

ADVISORY COMMITTEE ON GENETIC TESTING

PRENATAL GENETIC TESTING

Report for Consultation

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**Human
Genetics
Commission**

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FOREWORD

The Advisory Committee on Genetic Testing (ACGT)

1. ACGT was established, under the Chairmanship of the Rev Dr John Polkinghorne KBE FRS in 1996. A full list of ACGT's members is at Annex A. ACGT's remit covers the whole of the United Kingdom, and the Department of Health provides ACGT's Secretariat.
2. ACGT's Terms of Reference are:
 - to provide advice to Ministers on developments in testing for genetic disorders;
 - to advise on testing individuals for genetic disorders, taking account of ethical, social and scientific aspects; and
 - to establish requirements, especially in respect of efficacy and product information, to be met by manufacturers and suppliers of genetic tests.
3. ACGT has published the following documents:
 - Code of Practice and Guidance on Human Genetic Testing Services Supplied Direct to the Public (September 1997)
 - 1st Annual Report July 1998 - December 1997 (March 1998)
 - Genetic Testing for Late Onset Disorders (September 1998)
 - ACGT advice to Research Ethics Committees (October 1998)
 - 2nd Annual Report January 1998 – December 1998 (May 1999)

Copies of these documents are available from the Secretariat or on the DH Genetics website: www.open.gov.uk/doh/genetics.htm
4. Following a review of the regulatory framework for biotechnology by the Government, the work of ACGT has been subsumed into a new body, the Human Genetics Commission which is publishing this report on behalf of ACGT.

Prenatal Genetic Testing

5. In January 1998 ACGT agreed that a report should be prepared on Prenatal Genetic Testing, and invited Professor Sally Macintyre to chair the subgroup established to prepare this work. Mr Philip Webb subsequently took over the Chairmanship of the Subgroup. A full list of members of the subgroup is at Annex B.
6. The Subgroup was given the following terms of reference:
 - (i) to report on issues to be considered when providing prenatal genetic testing services; and
 - (ii) to work, with the National Screening Committee, on issues of prenatal genetic screening.
7. This report fulfils the first part of the terms of reference but excludes consideration of the following techniques:

Prenatal Genetic Screening - which applies risk assessment methods to pregnant women in the general population who are at a low collective risk of a genetic condition as opposed to individual women who are known to be at increased risk. However, some women identified to be at increased risk by screening tests will go on to have definitive prenatal diagnosis. This latter group is included within this report.

Preimplantation Genetic Diagnosis - which examines embryos *in vitro* prior to implantation. This technique, which may be provided to those undergoing IVF treatment or others with a higher risk of a particular genetic disorder, is the subject of a joint report from the Human Fertilisation and Embryology Authority and ACGT.
8. ACGT are grateful to Dr Julie McGaughran, Department of Genetics, Manchester for her invaluable help in completing this report.

Summary of recommendations

Service organisation

1. *Genetic and fetal medicine services should be available to enable local access to those who require them.*
2. *Sufficient resources should be made available both in the primary care and hospital setting for referral and subsequent care of appropriate patients who may wish to have prenatal genetic testing and genetic counselling.*
3. *A woman should have access to the prenatal genetic tests and expertise she requires appropriate to her risk.*
4. *Consideration should be given to the cost of the potential support needed by families in addition to the genetic tests when evaluating and commissioning prenatal genetic and fetal medicine services.*
5. *Prenatal genetic testing for rare disorders should be organised on a supra-regional or national level.*
6. *Appropriate funding for such testing should be identified.*

Undertaking testing

7. *At each pregnancy, bearing in mind advances in technology and knowledge, women should be offered information on prenatal genetic tests appropriate to their individual risk factors.*
8. *All women capable of giving consent can accept or refuse any or all of the tests offered.*
9. *In all cases of prenatal genetic testing of a woman capable of giving consent, specific consent - verbal and recorded or written - should always be obtained. Consent should be obtained for each procedure and each test.*
10. *Consent should be freely given, without pressure from third parties.*
11. *Where a woman is permanently incapable of giving consent (e.g. because of a learning disability) the testing decision will be made by the doctor responsible for her clinical care. Doctors will be guided by the best interests of the woman and where appropriate take into account the views of the family or other close carers.*

12. *If the incapacity is temporary, genetic testing should be delayed until consent is possible unless it is essential in the individual's therapy and/or in their best interests.*
13. *Appropriate support in preparation for and subsequent to genetic testing should be part of the prenatal genetic testing process.*
14. *Full information should be supplied to the woman in an appropriate form giving details of the tests. The information should enable the woman to understand the nature of the test, its scope and limitations, and the accuracy, significance and use of the result, and, where appropriate, its possible implications for family members. Information should also be provided on appropriate professional and voluntary bodies able to offer support, as they may be able to provide advice about information materials.*

Outcome of testing

15. *Pre-test genetic counselling and post-test consultation opportunities should be provided to women, and if appropriate to their partners, by suitably qualified and experienced professionals.*
16. *The general medical practitioner or other professionals who continue the care of the woman and, where appropriate, her family should be provided with appropriate information pre and post test.*
17. *Where diagnosis is unknown or uncertain, facilities should be available for further assessment by a paediatric/fetal pathologist and/or clinical geneticist to enable accurate information to be available to the parents.*
18. *There should be good communication between referring units and more specialised Fetal Medicine centres about the ongoing pregnancy of women who have prenatal genetic testing as appropriate.*
19. *If a termination of pregnancy is to be considered in the light of test results, access to a unit with appropriate medical and counselling services should be arranged. There should be close liaison between the diagnostic team and staff at the unit where the termination is carried out. Adequate support and care during and after termination should be available for the parents.*

