection of further and more detailed epidemiological data.

This report has discussed the social context relevant to genetic testing and screening programmes in developing countries; identified the associated primary ethical, legal and social issues; and suggested *principles* for managing these issues effectively. Responsibility for translating these principles and recommendations into specific *policies*, appropriate to the local context, rests with individual governments. The report has not aimed to cover *all* the ethical aspects of genetic testing and screening, but rather to expand and enrich the discussion of some of the major ethical, legal and social issues specific to developing countries. The report has brought together the increasing empirical evidence relating to the implementation of medical genetic services in developing countries.

The primary ethical issues associated with medical genetic services in developing countries are:

Distributive justice:

- Access to necessary genetic services is inequitably restricted, usually to the wealthy sectors of the community.

Non-discrimination:

- Stigmatization of, and discrimination against, people with genetic disorders and carriers of recessive genetic conditions result in direct harm and act as a barrier to genetic services.

Non-maleficence and beneficence:

- Appropriate safeguards to ensure quality and safety are lacking when genetic testing occurs outside of recognized genetic services, usually without adequate genetic counselling or informed consent.

The major themes and conclusions of the report are summarized below:

5.1 General principles

1. Distributive justice in health care requires fair consideration of macro-allocation issues about the prioritization of genetic health needs and medical genetic services, in light of local resources; and micro-allocation issues about who should have access to medical genetic services and on what basis.

2. Evidence relating to the cost-effectiveness of medical genetic services should play an important role in health resource prioritization; however, assumptions used in cost-effectiveness analysis and interpretation of the data generated by such analyses must be balanced against issues of equity and distributive justice.

3. The principles of fair process should be used to ensure public endorsement of difficult decisions about rationing health care and access to medical genetic services.

4. The development of medical genetic services that are both funded and governed publicly is the ideal manner for introducing genetic testing within countries because it promotes equitable access and facilitates regulation and oversight.

5. Genetic testing and screening programmes should be supported by public education and genetic counselling.

6. Participation in all genetic testing and screening programmes should be voluntary. Properly informed consent is only obtained if the person (1) understands the purpose of the test, including its benefits, risks and possible outcomes, as well as treatment options and reproductive implications, and (2) decides voluntarily whether to undergo testing, free from official or social pressure.

7. Autonomous decision-making regarding the use of medical genetic services depends on the availability of a range of options. Optimum genetic testing, screening and counselling can only occur where there are available and affordable resources for persons with genetic disorders. Available, affordable and safe abortion services for women who voluntarily choose to use this service should be provided.

8. Stigmatization of genetic disorders results in direct harm to those affected; the resulting social harm and actual discrimination (in marriage for example) create indirect barriers to accessing genetic services within the community. Such barriers unjustly restrict access to genetic services and therefore reduce the effectiveness of testing and screening programmes by limiting their ability to reach the target population. Education can be a key tool in minimizing stigmatization; while regulation may be needed to combat discrimination.

5.2 Recommendations

Education and dialogue

i. To ensure that health professionals have an adequate understanding of genetics and genetic services, national governments should require that genetics is a significant component of all medical training, and that health professionals have regular opportunities to access continuing education to update their knowledge about genetics, available medical genetic services, and the relevant ethical, legal, social and human rights issues.

ii. National governments should foster dialogue and cooperation among policy-

makers, patients and families, clinicians, geneticists, religious leaders and other stakeholders, to establish and implement genetic services in a manner that is culturally acceptable and maximizes the health benefit to patients.

Genetic counselling

iii. It is the responsibility of national governments to ensure that genetic testing and screening programmes have trained genetic counsellors available to provide genetic counselling.

iv. Due to the significant shortages of genetic counsellors in developing countries, short-term courses should be implemented as an interim measure to increase capacity in genetic counselling. These should be directed at existing primary health care workers (nurses, physicians, geneticists and other health care personnel providing medical genetic services). Graduate programmes in genetic counselling, though the accepted standard in developed countries, are unlikely to be feasible for many developing countries in the short to medium term.

v. The international organizations, in collaboration with civil society and relevant experts, should develop guidelines specifying the minimum skills required for genetic counselling to assist developing countries in designing short-term training in genetic counselling in order to scale-up local capacity.

vi. Patient-support organizations are a valuable resource and support groups should be encouraged to work alongside medical professionals and genetic counsellors; however, support organizations should not be viewed as an alternative to genetic counselling, which involves specialist skills and specific training.

