

Chapter 3

Genetic screening : current programmes

Introduction

- 3.1** Genetic screening programmes are not a new development. Since the 1960s pregnant women have been routinely tested for their **rhesus blood group**, so that damage to babies of rhesus negative women before and after birth can be prevented. Damage is prevented by ensuring that rhesus negative women are given an antibody within a few hours of delivery, miscarriage or abortion. Since 1973 it has been policy to screen all newborn babies in the UK for **phenylketonuria (PKU)**. Severe mental retardation is characteristic of this disease, but can be prevented if dietary treatment is started in the first weeks of life. These two tests have now become an accepted part of primary health care, and are essentially genetic screening programmes.
- 3.2** Genetic screening may be carried out in the following groups of people:-
- (i) the entire population, albeit a section defined by age or sex, where all within the group are at risk. This is appropriate for example in screening newborn babies for **PKU**;
 - (ii) sub-groups within the population, where the risk is known to be concentrated. This is appropriate, for example, within the Ashkenazi Jewish population for **Tay-Sachs disease**, a fatal brain disease of children especially frequent in this group, where healthy carriers can be detected in order to provide information;
 - (iii) broad groups in which genetic factors may be responsible for some but not all of certain disabilities. For example, individuals with learning difficulties could be screened in order to detect those with **fragile X syndrome**, and thus identify the families at further genetic risk.

3.3 Individuals with a family history of an inherited disorder may undergo genetic testing. Such testing should be distinguished from population screening, but has important similar societal effects which are considered in this report. Family studies provide the most practical strategy for detection of the abnormal gene in most dominantly inherited and X-linked disorders.

3.4 Screening programmes often have more than one component. A **primary screen** may be offered to all members of the population to identify a 'risk group', which would then be offered further **testing**, leading to **definitive diagnosis**. This sequence applies to many genetic screening programmes, depending on the methodology used. For example, the initial screening test for phenylketonuria (PKU) is by an indirect method (see paragraph 2.16). Babies with a positive result do not always have the disease and further tests are required to confirm the diagnosis. Where, however, direct methods are better (for example, testing for carriers for cystic fibrosis) no further testing is required for those with positive results. In the case of cystic fibrosis, a small proportion of individuals whose genetic defect is not detected by the current test will be missed.

3.5 Depending upon the mode of inheritance, the genetic abnormality, and the type of test, screening may detect individuals:-

- (i) who have the disorder, for example, phenylketonuria (PKU) as presently screened by blood spot in the newborn;
- (ii) who are themselves unaffected, but are carriers of a gene for a recessively inherited disorder (for example, sickle cell disease) and thus at risk of having an affected child;
- (iii) who may themselves develop a disease after many years, for example, Huntington's disease.

It follows that a variety of different practical and ethical problems may arise.

3.6 Screening may also be carried out for **congenital disorders** where a genetic basis **may** exist but has not been established; for example, ultrasound scanning of a fetus for malformations.

3.7 In the future, increased understanding of the genetic component in common diseases may lead to proposals for screening for genetic abnormalities that confer an **increased risk** for the individual rather than a **certainty** of developing the disease : for example, screening may point to an increased risk of cancer, or diabetes, or mental disease and there may not be simple or guaranteed ways of avoiding the risk or of treating the condition

if it develops. It is therefore important to assess, so far as possible, the character and degree of risk, to study existing experience as it increases, and to improve understanding of the social and ethical, as well as the technical, implications of genetic screening.

Principles of genetic screening programmes

3.8 The traditionally accepted principles and practice of screening for disease were set out in a WHO report in 1968:¹

- 1 An important disease
- 2 Known history
- 3 Latent or early symptomatic state
- 4 Reliable screening test available
- 5 Definite diagnosis possible and treatment available
- 6 Natural history improved by treatment
- 7 Cost effective

3.9 These criteria were designed for the detection of disease. They were formulated before prenatal diagnosis with the associated option of aborting an affected fetus was current. They are not entirely appropriate for genetic screening, for example for carriers for a recessively inherited disorder who are themselves healthy (see paragraph 3.5(ii)). For genetic screening three goals have been identified.² It should:-

- (i) contribute to improving the health of persons who suffer from genetic disorders; and/or
- (ii) allow carriers for a given abnormal gene to make informed choices regarding reproduction; and/or
- (iii) move towards alleviating the anxieties of families and communities faced with the prospect of serious genetic disease.