Service standards

20. *All laboratories undertaking prenatal genetic testing should be appropriately staffed and equipped, and:*

- (i) *be registered with a National Accreditation Body and conform to the requirements of BS 5750 (ISO9002). Continued registration is dependent on satisfactory audits performed every six months by the Accreditation Body to ensure compliance with appropriate standards;*
 - (ii) *be accredited by the Clinical Pathology Accreditation (UK) Ltd (CPA). Accreditation by CPA involves external audit to standards reflecting best professional practice for clinical laboratories;*
 - (iii) *perform adequate internal quality control;*
 - (iv) *undertake regular audit to identify areas where improvements in practice are possible and participate in relevant external quality assessment schemes.*
21. *All equipment, reagents and procedures used in testing laboratories should reflect current best practice and provide assured levels of accuracy and reliability as a prerequisite of good practice.*
22. *Some sampling devices and testing equipment may be required to comply with relevant UK Regulations and European Directives. In such cases the quality requirements set out in the General Product Safety Regulations 1994, the Medical Devices Regulations 1994 (the Medical Devices Directive (93/42/EEC)) and the In Vitro Diagnostic Medical Devices Regulations 2000 (Directive 98/79/EC) should be the minimum adopted.*
23. *Staff involved in prenatal diagnosis in regional genetic centres and fetal medicine centres should ensure their continued professional development. Clinicians should be able to demonstrate regular audit of their services.*

Research

24. *Research should only be performed when approved by an appropriate Research Ethics Committee.*
25. *Prenatal genetic tests undertaken for research purposes should only take place after the individuals participating have given their consent. Such consent should be recorded.*
26. *All test results obtained through research are confidential and should not be given to anyone without the consent of the participant.*
27. *Women taking part in genetic research should be fully aware of the use of their sample. No further tests should be undertaken on identifiable samples without explicit explanation to, and consent from, the woman.*
28. *It should be made clear to women that in some cases a test that is available on a research basis to individuals is not suitable or available for prenatal testing.*

Definitions used in this Report

Autosomal Dominant Disorders - Disorders where inheritance of a mutation from one parent only (or arising anew during egg or sperm formation) can be sufficient for the person to be affected. Important dominant disorders in the UK include familial hypercholesterolaemia, Huntington Disease, adult polycystic kidney disease and familial adenomatous polyposis.

Autosomal Recessive Disorders - Disorders, where for a person to be affected, a mutation has to be inherited from both parents. Such parents are usually unaffected carriers because they only have a single copy of the mutant gene. Recessive disorders commonly have onset in childhood and include cystic fibrosis, sickle cell disease and thalassaemia.

Diagnostic ultrasound - This is detailed fetal examination by an experienced operator using equipment of high imaging specification to detect specific abnormalities in a high risk pregnancy.

Fluorescent *in situ* hybridisation (FISH) - This is a recently developed molecular cytogenetic technique using a DNA probe for a small, specific area of one chromosome. The probe is fluorescently labelled enabling it to be seen. Normally two signals would be seen, one from each of the chromosome pair. In cases where there is a deletion of that part of a chromosome, only one signal is seen. Where there is an extra copy of a chromosome, for example chromosome 21 in Down syndrome, three signals are present. This technique is useful where specific abnormalities are being sought and can be used for rapid diagnosis of some conditions, for example Down syndrome on samples collected by amniocentesis.

Genetic Counselling - A process of consultation by which information is imparted to individuals or families affected by, or at risk of a genetic disorder. It includes information on the nature of the disorder; the size and extent of genetic risks; the options, including genetic testing, that may help clarify the risks; the available preventive and therapeutic measures, and the provision of psychological, social and practical support. In the context of genetic testing it may include responding to the concerns of individuals referred and their families, discussing the consequences of a test, and enabling them to choose the optimal decision for themselves, but not determining a particular course of action.

Genetic Testing - Testing to detect the presence or absence of, or alteration in, a particular gene, chromosome or a gene product, in relation to a genetic disorder.

Karyotype - A karyotype is the chromosome pattern present in an individual. The usual chromosome complement in humans is 46, arranged in 23 pairs. Chromosomes may be identified by staining techniques which give a characteristic pattern of alternating light and dark bands. Karyotype analysis looks at the number of chromosomes and assesses whether there are any visible structural abnormalities.

Late Onset Disorders - Disorders that normally become symptomatic in adult life.

Multifactorial Disorders - Disorders whose genetic components are not the sole cause, but which work with other, often environmental factors, in determining a disease outcome. Multifactorial disorders include many cardiovascular diseases, most Alzheimer's Disease of old age and some forms of diabetes.

Mutation - A change in the DNA sequence. Many changes cause a disorder or the inherited susceptibility to a disorder. Only heritable mutations are considered in this report.

Polymerase chain reaction (PCR); An enzyme-based cycling reaction in which a specific region of DNA, whose sequence is known, is amplified in large amounts from a small amount of DNA.

X-Linked Disorders - Disorders due to a mutation in a gene on the X chromosome. X-linked disorders usually only affect males, but the disorders can be transmitted through healthy female carriers. Examples include haemophilia and some forms of muscular dystrophy.

PART A BACKGROUND

CHAPTER 1

WHAT IS PRENATAL GENETIC TESTING?