Discrimination

vii. Privacy, confidentiality and anti-discrimination regulations are necessary measures to protect patients' rights and safeguard against discrimination and stigmatization on the basis of genetic information. As there is often a discrepancy between law or policy and practice, national governments should guarantee that these regulations have appropriate enforcement mechanisms to ensure that they are put into effect.

viii. As regulation and legislation are a necessary component of effective genetic testing and screening services, the international community should provide technical assistance to build capacity, not just in medical genetics but also in public policy and legislative drafting.

Quality and safety

ix. In order to foster patient well-being and protect patient safety, national governments should establish:

- appropriate quality assurance standards (addressing analytic validity, clinical validity and clinical utility) for genetic tests;
- regulations requiring genetic counselling and informed consent for genetic testing and screening; and
- appropriate enforcement mechanisms for the above.

x. National governments should ensure that both publicly and privately provided genetic services are governed by appropriate regulations regarding informed consent, genetic counselling and quality assurance.

xi. International agencies should provide technical guidance on quality assurance standards for genetic tests that are suitable for use in developing countries.

Termination of affected pregnancy

xii. Evidence demonstrates that a significant proportion of couples will chose to terminate affected pregnancies. In the absence of safe abortion services, some women will resort to unsafe abortion, thereby exposing themselves to the associated medical, financial, social and legal risks. National governments should take action to address unsafe abortion, which is a serious threat to women and women's health. Complications arising from unsafe abortion can also result in a significant burden to the public health system. In countries where abortion for fetal abnormalities is restricted or illegal, further debate is required at the academic and policy level regarding the ethical acceptability of introducing prenatal genetic testing in the absence of safe abortion services for medical purposes.

Patient rights

xiii. Privacy and confidentiality regulations are necessary to protect patients' rights and safeguard against potential discrimination and stigmatization. These regulations need effective enforcement mechanisms to ensure that actual practices align with law and policy.

xiv. The degree to which genetic information differs from other medical information in that national context is a question for national governments to resolve in determining whether *specific* legislation/regulation is needed on the uses of, and confidentiality requirements for, genetic information.

Sex selection

xv. The use of medical genetic services for sex determination and selective abortion of fetuses based on their sex for non-medical reasons is a serious problem in some developing countries. Legislative prohibitions on this practice have so far proved ineffective. National governments must directly address gender discrimination, "son preference" and the social incentives to have male children. National governments of countries where sex selection is a problem should initiate campaigns to promote equal treatment of girls and boys with respect to nutrition, health care, education, employment, inheritance rights and social, economic and political activity.

6
Abbreviations

ACHR: Advisory Committee on Health Research

AIDS: acquired immune deficiency syndrome

CEA: cost-effectiveness analysis

CEDAW: Convention on the Elimination of all Forms of Discrimination against Women

CF: cystic fibrosis

CFW: Cystic Fibrosis Worldwide

CH: congenital hypothyroidism

CVS: chorionic villus sampling

DNA: deoxyribonucleic acid

DMD: Duchenne muscular dystrophy

ELSI: ethical, legal and social implications

FAP: familial adenomatous polyposis

GDP: gross domestic product

HIV: human immunodeficiency virus

HUGO: Human Genome Organization

IVF: in vitro fertilization

NGO: nongovernmental organization

NSSP: National Student Screening Programme (Kingdom of Bahrain)

OECD: Organisation for Economic Development and Cooperation

PGD: pre-implantation genetic diagnosis

PKU: phenylketonuria

PND: prenatal diagnosis

PNTN: Programa Nacional de Triagem Neonatal (National Newborn Screening Program, Brazil)

RNA: ribonucleic acid

SCC: Sickle Cell Club

SUS: Single Health System [Sistema Único de Saúde], Brazil

TIF: Thalassaemia International Federation

UNESCO: United Nations Educational, Scientific and Cultural Organization

WFH: World Federation of Haemophilia

WHO: World Health Organization

7
Glossary

The glossary provides an explanation of technical terms used in the report, and does **not** represent a comprehensive description of genetic concepts, genetic diseases or congenital disorders.

Abortion: For the purposes of this report, the terms *abortion* and *termination of pregnancy* are used to refer to the deliberate interruption of pregnancy following the detection of fetal abnormality (unless otherwise specified).