3.10 Further experience of genetic screening can be expected to lead to a more precise definition of its principles and goals; **but at present the prime requirement is that the target disease should be serious.** The Clothier Committee on the Ethics of Gene Therapy³ recommended that the first candidates for consideration for such treatment should be those suffering from a disorder which is life-threatening, or causes serious handicap, and for which treatment is unavailable or unsatisfactory. Such disorders would clearly be classed as serious. In the context of

genetic screening the definition is likely to be much wider and it is difficult to define precisely what is serious. Furthermore the perception of seriousness may vary between societies and will vary according to treatment possibilities. The fact that the severity of some diseases can range from serious to slight, as in fragile X syndrome, adds to the difficulties. Perhaps it is easier to define what should not be included in genetic screening : these are characteristics with a genetic component, but which cannot be classed as diseases.

Existing screening programmes

- 3.11** In reviewing existing screening programmes, some of which are well established and others barely beyond the pilot stage, we have tried to identify the ethical problems that may arise.
- 3.12** Screening programmes are broadly divided into four groups, depending on the timing of the testing:-
- (i) neonatal (in the newly born)
 - (ii) older children
 - (iii) testing of couples or individuals before pregnancy (adults)
 - (iv) antenatal (during pregnancy).
- 3.13** There may be no single stage of life at which genetic screening is most suitable. Screening may best be offered in a variety of ways, and the optimal approach may change as the community becomes more informed. For example, genetic screening for thalassaemia in Cyprus and Sardinia (countries where this is particularly common) has progressed from the antenatal stage to the premarital stage towards screening in schools. This type of progression may prove to be a common pattern as genetic screening becomes a more established component of primary health care.

Neonatal screening

- 3.14** The blood spot test for **phenylketonuria** (PKU) has not created any major ethical problems, although the information given about the condition and the informed consent obtained in many instances have not met the criteria recommended in paragraph 4.6. Likewise the test for **congenital hypothyroidism**, which is carried out on the same sample, does not appear to have raised

any major ethical problems. This may in part be because both diseases are severe and can be adequately treated if detected.

- 3.15** Nevertheless, there is evidence that many women do not understand what the test is for. A recent study of new mothers' knowledge of the blood test for PKU and hypothyroidism showed that although two thirds said that the test had been fully explained, most did not in fact know what it was for, and a considerable number incorrectly believed the test detects more disorders than is the case.⁴ Such results clearly challenge any notion that women are giving informed consent for their babies to be tested, even though they believe themselves to be informed. This issue is discussed further in Chapter 4.
- 3.16** Some laboratories carrying out neonatal screening for PKU and hypothyroidism, both in the UK and other countries, have chosen to add tests for other serious conditions. It is not always clear to what extent parents are fully informed about these tests. A neonatal screening programme in Pittsburgh, USA, has chosen to employ 'informed dissent', where parents are required to express a wish to opt out if they so desire.⁵
- 3.17** The present method of screening for PKU, which is recessively inherited, is indirect and does not identify the genes involved. If direct gene testing were introduced, so that carriers as well as affected individuals were identified, a different order of ethical issues would clearly arise. The finding of a carrier child has no disease implications for the child, but may become important to that child in later life when reproductive decisions are being made. How and when the child should be told would require careful consideration.
- 3.18** Neonatal screening for **sickle cell disease** is cheap and reliable and is recommended for populations with a significant incidence of this disease. Early diagnosis of affected infants reduces childhood mortality and morbidity, and allows parents to be counselled about subsequent pregnancies. In some inner city areas in the UK, all newborns regardless of ethnic origin are now screened for sickle cell disease. Screening, however, does detect carriers as well as affected individuals, and thus raises ethical issues for the families as discussed above.
- 3.19** Neonatal screening for **cystic fibrosis** (CF) by indirect testing (for trypsin in the blood) is only carried out in certain areas and is still under evaluation. There is some, but not conclusive, evidence that neonatal identification of infants with cystic fibrosis may improve their prognosis, because preventive management can be started before their lungs are damaged. Parents of affected children can also be offered prenatal diagnosis in subsequent

pregnancies. DNA techniques, which identify carriers as well as affected children, have been used for confirmation of the diagnosis in the newborn period.