- 1.1 Prenatal genetic testing is testing which is provided to women to investigate individual pregnancies where the fetus, because of a specific reason such as maternal age, consanguinity, family history or a positive screening test, is judged to be at an increased risk of a genetic disorder. The primary aim of prenatal diagnosis is to provide an accurate diagnosis that will allow the widest possible range of informed choice to those at increased risk of having children with genetic disorders, within the boundaries established by society.
- 1.2 Prenatal genetic testing may involve specific genetic or biochemical tests to confirm or exclude the presence, in the fetus, of a specific genetic disorder. In some cases, the test result may be less than definite, for example if linkage analysis is employed error rates due to genetic recombination are generally from less than 1% to 5%. For some conditions, other tests e.g. ultrasound scanning, may be required.
- 1.3 Diagnostic ultrasound may also be used for prenatal testing and diagnosis. The results of such testing may suggest the need for further DNA, chromosomal or cytogenetic tests.
- 1.4 Prenatal genetic diagnosis informs the woman, and, where appropriate, her partner of a specific fetal diagnosis which enables those concerned to consider the options. A normal test result affords reassurance to many, especially to families with a known genetic disorder. An abnormal result may lead to consideration of options which may include continuation of the pregnancy, termination under the terms of the Abortion Act 1967, treatment of the neonate and, largely in the future, treatment of the fetus *in utero*.

Ethical Principles

- 1.5 The decisions involved in first undergoing and then acting upon the results of prenatal tests are difficult and often require information and support through the process of genetic counselling and more general consultation. Three core ethical principles are recognised for genetic counselling:
- (i) the autonomy of the individual;
 - (ii) the right to information which is as full and complete as possible, and the right to decline information; and
 - (iii) the maintenance of professional standards of confidentiality.

CHAPTER 2

METHODS OF PRENATAL GENETIC TESTING

The following paragraphs reflect widespread usage; there may be regional and local differences in the methods offered.

2.1 Sampling Techniques to Obtain Fetal Tissue

- (i) **Amniocentesis** - This procedure may be undertaken at a range of gestational ages and is usually undertaken during the mid-trimester of pregnancy between 15-17 weeks. It accounts for about 90% of prenatal tests. A needle is inserted through the woman's abdominal wall and into the amniotic sac around the fetus, under ultrasound guidance and a sample collected. The cells in the amniotic fluid have been shed from the surface of the fetus and membranes. These cells are then usually cultured for around 10 days before performing the prenatal diagnostic tests. Testing may involve chromosomal, biochemical or DNA analysis. There is a procedure-related fetal loss or miscarriage rate of 0.5-1.0%. The main limitation of amniocentesis is the relatively advanced gestational age at which it is performed and the need to culture cells in the laboratory.

- (ii) **Chorionic Villus Sampling (CVS)** - CVS can be performed in the first trimester of pregnancy, usually at 10-12 weeks of gestation. It can be performed transabdominally when a needle is passed through the woman's abdominal wall and the wall of the uterus, or transcervically, when a catheter or biopsy forceps is passed through the cervix into the uterus. Both procedures are performed under ultrasound guidance and the aim of the procedure is to obtain a sample of actively proliferating placental tissue. Both operator preference and the position of the placenta may determine the approach used. DNA analysis, limited cytogenetic analysis and some biochemical studies can be performed on uncultured chorionic villus tissue. Full cytogenetic analysis requires cells to be cultured. Fetal loss rates vary from 1-3%. CVS is particularly useful where DNA analysis is required e.g. Duchenne muscular dystrophy.

- (iii) **Fetal blood sampling** - Cordocentesis or percutaneous umbilical blood sampling under ultrasound guidance are means of obtaining fetal blood cells. These cells can be used for the detection of haematological and some metabolic abnormalities. Chromosome analysis can also be undertaken and this method may be used to clarify some ambiguous chromosome results on amniocentesis or CVS. The fetal loss rate may be 1-3% when experienced personnel perform the procedure.
- (iv) **Other fetal tissue sampling** - Sampling of other fetal tissues is sometimes required for prenatal genetic diagnosis where no other tests are available e.g. fetal skin biopsy for junctional epidermolysis bullosa, a severe genetic skin disorder. These tests are carried out infrequently.
- (v) **Analysis of fetal cells obtained from maternal circulation** - Techniques are being developed to isolate fetal cells from the maternal circulation and to then perform genetic diagnostic tests on these fetal cells. These techniques are not yet sufficiently developed to have application outside a research setting.

2.2 Diagnostic Ultrasound

- 2.2.1 Ultrasound is often used routinely in pregnancy as a general guide to fetal development, stage of gestation or twinning, but ultrasound scanning by an experienced operator, a sonographer, with a special interest in fetal imaging, using high-resolution equipment, can accurately assess fetal anatomy at 18-20 weeks gestation.
- 2.2.2 In tertiary fetal medicine centres, specialist obstetricians work with a multidisciplinary team which should include radiologists, midwives and geneticists. Adequate facilities for the performance of various diagnostic and therapeutic procedures should be available as amniocentesis, CVS or fetal blood sampling may be indicated following detection of a fetal abnormality on ultrasound. Even with additional tests, definitive diagnosis may not be possible in all cases. In some cases, ultrasound scans may be the only means of diagnosis.

- 2.2.3 The equipment to identify fetal abnormality needs to be of a higher imaging specification than that commonly used in more general ultrasound testing in pregnancy. A range of transducer frequencies of between 3 and 5 MHz and transvaginal capability are essential, as are hard copy facilities including Video recording. Equipment should be no more than 5 years old unless electronic hardware and software upgrades are available, in which case the most recent relevant upgrade should be no more than 5 years old. A quality assurance programme should regularly monitor equipment performance. The equipment should also have colour flow Doppler capability for the diagnosis of complex cardiac abnormalities.
- 2.2.4 Many units have found it important to appoint a clinical co-ordinator to facilitate liaison between personnel from various specialities involved and to ensure optimum patient care is provided. Regular interdisciplinary fetal abnormality meetings should be carried out between those undertaking ultrasound scanning in pregnancy and all relevant professionals to discuss current and recently delivered cases and to review the latest developments. The development and maintenance of population-based congenital abnormality registers (which should be in accordance with legal provisions concerning confidentiality and data protection) is also encouraged to provide information for counselling, audit and research.