Alleles: Alternative variants of a gene at the same chromosomal locus.

Amniocentesis: A test that can be performed after 14 weeks of pregnancy, where a sample of amniotic fluid containing fetal cells is taken from the womb through the abdomen of the mother to enable clinical analysis, which can include chromosomal analysis and/or genetic testing of the fetus.

Anencephaly: A neural tube defect in the same family of developmental disorders as spina bifida, which occurs when the 'cephalic' or head end of the neural tube fails to close, resulting in the absence of a major portion of the brain, skull and scalp. The infant is usually blind, deaf, unconscious, and unable to feel pain. Although some individuals with anencephaly may be born with a rudimentary brain stem, the lack of a functioning cerebrum permanently rules out the possibility of ever gaining consciousness. Reflex actions such as respiration (breathing) and responses to sound or touch may occur (*17*).

Aneuploidy: The occurrence of an additional or missing chromosome to give an unbalanced chromosome complement (for example Trisomy 21, or three copies of chromosome 21, resulting in Down syndrome) (see *Chromosomal disorder*).

Antenatal: (see *Prenatal*).

Ashkenazi: A Jewish community originating in Eastern Europe. There are a number of disease alleles which are more prevalent in the Ashkenazi Jewish population as compared to the general population, due to endogamous marriage and founder effect in the small original population (for example Tay Sachs disease and *BRCA2*-associated breast cancer).

Autosome: Any of the 22 pairs of chromosomes that are not classified as sex chromosomes.

Carrier: A person who carries one allele (heterozygous) for a recessive disease, and hence is not fully affected by the disease phenotype, but can pass the allele on to the next generation.

- **Asymptomatic carrier:** A carrier who displays none of the symptoms of the disease phenotype. Carriers for most recessive diseases are asymptomatic.
- **Obligate carrier:** When a person is found to be a carrier from family history alone (for example a person can be identified as an obligate carrier of an X-linked condition when they have both an affected sibling and an affected child).

- **Probable carrier:** Without further pedigree information, parents of affected children are considered probable carriers.

Carrier testing: The use of a genetic test to identify carriers.

Chorionic villus sampling: A procedure that can be carried out between 8 to 14 weeks of pregnancy through the vagina or through the abdomen to obtain cells of the chorion (which will become the placenta) to enable genetic testing of the fetus.

Chromosomal disorder: A disorder occurring when there is an additional or missing chromosome or section of chromosome. The genes on the chromosome are not necessarily abnormal; it is the dosage of those genes that causes the disorder. For example, Down syndrome is usually caused by the inheritance of three complete chromosomes 21.

Chromosomes: DNA and protein, organized into distinct molecular structures, located in the nucleus of each cell. Humans have 23 pairs of chromosomes. These pairs consist of one chromosome each of paternal and maternal origin.

Coefficient of inbreeding: The coefficient of inbreeding *(F)* is the probability that an individual with two identical alleles of the same gene received both alleles from a common ancestor.

Congenital disorder: Any potentially pathological condition arising before birth. This includes all disorders caused by environmental, genetic and unknown factors, whether they are evident at birth, or become manifest later in life (*266*).

Consanguineous marriage: A marriage between people who are blood relatives.

Consanguineous: A genetic relationship defined as descent from at least one common ancestor.

Consanguinity: (see *Consanguineous*; see also Appendix B).

Cystic fibrosis: A common autosomal recessive hereditary disease in populations of northern European origin (birth prevalence of 1:3500; heterozygote frequency 1:22). The CF gene encodes a membrane-bound protein that regulates a chloride ion channel designated CFTR (cystic fibrosis transmembrane conduction regulator). Cystic fibrosis is often severe and progressive; the average life expectancy is currently between 20–30 years. The bronchial system is especially affected. Males are almost always infertile and females are sometimes so. The sweat test is the standard diagnostic test for CF and a high salt level is indicative of CF. Treatment, depending upon the stage of the disease and the organs involved, involves clearing mucus from the lungs by chest physical therapy.

Diploid: A full set of genetic material, consisting of paired chromosomes, one chromosome from each parental set. Most animal cells except the gametes have a diploid set of chromosomes. The diploid human genome has 46 chromosomes.