- 3.20** Pilot neonatal screening programmes for early identification of **Duchenne muscular dystrophy** have been set up in the UK (in Wales) and several other countries.⁶ All of these programmes have been based on an indirect method; the detection of the level of the enzyme, creatine kinase, in the blood. These programmes vary somewhat in detail, and in the manner of obtaining consent : the Pittsburgh study, for example, employs informed dissent (see paragraph 3.16). The X-linked nature of this disease raises particular ethical issues in terms of implications for the extended family (see paragraph 5.13).
- 3.21** Because neonatal screening for Duchenne muscular dystrophy is essentially still in the pilot stage, evaluation of all the ethical issues is not possible. Most of those involved consider that extensive, well-monitored pilot phases should precede a decision on more general implementation.⁶
- 3.22** All newborn babies have a **physical examination** which may detect **congenital disorders**, some of which may have a genetic component. Examinations are often carried out in the presence of the mother and the parents are informed about any abnormalities and their implications.

Later childhood screening

- 3.23** As part of **routine child health surveillance**, all children have a physical examination for a variety of diseases which may in part have a genetic basis; for example, hearing defects may be detected. Programmes of screening for specific genetic disorders are at present in the pilot stage.
- 3.24** In Montreal, genetic screening programmes directed at high school students have been conducted for **Tay-Sachs disease**, **beta thalassaemia** and **cystic fibrosis**.^{7,8,9} All three projects appear to have been well accepted. The vast majority (over 90%) in all programmes approved of screening in high school and understood the significance of the findings. Clearly the community was well informed as genetic screening in the local high schools is regarded as a 'normal activity'. Most carriers for Tay-Sachs or beta thalassaemia claimed they would want to know the carrier status of an intended spouse; a small minority of the Tay-Sachs carriers would 'reconsider' if the prospective partner proved to be a carrier. A follow-up survey of attitudes towards screening for

Tay-Sachs concluded that “students have a very positive attitude toward genetic screening in general. These findings are associated with an effort to expand the human genetics content in the biology curriculum....The screening clinic in the schools, and literature provided by the screening authority, was an effective source of knowledge about the significance of Tay-Sachs heterozygosity [ie of being a Tay-Sachs carrier].”⁷

Adult screening

- 3.25** Screening of adults may be carried out to detect existing disease or predisposition to a disease, or may identify carriers with a reproductive genetic risk. Most presymptomatic testing for late onset genetic diseases (for example, Huntington’s disease) is currently offered to family members at risk. General screening for such late-onset genetic diseases is increasingly becoming technically feasible, though not necessarily desirable.
- 3.26** Screening programmes for various forms of cancer which may have a genetic basis are currently the main form of genetic screening in the adult population. Testing of the gene itself is now possible for **familial adenomatous polyposis**, an inherited form of **colorectal cancer**. It may shortly become possible to screen a sub-group of women at high risk of familial **breast cancer**, though at present such screening is aimed at early detection of the cancer itself. These testing programmes in families already known to be at risk may be the forerunners of future screening programmes.
- 3.27** The general screening of individuals who may be carriers for inherited disease genes is currently used only as a service to those in an ethnic group known to have a high incidence of an inherited disease, for example the **haemoglobin disorders** and **Tay-Sachs** disease.
- 3.28** Pilot projects have been undertaken in several centres to detect carriers for **cystic fibrosis** in adults aged between 16 and 45 years through screening in general practice.^{10,11} Preliminary results suggest a high uptake when individuals are offered testing and counselling through personal contact. These projects are discussed more fully in Chapter 4.