2.3 Laboratory Techniques

- (i) **Cytogenetic analysis:** Chromosome analysis may be performed when there is a high prior risk because of family history or maternal age. Analysis of cultured fetal cells is available nationally within the UK, with the majority of diagnoses (about 90%) being made on amniotic fluid cells and only about 10% on chorionic villi. The number performed on fetal blood is less than 1%.

Increasingly FISH analysis may be used for rapid diagnosis of some cases, particularly in women at an advanced gestational age. This technique is for specific disorders only, for example trisomy 21 (Down syndrome), and may in future become the preferred test because of minimal delay before results are available. It does not provide a full karyotype analysis.

- (ii) **Biochemical analysis:** This involves direct analysis of samples for levels of chemicals which are abnormal in some genetic conditions. Cells from CVS or cultured amniotic fluid cells may be used in the analysis, particularly of enzyme levels. Amniotic fluid may also be used for the diagnosis of certain conditions. These tests require prior diagnosis of the condition in the family.

(iii) Molecular genetic tests: These involve analysis from CVS, amniotic fluid cells or blood samples where a disease-causing mutation has been identified in the family. This usually requires prior diagnosis of an affected individual, or identification of a carrier couple (for recessively inherited disorders), with molecular investigation to define the precise mutation. In some cases, such definitive testing may not be possible and linkage analysis may be required e.g. in a family where there is Duchenne muscular dystrophy but where no mutation has been defined. Close liaison should exist between the doctor undertaking the prenatal test and the molecular laboratory to ensure that appropriate samples are taken. All genetic laboratories should participate in Quality Assurance schemes, and have close links with the clinical section of Regional Genetic Services.

CHAPTER 3

THE CONDITIONS TESTED

3.1 Cytogenetic (chromosome) Disorders

Cytogenetic disorders fall into two main groups; numerical and structural.

(i) Numerical group

The commonest numerical chromosome aberration is trisomy 21 (Down syndrome). The risk of Down syndrome, as well as the more rare disorders trisomy 18 and trisomy 13, increases with increasing maternal age. Abnormalities of the sex chromosomes include 45,X (Turner syndrome); 47,XXY (Klinefelter syndrome); and 47,XXX (triple X syndrome). The risk of the latter two also increases with increasing maternal age.

(ii) Structural group

This group includes rearrangements between chromosomes (translocations) and rearrangements within a chromosome (inversion). If an individual carries a translocation or inversion in a balanced form they are healthy themselves but at risk of transmitting a gamete with an unbalanced chromosome pattern.

3.2 Cytogenetic analysis in patients undergoing tests for other reasons

Some women, when having a test for a specific genetic condition may request, or may be offered, cytogenetic analysis on the fetal sample. This may be carried out if sufficient fetal material is available.

3.3 Single Gene Disorders

These are conditions due to mutations in single genes inherited in three principal ways:

- (i) autosomal dominant (e.g. Huntington Disease, myotonic dystrophy),
- (ii) autosomal recessive (e.g. cystic fibrosis, sickle cell disease) or
- (iii) X-linked recessive (e.g. Duchenne muscular dystrophy, Fragile X syndrome).

The biochemical defect in most single gene disorders is unknown or is not readily analysable. For those inherited biochemical disorders for which a biochemical diagnosis is available there is increasingly also the possibility of direct mutation analysis where the mutations are defined, for example the mucopolysaccharide disorder, Hunter syndrome. Prenatal diagnosis for haematological conditions, for example thalassaemia, may also be undertaken by direct mutation analysis of fetal samples.

3.4 Structural malformations

3.4.1 Many structural malformations can be identified by diagnostic ultrasound scanning. A normal scan result does not completely exclude abnormality in the fetus. It simply means that no abnormality was observed by the sonographer. Apart from technical factors, sub-optimal scan images may in part be related to maternal and pregnancy factors, for example it is difficult to obtain optimum images if the mother is overweight or if there is too little fluid around the fetus.

(i) **Single malformations:** The commonest single malformations detected by diagnostic ultrasound scanning are those affecting the heart, central nervous system and urinary tract although malformations can be detected in all systems and organs. If a single malformation is identified, it is important to examine closely all other systems for evidence of any associated anomalies. This should be undertaken at a fetal medicine centre.

(ii) **Multiple malformations:** In some genetic conditions, detection of structural malformations may be the only prenatal test available. Where there is a family history of malformations, precise diagnosis of the affected family member is crucial. Liaison between the clinician involved in the diagnosis and the specialist performing the imaging is important to ensure the optimum time for investigations.

3.4.2 In some pregnancies, multiple malformations are detected initially by ultrasound scanning. Detailed diagnostic scanning should then be undertaken at a fetal medicine unit. Other tests, such as amniocentesis may then be undertaken to give a more definite diagnosis. If the pregnancy is to continue, provision may be required for ongoing care at a specialist antenatal clinic and contacts established with neonatologists and neonatal surgeons.