DNA: A polymer of subunits in human cells which comprise the genetic code. DNA occurs naturally in very long paired strands that form a double helix. A gene is a length of DNA that encodes a functional product (a polypeptide or RNA).

DNA microarray: A grid of nucleic acid molecules of known composition linked to a solid substrate, which can be probed with total messenger RNA from a cell or tissue to reveal changes in gene expression (i.e. the amount of mRNA produced) relative to a control sample. Microarray technology, which is also known as 'DNA chip' technology, allows analysis of the expression of many thousands of genes by a single experiment.

Dominant inheritance: A single allele inherited from one parent, father or mother, is sufficient for phenotypic expression.

Dominant: An allele is described as dominant if it exerts its phenotypic effect when present in the heterozygous state (see *Dominant inheritance*).

Duchenne muscular dystrophy: An X-linked disease in which there is gradual wasting and weakening of skeletal muscles, usually affecting boys and causing early death, often before reproductive age.

Early-onset disorders: Disorders that present symptoms between birth and early childhood, generally before reproductive age.

Endogamous marriage: Marriage within the limits of a specific group, clan, tribe or caste as required by custom or law.

Epidemiology: The study of the distribution and determinants of healthy-related states or events in populations and the application of these studies to control health problems.

Gene expression profile: A determination of the activity of many genes at the same time in a particular tissue, usually measured by the presence of their RNA in microarray analysis.

Gene mutations: Structural changes in the DNA sequence of a gene resulting from uncorrected errors during DNA replication.

Genes: Units of hereditary information that are composed of DNA, encode a functional product, and are located on chromosomes.

Genetic counselling: The process by which individuals or families at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it, and the ways in which this may be prevented, avoided or ameliorated, in a respectful, non-directive and confidential manner.

Genetic drift: Cumulative changes in gene frequency over successive generations because of chance fluctuations; this may eventually result in certain alleles being completely lost from a population.

Genetic test: A laboratory test that analyses a particular configuration of the genetic material, be it (a) by direct analysis at the level of a gene or a chromosome, or (b) by testing a *direct* gene product (such as RNA, a structural protein or an enzyme or key metabolite).

Genetic testing: Testing offered to people already known to be at increased genetic risk (e.g. the partner of a carrier of a haemoglobin disorder, an older pregnant woman, a woman with a fetus with increased nuchal translucency, a biological relative of a person with a genetic condition) in order to achieve a definitive diagnosis of a genetic condition or state of risk (*266*).

Genetics: The study of heredity, or the transmission of genetic factors from one generation to the next, and of the variation within those factors.

Genome: With respect to humans, the genome is the sum total of the genetic material present in an individual, including DNA present in the chromosomes and that in the mitochondria.

Genomic epidemiology: The branch of medical science that deals with the study of genes and their functions in relation to the incidence and distribution of disease in a population.

Genomics: The study of the genome and its action.

Genotype: The total genetic constitution of an individual.

Haemoglobin: The molecule in red blood cells which transports oxygen from the lungs to body tissues.

Haemoglobinopathies: Inherited disorders of haemoglobin, including thalassaemia and sickle cell disease, among others.

Haemophilia: The first major disease recognized as being genetically determined, haemophilia is a classic example of X-chromosomal inheritance, occurring with a frequency of about 1:10 000 male newborns. Haemophilia A is a hereditary blood disorder characterized by a deficiency of the blood clotting protein Factor VIII that results in abnormal bleeding. Haemophilia B results from a deficiency of Factor IX. Factor VIII (synthesized mainly in the liver) is one of the many factors involved with blood coagulation. The severity of haemophilia and the frequency of bleeding depend upon the degree of residual Factor VIII or Factor IX activity.

Haploid: A single set of chromosomes (half the full set of genetic material), present in the egg and sperm cells of animals. Human beings have 23 chromosomes in their reproductive cells.

Hereditary: The passing of characteristics genetically from one generation to the next, from parent to offspring.

Heterozygote: A heterozygote has a different allelic form of a specific gene on each of the pair of chromosomes (often represented as Hh).

Homologous chromosomes: A pair of chromosomes in which one member of the pair is obtained from the organism's maternal parent and the other from the paternal parent; found in diploid cells. These are also commonly referred to as 'homologues'.

Homozygote: A homozygote has the same allelic form of a specific gene on each of the pair of chromosomes (often represented as HH or hh).