Pre-pregnancy and pre-marital screening

- 3.29** Testing before pregnancy is not systematically practised to any extent in the UK. Screening for carriers for the **haemoglobin disorders** may be offered through family planning clinics and general practice. Insufficient information is available to evaluate such programmes.
- 3.30** In Cyprus, antenatal screening for **thalassaemia** has been almost totally superseded by premarital screening. The religious authorities had ethical objections to screening during pregnancy on the grounds that it excluded most options other than termination of affected pregnancies. The church in Cyprus therefore insists on testing as a formal prerequisite to church weddings. The certificate required states merely that the partners have been tested and appropriately advised. In this way the confidentiality of the test result is preserved and the couple can exercise an informed choice about reproduction.
- 3.31** General population carrier screening programmes for **thalassaemia** have been established throughout the Mediterranean area. A comparative study of these programmes has shown they are most rapidly and equitably implemented when a small community at high risk is served by motivated staff working from a single centre, with the help of a lay support association (for example, Sardinia and Cyprus).¹² Such programmes have developed more slowly in larger countries, as they must be delivered through the general health care system, and staff must be trained to integrate screening and counselling into routine services. It has proved particularly difficult to organise carrier screening for haemoglobin disorders when they are not a problem for the whole community but primarily affect ethnic minorities, as in the UK. This problem is the subject of the forthcoming Standing Medical Advisory Committee report on sickle cell, thalassaemia and other haemoglobinopathies. This report, it is hoped, will give guidelines to health service purchasers and providers on the provision of information, screening and counselling services.

Screening during pregnancy

- 3.32** Screening during pregnancy may be carried out on the mother, on the baby, or on both. If, through screening, a woman is found to be a carrier for a gene for a recessive disorder, her partner may be offered genetic testing in order to find out whether the couple is at risk of having an affected child. If both parents carry the gene for a recessive disorder, or if the mother carries the gene for

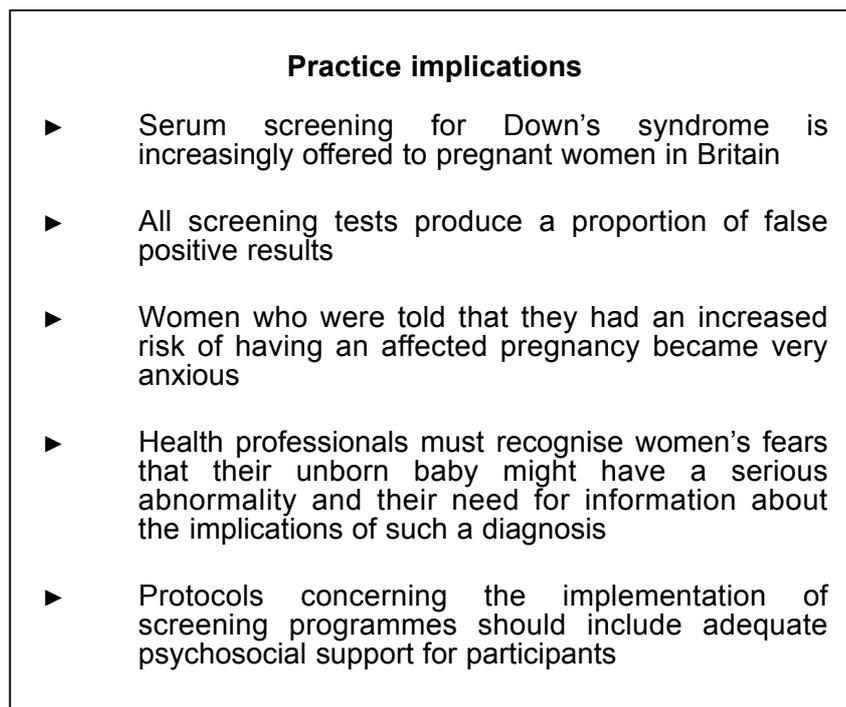
an X-linked disorder or if either parent has the gene for a dominant disorder, then tests may be done on the developing fetus. There are several methods of obtaining samples for genetic tests on the fetus, the most common being **amniocentesis** and **chorionic villus sampling (CVS)**. Genetic diagnosis can be achieved before 12 weeks' gestation with CVS, compared with about 16-20 by amniocentesis. However, the risk of miscarriage is slightly higher for CVS (about 1-2% in excess of expectation at this stage of pregnancy) than for amniocentesis (0.5-1%). The emotional trauma engendered by the need to consider a termination and decide whether or not to have one must not be ignored. This is a major ethical issue which applies to many screening procedures where the disease is serious and where there is no effective treatment. Informing parents of the reproductive choices places a considerable burden on them, and counselling and support will be needed whatever the decision.