3.5 Late Onset Disorders

- 3.5.1 Requests for prenatal genetic testing are relatively uncommon for late onset disorders in comparison with other genetic diseases. In general, requests are related to severe and untreatable disorders where the family concerned has experienced particular adverse effects of the disorder. Prenatal testing can also provide an option for healthy individuals with an abnormal presymptomatic test result to find out whether the fetus is affected by the genetic disorder in question. There may be complex situations when someone simultaneously requests presymptomatic genetic testing for themselves and for the pregnancy. In all cases prenatal genetic testing for late onset disorders should only be undertaken in the context of full genetic counselling. Further advice on testing for late onset disorders can be found in ACGT's 1998 report on this subject.
- 3.5.2 Prenatal "exclusion testing" – i.e. a test to exclude the risk of a condition in a fetus - is another option that may need to be considered. For example, an individual at 50% risk of developing Huntington Disease may wish to exclude the disorder in a pregnancy, whilst not wishing to know their own genetic status. Here the pregnancy is tested with linked markers and not mutation analysis to determine whether the parent at risk has passed on the chromosome region in question of the affected or unaffected grandparent. This would either place the pregnancy at 50% risk or exclude the risk.
- 3.5.3 A particular issue arises in a late onset condition when a woman decides to continue a pregnancy after an abnormal prenatal test result when a mutation has been identified. This effectively gives presymptomatic diagnosis or carrier test for the child before it has been born.
- 3.5.4 There may also be implications for the existing children of a woman when prenatal testing is being considered. Whilst those children born after prenatal testing may be known to be free of a specific condition, their older siblings continue to have the uncertainty of remaining at risk. Full discussion through genetic counselling in advance of prenatal testing should allow discussion of these points and may minimise later problems.

PART B THE ISSUES

CHAPTER 4

ORGANISATION AND STRUCTURE

4.1 Discussion

- 4.1.1 Nearly all prenatal genetic testing in the UK is undertaken within the National Health Service and the overwhelming majority of tests reveal normal results. Between 1997-1998, 4.1% of the 36,817 amniotic fluid samples for cytogenetic analysis were abnormal. In 1996-1997, 802 tests were undertaken in UK molecular genetics laboratories, with 769 tests being undertaken in 1997-1998. No national figures are available for outcomes but in one laboratory where 74 prenatal tests were undertaken, 62 reported a normal pregnancy outcome or enabled prenatal treatment. These figures are likely to be representative of most laboratories. In this context, normal means that the fetus did not have the specific condition for which the test was undertaken; it does not exclude other causes of abnormality.
- 4.1.2 Many people having prenatal genetic tests are at an increased risk of having a baby with a genetic or chromosomal abnormality. Once a diagnostic test is available, those who were afraid previously to undertake a pregnancy without testing, have the option of prenatal genetic testing. Most pregnancies tested are shown to be normal for the condition being tested especially where the risk is moderate or low.
- 4.1.3 An individual with a concern about a genetic problem usually visits their GP as a first step, receives information and may be referred to a specialist. This may either be a hospital specialist with an interest in that particular field or a medical genetics department. The hospital specialist may also make a tertiary referral to the clinical genetics service for diagnostic confirmation and/or genetic counselling.
- 4.1.4 Where prenatal genetic diagnosis is to be undertaken, collaboration between the clinical genetics service and fetal medicine centres is invaluable to ensure accurate diagnosis, risk assessment and counselling of families at risk of having a child with a genetic condition.

4.2 Genetic Services

- 4.2.1 Genetic services in the UK are organised on a regional basis, with most centres dealing with a population of between 1 and 5 million. There are 19 centres in England covering a population of approximately 49 million and in Wales and Northern Ireland there is 1 centre each for populations of approximately 2.9 and 1.6 million respectively. In Scotland there are 4 genetics centres for a total population of approximately 5.1 million. The centres are mostly now integrated with clinical, cytogenetic and molecular teams all working in one unit. Where the different teams are not based in the same location, they nevertheless work in conjunction with the other teams in the development of their service. Between 1991 and 1997, the workload covered by the regional genetic centres increased by between 50-100%.
- 4.2.2 It is clear that genetics centres see only a proportion of the individuals and families who would benefit from comprehensive genetic services. It may be that in some cases, neither the family nor the family doctor may be aware of the genetic implications of a condition and the possible options available to them. Both professional and public education is an important part of increasing awareness of genetic conditions. Easy access to a genetics department to discuss whether testing is available or appropriate in a pregnancy is an important part of liaison between primary care and the genetics clinic in the management of women who may require prenatal genetic diagnosis.
- 4.2.3 In many centres, as well as an appointment with a clinical geneticist to discuss diagnosis, investigations and recurrence risks in the context of genetic counselling, a specialist nurse or counsellor (co-worker) continues counselling. The co-worker often then becomes the contact person in the department for that individual or family, often following the confirmation of a pregnancy.

4.3 Fetal Medicine Services

- 4.3.1 There is at least one fetal medicine centre in most NHS regions in the UK (see Annex C). These centres are usually located in the obstetric wing of tertiary referral centres and situated close to a regional genetics centre and other appropriate specialities e.g. paediatric surgery.

CHAPTER 5

ACCESS TO PRENATAL GENETIC TESTING DIAGNOSTIC SERVICES

Discussion

- 5.1 Most patients access prenatal diagnostic services through one of three routes. Initial referral may be from the patient's general practitioner or primary care team, through a genetics or fetal medicine department with whom the patient is already familiar or through the obstetrician at presentation in the antenatal clinic.
- 5.2 Early referral from the GP or medical genetics centre and early assessment by the obstetrician is important. It is suggested that women who think they may be at risk of having a child with a genetic abnormality should be encouraged to notify their GP or other involved health professional as soon as the pregnancy is confirmed. An early dating scan to date accurately the pregnancy for subsequent tests may be needed. In some cases other special arrangements may have to be made prior to testing so early awareness is helpful. The test can then be carried out at the appropriate stage in pregnancy.
- 5.3 Laboratory analysis of CVS is widely available, but the sampling procedure is less so. This procedure tends to be restricted to fetal medicine centres which are competent to perform the sampling. This may necessitate the patient travelling to other centres.
- 5.4 Professional guidelines for sampling procedures were recommended in the European Association of Perinatal Medicine Report (1993). This report recommends that before being admitted to a clinical programme, clinicians' sampling success rate should approach 95% for cordocentesis and 100% for amniocentesis and CVS. The Royal College of Obstetricians and Gynaecologists has suggested that at least 30 amniocenteses should be performed under supervision, with a successful tap on each occasion before the operator is deemed as competent. It also suggests that a minimum number of 20 procedures per annum would be reasonable in order to maintain competence.