In vitro fertilization (IVF): A laboratory procedure in which eggs and sperm harvested from the parents are combined outside the body resulting in fertilized egg(s) that can later be replaced in the uterus to complete embryonic and fetal development.

Inherited blood disorders: A group of disorders that may be hereditary and that affect the blood, including haemophilia, sickle cell disease and thalassaemia, among others.

Late-onset disorders: Disorders that do not present with symptoms until later in life, generally after reproductive age has been reached.

Locus: The specific site on a chromosome at which a particular gene or other DNA marker is located.

Maternal age: The age of the mother at the time of conception, which is correlated with a risk of chromosomal disorders in the offspring. This risk factor is often referred to as advanced maternal age, and is generally considered to be over the age of 35 years, when the risk of these disorders begins to increase exponentially.

Mendelian disorder: Disorders that respond to the genetic laws of dominant and recessive inheritance discovered by the monk Gregor Mendel in peas in the nineteenth century (see *Monogenic disorder*).

Mitochondria: Cellular organelles present in eukaryotic organisms that enable aerobic respiration, which generates the energy to drive cellular processes. Each mitochondrion contains a small amount of DNA encoding 37 genes.

Molecular epidemiology: The branch of medical science that deals with the incidence, distribution and control of disease in a population through identification and characterization of certain molecules and gene sequences.

Monogenic disorders: (see *Mendelian disorder*).

Multifactorial disorders: Disorders whose pathology is dependent on the complex interplay of several genetic and environmental factors.

Non-disjunction: An error in cell division where the chromosomes fail to separate during meiosis, so that both pass to the same daughter cell.

Nucleotides: Biochemical molecules (bases) from which DNA and RNA molecules are assembled.

Penetrance: the probability that a genetic trait will be expressed. An allele may have complete or incomplete penetrance. The latter refers to cases where having the particular allele leads to a less than 100% likelihood of manifesting the phenotype.

Perinatal: Relating to or occurring during the period around childbirth, specifically from around week 28 of pregnancy to around one month after birth.

Phenotype: The visible properties of an organism produced by its genotype in interaction with the environment; the clinical presentation of a specific disorder (see *Genotype*).

Phenylketonuria (PKU): An early-onset disease in which the body lacks the enzyme to metabolize dietary phenylalanine to tyrosine, which results in a toxic by-product that causes developmental deficiency, seizures and tumours.

Polygenic: Involving more than one gene (see *Multifactorial disorder*).

Polymerase chain reaction (PCR): A molecular biology technique developed in the mid-1980s, and now one of the most widespread DNA technologies, through which specific DNA segments may be selectively amplified.

Polypeptide: A single chain of covalently attached amino acids joined by peptide bonds. Polypeptide chains usually fold into a compact, stable form that is part (or all) of the final protein.

Postnatal: Occurring immediately or soon after childbirth.

Predictive testing: (see *Presymptomatic testing*).

Predisposition genetic testing: Analysis of a genotype to ascertain whether there is an increased risk of disease. While the genotype alone may be insufficient to cause the disease, impaired expression of alleles and/or environmental factors may be necessary conditions for the disease.

Pre-implantation genetic diagnosis: Genetic testing of embryos created through IVF to identify those at risk of a particular condition.

Prenatal diagnosis: Diagnostic investigations that are performed during fetal development.

Prenatal: Existing or happening during pregnancy but before childbirth.

Presymptomatic testing: Detection of late-onset diseases that develop in adults, identifying either a predisposition to disease or making a definitive diagnosis.

Protein: Biological effector molecules encoded by an organism's genome. A protein consists of one or more polypeptide chains of amino acid subunits. The functional action of a protein depends on its three-dimensional structure, which is determined by its amino acid composition.

Recessive inheritance: Two abnormal alleles (if fully penetrant) must be inherited from each parent for full phenotypic expression in the offspring.

Recessive: An allele (if fully penetrant) is described as recessive if it must be homozygous to confer the full phenotypic effect (see *Recessive inheritance*).

Screening: The systematic application of a test or enquiry to identify individuals at sufficient risk of a specific disorder, to benefit from further investigation or direct preventive action, among people who have not sought medical attention for the symptoms of that disorder (*246*).

- **Newborn screening:** Screening of all newborns in a population for prevalent diseases, including genetic diseases, that can be ameliorated or prevented by treatment from birth or shortly thereafter.
- **Carrier screening:** Isolation of potential carriers from a larger population for fur-

ther testing and genetic counselling for family planning.