- 3.33** In the UK, antenatal screening tests are carried out on all women for **rhesus haemolytic disease** (see paragraph 3.1) and **rubella** (German measles). Rubella screening was the first screening programme undertaken with the objective of offering detection and abortion of potentially affected fetuses. Severe congenital disorders can result from rubella infection during pregnancy.
- 3.34** Both rhesus and rubella screening appear to be well accepted. Whereas the finding of a rhesus negative blood group results in preventive treatment, a positive rubella test gives rise to the need for very painful decisions.
- 3.35** Ultrasound scanning of the fetus is generally practised and routine ultrasound may reveal **congenital abnormalities**, some of which may have a genetic basis. Expert fetal anomaly scanning, a specialised form of ultrasound scanning, is offered to women known to be at increased risk of having a malformed fetus because of genetic or other reasons. In addition, it is increasingly offered to all women on a routine basis, as about 70-80% of all severe malformations can be detected. Although the majority of women are aware of ultrasound, the amount of explanation given regarding the possibility of detecting abnormalities varies greatly, as does expertise in interpreting the results.
- 3.36** The offspring of women with **insulin dependent diabetes mellitus** have an increased risk of stillbirth, neonatal ill health, and major congenital malformations, especially if their diabetes is poorly controlled. In many women with diabetes the diagnosis will already be known, but all women are screened early in pregnancy by blood and urine tests to detect undiagnosed cases. Expert fetal anomaly scanning by ultrasound is offered to all those having the condition.

- 3.37** In many areas, screening is carried out to detect **neural tube defects (spina bifida and anencephaly)**. Maternal serum **alphafetoprotein (AFP)** estimation is now offered routinely to all pregnant women between 16 and 18 weeks of gestation, but in about half of all pregnancies with a raised maternal serum AFP, no cause can be found, either pre- or post-natally. A raised maternal serum AFP normally leads to expert ultrasound examination for a fetal malformation, with or without amniocentesis for confirmatory biochemical tests.
- 3.38** Pilot studies of screening during pregnancy for carriers for the common disorder **cystic fibrosis** are currently being undertaken in a number of centres.^{13,14,15} In the UK, 85-90% of carriers can be detected by a simple DNA screening test based on a mouthwash sample.
- 3.39** The various studies of cystic fibrosis screening have devoted considerable effort to the psychological and ethical issues surrounding genetic screening programmes, especially since not all carriers can be detected.
- 3.40** A study in Edinburgh showed that, of the 2207 women invited for cystic fibrosis carrier screening during pregnancy, 85% accepted it.¹⁶ Only 325 (15%) declined to be tested. Of those who declined, over half did so because of opposition to termination of pregnancy. Other reasons given included the partner's disapproval or non-participation, perceived risk of a CF child being low, the error rate of the test and the generation of unacceptable levels of anxiety.
- 3.41** The Edinburgh study has assessed the attitudes and responses of the participants and the psychological effects on carriers and their partners. The majority felt that they had had adequate information and were glad to have participated (see paragraph 4.13). There was a consensus that CF carrier testing should be routinely offered to pregnant women, and also that it should be available in family planning clinics and GP health centres, but not in schools. Carriers showed significant symptoms of anxiety and depression whilst awaiting their partner's test result (at this time partners were only tested if the pregnant woman was a carrier : this problem should not occur if couples are tested simultaneously). On receiving the partner's negative test result the carriers returned to normal equilibrium and maintained this.
- 3.42** Antenatal screening is offered to women in specific risk groups. All **women over an age that varies by area between 35 and 37** are offered testing by chromosome studies for the presence of **Down's syndrome** in the baby. Down's syndrome occurs in approximately 1 in 600 of all births; but it is much less common in