- 5.5 Those performing diagnostic ultrasound scans should undertake appropriate training. Training in obstetric sonography should be undertaken. For medical practitioners this might include a postgraduate qualification in medical ultrasound or the Joint Diploma administered by the Royal College of Obstetricians and Gynaecologists and the Royal College of Radiologists in Obstetric and Gynaecological Ultrasound. To maintain their expertise in obstetric scanning, medical practitioners would be expected to perform the equivalent of two obstetric scanning sessions per week. Guidelines are available in the report of a joint working party of the RCOG and the RCPCH “Fetal abnormalities. Guidelines for screening, diagnosis and management” and a report of the RCOG working party “Ultrasound screening for fetal abnormalities”.
- 5.6 The time it takes to achieve a result varies between tests and should be explicitly discussed with the woman before having the test. The result should be given as soon as it is available. The woman should also be asked how she wishes to receive the test result; some wish to be telephoned at any time, others only when someone is there to support them. In some cases, the woman may choose to receive the result in person. The name and telephone number of a contact should be provided for her to contact if she has any concerns. When referral for testing is carried out through a genetics department, there is usually one person involved in co-ordinating the information and results for that patient.
- 5.7 On receipt of the result, the options available to the woman may need to be reiterated and the primary care team contacted directly to inform them of the result. The woman may have been referred from another hospital for testing and if the result is unfavorable may wish to have a termination of pregnancy if the grounds of the Abortion Act are met. Such a termination is usually carried out in the referring hospital under the care of the referring obstetrician. Close liaison is important between the unit involved in undertaking the testing and the unit providing ongoing care. The GP and other appropriate support services should be made aware of her decision. In some cases, the fetal abnormality may not be detected until later in pregnancy and tests and results not be available until after 21 weeks gestation. If a pregnancy is to be terminated the appropriate facilities should be made available.

Recommendations

Genetic and fetal medicine services should be available to enable local access to those who require them.

Sufficient resources should be made available both in the primary care and hospital setting for referral and subsequent care of appropriate patients who may wish to have prenatal genetic testing and genetic counselling.

A woman should have access to the prenatal genetic tests and expertise she requires appropriate to her risk.

There should be good communication between referring units and more specialised Fetal Medicine centres about the ongoing pregnancy of women who have prenatal genetic testing as appropriate.

If a termination of pregnancy is to be considered in the light of test results, access to a unit with appropriate medical and counselling services should be arranged. There should be close liaison between the diagnostic team and staff at the unit where the termination is carried out. Adequate support and care during and after termination should be available for the parents.

CHAPTER 6

APPROPRIATENESS OF TESTING - THE DECISIONS TO BE MADE

- 6.1 The decision to have prenatal genetic testing may be made before or during pregnancy. The use of prenatal genetic testing must only follow an informed decision. Ideally in those at an increased risk of having a baby with a genetic condition, the risk should be identified and discussed before pregnancy so time to consider the options and a decision on the best one for the woman and her partner can be taken. In some cases, other family members may be involved in the decision-making process. In other instances, discussion and decisions are taken once the pregnancy has been confirmed, and the potential for an actual fetal abnormality has been discovered. It is in the light of this information and in the context of her own life that a woman, usually with her partner, may then choose to have prenatal genetic testing.
- 6.2 In this report we consider in the context of the particular circumstances of the woman when testing should be undertaken to investigate an individual pregnancy at high risk of a genetic disorder to confirm or exclude the presence, in the fetus, of that genetic disorder. The risk factors identified should indicate which, if any, prenatal genetic tests may be offered.
- 6.3 There are five main groups of women who may undergo prenatal genetic testing:
- (i) **High risk indicated by a positive family history** - Many in this group have a high risk of a problem recurring, possibly having had previous affected children. Genetic counselling may have been provided beforehand so that they are aware of the risks, and of the tests available in pregnancy. They may have made a decision to embark upon prenatal diagnosis before pregnancy and, in some cases, delayed having a family until tests were available.

To enable accurate information to be given to the individuals making these decisions, there should be -

- (a) precise diagnosis of the affected individual in the family;
- (b) estimation of genetic risk of an affected pregnancy;
- (c) communication of the genetic risk and options for prenatal testing;
- (d) help in assimilating and evaluating the information;