- **Genetic screening:** A basic test that is systematically offered to a defined population in order to identify a group at increased genetic risk, which may then be offered further tests that enable a definitive diagnosis (*266*).

- **Family-based screening:** Genetic screening offered to relatives of a person identified as carrying a disease-causing gene mutation. When a carrier is detected, further testing is then offered to their relatives (*81*).

- **Premarital screening:** The screening of couples prior to marriage for carrier status for common recessive disorders which could result in their producing affected offspring.

Sex chromosome: The pair of chromosomes that determines the sex of an individual (XX for females and XY for males).

Sex selection: Identification, and selective termination of pregnancies on the basis of sex, for medical or non-medical purposes.

Sickle cell disease: An inherited disorder caused by defects in the haemoglobin-ß gene. The disorder produces abnormal haemoglobin, which causes the red blood cells to sickle or become crescent-shaped. The rapid breakdown of sickle-shaped red blood cells causes a decrease in red blood cells (anaemia) and jaundice. Other clinical features include: pulmonary hypertension, infections and periodic episodes of pain caused by oxygen deprivation in tissues. Symptoms usually begin in early childhood and can vary from mild to severe. Sickle cell anaemia affects millions of people worldwide, and is most common in Africa, the Arabian peninsula and India; sickle cell disease is also frequent in countries where people of African descent live (such as the United States). The condition is inherited in an autosomal recessive pattern. Carrier status also confers some resistance to malaria.

Sporadic genetic mutation: In terms of genetics, sporadic describes new mutations that cause disease; occurring either in a germ cell or somatic cell of an individual at any stage of life, and are therefore not present in the parents. Also called *de novo* mutations.

Tay Sachs disease: A rare autosomal recessive disorder that causes accumulation of lipids resulting in progressive destruction of nerve cells in the brain and spinal cord. The most common form begins in infancy. An infant with the disorder appears normal until the age of 3 to 6 months, when development slows and the baby is often unable to crawl, turn over or grasp objects. As the disease progresses, infants develop seizures, vision and hearing loss, mental retardation and paralysis. Children with this severe form of Tay Sachs disease have a life expectancy of about 1–4 years. Tay Sachs disease is more common in people of Ashkenazi Jewish heritage (*85*).

Termination of pregnancy: (see *Abortion*)

Thalassaemia: A group of hereditary forms of anaemia caused by a reduction in, or lack of, synthesis of the globin chains (most commonly alpha [a] or beta [ß] chains) that form the red blood pigment haemoglobin. Carriers may also show mild haematological symptoms. The condition was first described in Mediterranean populations; however, it is also prevalent in Africa, the Middle East and Asia. This group of disorders may range from mild blood abnormalities, to severe or fatal anaemia. Adult haemoglobin is composed of two a and two ß polypeptide chains. In a-thalassaemia, there is deficient synthesis of a-chains. In ß-thalassaemia there is a defect of ß-chains. Currently, severe thalassaemia is treated by blood transfusions, and a minority of patients are cured by bone marrow transplantation. This condition is inherited in an autosomal recessive pattern. Carrier status also confers some resistance to malaria.

Trisomy 18: (Also Edwards syndrome) A chromosomal condition that occurs when there are three copies of chromosome 18 in each cell instead of two. Trisomy 18 confers an extremely high mortality rate with about 90–95% mortality within the first year of life. This condition is characterized by low birth weight, a small, abnormally shaped head, clenched fists with overlapping fingers, mental retardation, heart defects and other organ malformations. Trisomy 18 affects about 1 in 5000 to 6000 live births. Approximately 80% of cases are female. The risk of having a child with Trisomy 18 increases with maternal age (*85*).

Trisomy 13: (Also Patau syndrome) A chromosomal condition that occurs when there are three copies of chromosome 13 instead of two. Trisomy 13 is associated with severe mental retardation, small eyes that may exhibit a split in the iris (coloboma), a cleft lip and/or palate, weak muscle tone (hypotonia), an increased risk of heart defects, skeletal abnormalities and other medical problems. Affected individuals rarely live past infancy. Trisomy 13 affects approximately 1 in 10 000 live births. The risk of having a child with Trisomy 13 increases with maternal age (*85*).