children born to younger women (1 in 1,500 at age 20). Its birth incidence increases with maternal age, being about 1 in 350 at age 35, and as high as 1 in 100 at age 40. Recently, **maternal serum screening** tests have been developed that can be offered to all pregnant women to detect those who may be at increased risk of having a child with Down's syndrome regardless of age, in order to offer them the choice of amniocentesis and chromosome testing.¹⁷ This type of screening is now entering widespread practice and it is estimated that nearly 70% of British districts and health boards have opted to introduce such screening. There are, however, major problems. There is a high false positive rate (about 65 false positives for every true positive or about 1 pregnancy in 10) and false negative rate (about 40%). The practical difficulties relating to consent and counselling and the psychological consequences do not appear to have been given sufficient attention and these are discussed further in Chapter 5. A small study of the experiences of some women who had abnormal results showed that all women were made anxious by their abnormal screening test no matter how they were told.¹⁸ Even after a normal amniocentesis result (ie an unaffected baby) some remained anxious. The practice implications arising from the study are reproduced in Fig A and are, of course applicable to many other conditions for which screening may be introduced.

Fig A¹⁸



- 3.43** **Women with epilepsy** requiring treatment with drugs are usually offered expert fetal anomaly scanning by ultrasound in the second trimester of pregnancy because of the increased risk of congenital malformation caused by some drugs.
- 3.44** It is standard practice in the UK to undertake carrier screening for **haemoglobin disorders** of individuals in antenatal clinics (and increasingly in primary care) who are “not of Northern European origin”. Historically the tests used to be part of routine blood investigations, undertaken to detect clinical conditions such as sickle cell disorders. In the process carriers of haemoglobin disorders were identified, but the women were not always informed either that they had undergone a form of genetic screening or of the result. Women found to be carriers are now told by a variety of staff including obstetricians, midwives, haematologists and, increasingly, haemoglobinopathy counsellors (usually nurses and health visitors who have undertaken specialist training).
- 3.45** Most couples at risk of having children with a major thalassaemia, and about 50% of those at risk of sickle cell disease, request diagnostic tests on the fetus and decide on abortion if the results show the fetus is affected. Screening and counselling may therefore lead to a great reduction in births of affected children, but the emotional costs of the decision to terminate should not be ignored (see paragraph 3.32).
- 3.46** It is likely that by the time this report is published, some pilot screening programmes may have been extended into more general use and others will be being evaluated. The table opposite summarises current (September 1993) genetic screening programmes in the UK.

CURRENT GENETIC SCREENING PROGRAMMES IN THE UK (September 1993)

It is likely that by the time this report is published, some pilot screening programmes will have extended into more general use and others will be being evaluated. The following table summarises current genetic screening programmes in the UK.

Age Group	Disease	Population screened	Type of screening test	Confirmation required	Other comments
Neonatal	Phenylketonuria	All newborn infants	Indirect	Yes	Also detects carriers
	Hypothyroidism	All newborn infants	Indirect	Yes	
	Sickle cell disease	All newborn in some areas; confined to certain ethnic groups in others	Indirect	Yes	
	Cystic fibrosis	Some areas only (still at pilot stage)	Indirect	Yes	
	Duchenne muscular dystrophy	Pilot studies	Indirect	Yes	
	Other rare metabolic disorders	Family testing	Usually indirect	–	
Later childhood		NONE IN THE UK			
Pre-marital and pre-pregnancy	Cystic fibrosis	Pilot projects in general practice	Direct	No	Detects 85 – 90% of carriers
During pregnancy	Rhesus haemolytic disease	All mothers	Indirect	Yes fetal anomaly ultrasound Amniocentesis with chromosome tests on fetus required for confirmation No Fetal anomaly ultrasound	Fetuses have expert fetal anomaly scanning
	Diabetes mellitus	All mothers	Indirect		
	Congenital malformations	Most fetuses	Routine ultrasound		
	Down's syndrome	1) All mothers in some areas 2) All mothers over 35–37	Serum screening tests		
			Chromosome tests on fetus		
	Neural tube defects (spina bifida and anencephaly)	All mothers in many areas	Indirect		
Haemoglobin disorders	All mothers not of North European origin	Indirect		Detects carriers	
Cystic fibrosis	Pilot studies	Direct	No	Detects 85 - 90% of carriers	