- (e) accessibility to specialist services for ongoing and long term contact; and
 - (f) awareness of options available in the event of a pregnancy if prenatal testing is to be requested.
- (ii) **Low risk with previous history** - In some instances, a woman may have had a previous affected child where there is only a low recurrence risk of a further affected child. In these cases, there may be a high level of anxiety relative to the risk of an abnormal fetus and prenatal tests may be requested primarily for reassurance.
- (iii) **Increased risk without family history** - public awareness about the age related increased risks to a pregnancy for trisomy 21 (Down syndrome) means that many older mothers are aware of the increased risk. These women do not routinely receive genetic counselling in specialist centres and as a group constitute a large number of the prenatal genetic tests carried out. Most women in this situation do not require detailed genetic counselling but should receive adequate information at the obstetrics clinic about the options available to them, the sensitivity and specificity of the tests and the chance of any definitive test result. The possible results, their significance and options then available to them should also be discussed.
- (iv) **Increased risk identified clinically during pregnancy** - In some pregnancies, a clinical abnormality may be detected which suggests that an underlying abnormality may be present in the fetus. Depending on the abnormality, prenatal genetic testing may be offered, perhaps in conjunction with ultrasound scanning. This group of patients is likely to need detailed counselling, often when the pregnancy is fairly well advanced.
- (v) **Screened pregnant population** – An offer of screening the whole pregnant population or a large sub-group, which is collectively at a low risk, may be undertaken with the aim of identifying those at a higher risk so that more specific tests may be offered. Where a potential abnormality is identified, there is a need for urgent detailed counselling about the options available, often when the pregnancy is fairly well advanced. Such screening programmes should be reviewed by the Department of Health's National Screening Committee.

- 6.4 Appropriate protocols should be constructed to ensure that those who may benefit from a particular test are offered the opportunity. There should be no presumption that prenatal testing would be unacceptable to a particular woman. There should also be no presumption by clinicians that each woman should accept all or any tests offered, and the informed decision not to have tests must be accepted.
- 6.5 The rapidly increasing number of genes identified with potential for prenatal diagnosis, the special features of genetic testing and the particular nature of the testing itself, contribute to a range of issues that should be given careful consideration before prenatal genetic testing is offered. At present these issues arise mainly in relation to families with a history of serious disorders, and/or population groups with a high incidence of a particular disorder with a clear genetic basis.
- 6.6 Some women may request prenatal genetic testing because of a perceived risk from their family history, or that of their partner, of passing on a disorder. It is important that, through the process of genetic counselling, the actual risk of abnormality is conveyed to the woman. The actual may be different from the perceived risk. The risk of the condition, the availability of tests and the potential benefits of testing should be compared to the risk of any prenatal testing procedures. It is then the decision of the woman as to whether she wishes to proceed with testing.
- 6.7 The potential perceived benefits of prenatal genetic testing may be:
- (l) Personal –
 - (a) to give couples at high risk of genetic disease in their offspring enough confidence to start a pregnancy that they would not have risked without prenatal diagnosis and thereby increase the prospect of healthy children;
 - (b) allowing the woman tested, and others who she may have involved in her decision-making, the ability to plan major life decisions and freedom from uncertainty. For some even an abnormal result may be preferable to continuing uncertainty.

(ii) Medical –

(a) *where an abnormality is identified:*

➤ Antenatal - It may be possible to offer:

- *in utero* treatment. While options for this are limited at present, this may become a more widely available option in coming years. Early prenatal diagnosis may enable optimum intervention to be undertaken;
- termination of pregnancy.

➤ Postnatal - appropriate treatment to be instigated as soon as possible

(b) *where no abnormality is identified* – avoid further *in utero* procedures

Many people requesting genetic testing have a combination of these aims and concerns.

6.8 Different women with apparently comparable circumstances and genetic risks of an abnormal fetus, may make different decisions when testing is offered. While one may wish to have as much certainty as possible, another may decline any testing if it is offered.

6.9 Whatever the reason for an individual choosing or declining testing, the aim should be for each woman to have autonomy and support in the decision she makes for each pregnancy.

Recommendations

At each pregnancy, bearing in mind advances in technology and knowledge, women should be offered information on prenatal genetic tests appropriate to their individual risk factors.

All women capable of giving consent can accept or refuse any or all of the tests offered.

CHAPTER 7

LEGAL AND ETHICAL ISSUES

Consent to Prenatal Genetic Testing

- 7.1 In all cases of prenatal genetic testing consent should always be obtained for both the sampling procedure and the prenatal test. The main purpose of recording oral consent or obtaining written consent is to provide evidence that consent was sought and obtained and that an explanation of the proposed testing procedure was given. Written consent is not in itself a substitute for careful face to face explanation.
- 7.2 New technology may make it possible to test for many genetic diseases at one time. Testing should only be undertaken for a condition(s) for which an explanation of the proposed testing procedure and its associated risks, and the potential implications of a test result, were given. If testing is for a group of allied disorders, this should be made clear when consent is being obtained.
- 7.3 Where an adult is permanently incapable of giving consent (e.g. because of a learning disability) the legal position is that the decision will be made by the doctor responsible for the person's clinical care. Doctors will be guided by the best interests of the woman and where appropriate take into account the views of the family or other close carers. Testing in the pregnancy would provide information about the fetus. Depending upon a number of factors including the feelings of the mother, the nature of the condition affecting the baby, legal and ethical considerations, the information from the test could then be used to come to the best decision for the woman. The options available and their subsequent implementation present other considerations which are not within the remit of this report.
- 7.4 It should be noted that the best interests of the woman and of the family and close carers might not necessarily be the same. When assessing a woman's best interests consideration should not be limited to "best medical interests". Other factors that may be taken into account include: the woman's psychological health, well being, quality of life, ethical, moral, spiritual and religious welfare, relationships with other family members and financial interests.

- 7.5 If the incapacity is temporary, genetic testing should be delayed until consent is possible unless it is essential in the individual's therapy and/or in their best interests. The issues of testing of the incapacitated are complex. In relation to prenatal genetic testing it is necessary to distinguish between the situation in which testing is necessary in furtherance of the individual's care and treatment, when it will be clearly in their best interests and where testing might be proposed essentially in the interests of furthering the diagnosis, without implications for immediate treatment but for longer term planning.
- 7.6 There may be pressure for prenatal genetic testing from family members. This may only be recognised when the issues are discussed before testing. Clinicians should not exert pressure and should present information in a way that permits a woman who is capable of giving consent to make a free and informed decision. It should be noted that consent given under pressure is not valid.