Ultrasound: An imaging method in which high-frequency sound waves are used to outline a part of the body. The sound wave echoes are picked up and displayed on a television screen. This test is used to monitor pregnancy and to identify some congenital disorders.

X-linked inheritance: The gene in question is situated on the X chromosome. In the context of disease, the inheritance is normally recessive and leads to disease in boys, since they only have one X chromosome, and there is generally no equivalent gene locus on the Y chromosome. Women who are carriers have a disease allele on one X chromosome and a normal allele on the other, and so do not usually express the disease. In some cases, however, the carrier may show mild or even severe forms of the disorder.

8
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9
Notes

1 There are, however, many other important principles in bioethics, particularly in relation to genetics, for example the ethical principles of reciprocity, mutuality, solidarity, citizenry and universality, as discussed in Knoppers BM, Chadwick R (2005). Human genetic research: emerging trends in ethics. *Nature Review Genetics* 6(1):75–79.

2 A table of degrees of kinship is available in Appendix B.

3 See Appendix B for the relationship between degrees of relatedness and the coefficient of inbreeding *(F)*.

4 WHO refers to the United Nations Report of the International Conference on Population and Development: "In no case should abortion be promoted as a method of family planning… All Governments and relevant intergovernmental and non-governmental organizations are urged to strengthen their commitment to women's health, to deal with the health impact of unsafe abortion as a major public health concern … Any measures or changes related to abortion within the health system can only be determined at the national or local level according to the national legislative process" (*230*, para 8.25).

5 See Case Study 3.

6 FAP is an autosomal dominant disorder; therefore consanguinity will not affect the prevalence of the condition in the community. However, it will increase the likelihood that multiple branches of a family will have affected individuals.

7 A more detailed discussion of disclosure and confidentiality of test results is available in World Health Organization Human Genetics Programme (2001). *Review of ethical issues in medical genetics: report of consultants to WHO, Professors DC Wertz, JC Fletcher, K Berg*. Geneva, World Health Organization (WHO/HGN/ETH/00.4).

8 These principles are outlined in Fletcher, Berg & Tranoy, 1985:199–205 (*77*).

9 However, the expansion of genetic testing has resulted in performance of some genetic tests, particularly those frequently done by non-geneticists (such as Factor V Leiden testing for hereditary thrombotic disorders), without adherence to formal informed consent procedures.

10 Under the Fijian Constitution, the right is justiciable; it binds all branches of government, and all laws made and administrative and judicial actions taken after the commencement of the Constitution are subject to it and the Bill of Rights

generally (*54*, §21). It should be noted, however, that this is not the case for any constitutional rights; in some countries and for some rights, rights outlined in the constitution may only be standards which government aims to meet but is not bound by.

11 This provision is in accordance with the Marriage Law of 1980, which provides that no marriage may be contracted "if the man or the woman is suffering from any disease, which is regarded by medical science as rendering a person unfit for marriage" (*152*, Art. 7).

12 Comparative literacy rates for some of the countries we have discussed are as follows. Brazil: male literacy 86%, female literacy 87%; China: male literacy 95%, female literacy 87%; India: male literacy 70%, female literacy 48%; Nigeria: male literacy 75%, female literacy 61%. All figures based on 2003 data; these and other literacy statistics are available on the CIA website *The World Fact Book*, United States Government (http://www.cia.gov/cia/publications/factbook/, accessed 8 June 2005).

Appendix A
Developing and developed countries

Based on World Bank classifications (*259*)

Developing countries

Low-income economies

Afghanistan
Angola
Bangladesh
Benin
Bhutan
Burkina Faso
Burundi
Cambodia
Cameroon
Central African Republic (the)
Chad
Comoros (the)
Congo (Democratic Republic of)
Congo (the)
Côte d'Ivoire
Equatorial Guinea
Eritrea
Ethiopia
Gambia (the)
Ghana
Guinea
Guinea-Bissau
Haiti
India
Kenya
Korea (Democratic People's Republic of)
Kyrgyz Republic
Lao People's Democratic Republic (the)
Lesotho
Liberia
Madagascar
Malawi
Mali
Mauritania
Moldova (the Republic of)
Mongolia
Mozambique
Myanmar
Nepal
Nicaragua
Niger (the)
Nigeria
Pakistan
Papua New Guinea
Rwanda
Sao Tome and Principe
Senegal
Sierra Leone
Solomon Islands
Somalia
Sudan (the)
Tajikistan
Tanzania (the United Republic of)
Timor-Leste
Togo
Uganda
Uzbekistan
Viet Nam
Yemen
Zambia
Zimbabwe

Lower-middle-income economies

Albania
Algeria
Armenia
Azerbaijan
Belarus
Bolivia
Bosnia and Herzegovina
Brazil
Bulgaria
Cape Verde
China
Colombia
Cuba
Djibouti
Dominican Republic (the)
Ecuador
Egypt
El Salvador
Fiji
Georgia
Guatemala
Guyana
Honduras
Indonesia
Iran (Islamic Republic of)
Iraq
Jamaica
Jordan
Kazakhstan
Kiribati
Macedonia (the former Yugoslav Republic of)
Maldives
Marshall Islands (the)
Micronesia (Federated States of)
Montenegro
Morocco
Namibia
Paraguay
Peru
Philippines (the)
Romania
Russian Federation (the)
Samoa
Serbia
South Africa
Sri Lanka
Suriname
Swaziland
Syrian Arab Republic (the)
Thailand
Tonga
Tunisia
Turkey
Turkmenistan
Ukraine
Vanuatu
West Bank and Gaza

...Developing countries

Upper-middle-income economies

American Samoa
Antigua and Barbuda
Argentina
Barbados
Belize
Botswana
Chile
Costa Rica
Croatia
Czech Republic (the)
Dominica
Estonia
Gabon
Grenada
Hungary
Latvia
Lebanon
Libya
Lithuania
Malaysia
Mauritius
Mayotte
Mexico
Northern Mariana Islands
Oman
Palau
Panama
Poland
Saudi Arabia
Seychelles
Slovak Republic
St Kitts and Nevis
St Lucia
St Vincent and the Grenadines
Trinidad and Tobago
Uruguay
Venezuela (the Bolivian Republic of)

High-income economies

Hong Kong SAR (China)
Israel
Kuwait
Singapore
United Arab Emirates (the)

Developed Countries

High-income economies

Andorra
Aruba
Australia
Austria
Bahamas (the)
Bahrain
Belgium
Bermuda
Brunei
Canada
Cayman Islands
Channel Islands
Cyprus
Denmark
Faeroe Islands
Finland
France
French Polynesia
Germany
Greece
Greenland
Guam
Iceland
Ireland
Isle of Man
Italy
Japan
Korea (the Republic of)
Liechtenstein
Luxembourg
Macao, China
Malta
Monaco
Netherlands (the)
Netherlands Antilles
New Caledonia
New Zealand
Norway
Portugal
Puerto Rico
Qatar
San Marino
Slovenia
Spain
Sweden
Switzerland
United Kingdom of Great Britain and Northern Ireland (the)
United States of America (the)
Virgin Islands (USA)

Appendix B
Degrees of relationship in consanguinity

This appendix is based on references *99*; *25*.

Relationship	Proportion of genes shared	Coefficient of inbreeding (F)
First degree		
Sibling including dizygotic (fraternal) twin Parent–child	1/2	1/4 = 0.25
Second degree		
Half-sibling Uncle/aunt–niece/nephew Double first cousin	1/4	1/8 = 0.125
Third degree		
First cousin Half uncle/aunt–half niece/nephew Half niece/nephew (child of half-sibling)	1/8	1/16 = 0.0625
Fourth degree		
First cousin once removed Half first cousin including half-uncle/aunt	1/16	1/32 = 0.031
Fifth degree		
Second cousin	1/32	1/64 = 0.0156

Appendix C
Fair process

Fair process for health care rationing and delivery of genetics services involves the following elements (based on *62*; *275*):

1. A **public mechanism** for setting priorities that is transparent, broadly inclusive of stakeholders, and whose principles, procedures and priorities are widely publicized to stakeholders and the public at large.

2. **Relevant reasons**, principles, evidence and information that are widely viewed by stakeholders as appropriate and pertinent to fair decision-making about policies and priorities.

3. An **appeals mechanism** that permits the reconsideration and revision of decisions and priorities concerning equitable provision of genetics services, in light of further evidence or arguments.

4. An **enforcement mechanism** to ensure that there is either voluntary or public regulation to ensure that conditions 1–3 are met.