Confidentiality

- 7.7 There is a common law duty of confidence and to keep the testing data confidential, and storage and security of samples and data should be such as to ensure confidentiality.
- 7.8 All staff with access to individuals samples or data should be bound by a code of confidentiality. Before taking samples women should be informed of the procedures for ensuring confidentiality and the arrangements for storage and disposal of samples and records. The Data Protection Act 1998 will come into force on 1 March 2000 and compliance with its provisions which govern both information stored on a computer and in certain manual records, will be necessary. Rechecking in cases where the test result are challenged, or where DNA from an affected fetus is needed for reliable future testing in that family, are the only valid reasons for long term retention of samples in an individually identifiable form. Information that may identify the woman gathered during testing should only be used for the provision of individual patient test results and as part of the woman's health record. In all normal circumstances, information on any test sample or result or any individually identifiable patient samples and data should not be passed on without explicit consent from the woman. Where the woman is not capable of giving consent, identifiable patient information may be passed on in the women's best interest (for example to her general practitioner).

The Law on Termination of Pregnancy

7.9 Women seeking a termination for whatever reason must have grounds under the Abortion Act 1967, as amended. A pregnancy may only be terminated if two registered medical practitioners are of the opinion, formed in good faith that an abortion is justified within the terms of the Act, in the light of their clinical judgement of all the particular circumstances of the individual case. Under the Act the grounds for an abortion are:

- (i) "that the pregnancy has not exceeded its twenty-fourth week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman or any existing children of her family; or
- (ii) that the termination is necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman; or
- (iii) that the continuance of the pregnancy would involve risk to the life of the pregnant woman, greater than if the pregnancy were terminated; or
- (iv) that there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped."

7.10 The Act goes on to state that "in determining whether the continuance of pregnancy would involve such risk of injury to health as is mentioned in paragraph (a) or (b), account may be taken of the pregnant woman's actual or reasonably foreseeable environment."

7.11 The Abortion Act 1967 does not apply to Northern Ireland where it is not legal to carry out a therapeutic termination of pregnancy, other than to save the life of the mother or to prevent serious damage to her physical or mental health (R v. Bourne [1938] 3 All E.R. 615)

Recommendations

In all cases of prenatal genetic testing of a woman capable of giving consent, specific consent - verbal and recorded or written - should always be obtained. Consent should be obtained for each procedure and each test.

Consent should be freely given, without pressure from third parties.

Where a woman is permanently incapable of giving consent (e.g. because of a learning disability) the testing decision will be made by the doctor responsible for her clinical care. Doctors will be guided by the best interests of the woman and where appropriate take into account the views of the family or other close carers.

If the incapacity is temporary, genetic testing should be delayed until consent is possible unless it is essential in the individual's therapy and/or in their best interests.

CHAPTER 8

INFORMATION

What information should be supplied?

- 8.1 It is important that a woman should have a good understanding of the condition for which fetuses would be tested, ideally through preconceptual genetic counselling, and the likely short and long-term effects on a child. She should be aware of the risk in both the current and any subsequent pregnancy of having an affected child. A woman with a high risk of a potentially abnormal fetus should be able to discuss the effects of the abnormality with a consultant with a specialist knowledge of the condition e.g. geneticist, paediatric neurosurgeon. Where there is a difference in opinion between the doctors, an independent opinion should be sought as quickly as possible.
- 8.2 The first health care professional a woman contacts following the confirmation of pregnancy is likely to be her general practitioner. It is to her GP that she may enquire about prenatal genetic testing either for a specific family condition or because of personal concerns. The general practitioner booking appointment is an opportunity to review the women's medical and family history and to discuss antenatal tests that may be appropriate. Community midwives may also be involved in this process. When indicated, referral to a genetics clinic or fetal medicine centre may be appropriate.
- 8.3 If previous genetic counselling has been undertaken, a copy of correspondence should have been sent to the GP with information about any action which may be needed in pregnancy. If contact with the genetics clinic was some time previously, there may have been new developments in the availability of tests. Easy access to a local genetics department should be available to GPs in this situation to enable them to provide accurate and up to date information or appropriate referral for the patient. There should be good communication between the obstetrician and general practitioner about the decisions made by the woman and the practical considerations this entails. Information similar to that given to the woman (see below) should be available to the GP.
- 8.4 Information about specific prenatal testing should be clear and updated in the light of any changes in policy or advances in prenatal testing technology. Women undergoing prenatal genetic testing and their General Practitioner will require the following information;

- (i) a description of the prenatal genetic tests which are offered during antenatal care;
- (ii) the risks associated with the tests;
- (iii) the accuracy of the tests;
- (iv) the timing of the tests offered, and how long the results take; and
- (v) a named person and their contact responsible for providing the results.

8.5 Often following initial discussion of genetic risks, women are provided with an information leaflet.

8.6 Where appropriate, provision should be made for interpreters, translation of information leaflets and counselling for patients who have limited command of English.

Sources of information

8.7 Further information on prenatal genetic testing and genetic disorders can be obtained from the voluntary and professional bodies listed in Annex C.

Support in relation to prenatal genetic testing

8.8 Prenatal genetic testing may have consequences extending many years ahead and affecting many family members. Counselling throughout the testing process, from the decision to undertake a test to dealing with the result, helps to minimise the effects on the family even when there are serious adverse results. Adequate support during this process should be considered and planned for as part of the testing process, otherwise problems, in both the short and long terms, could be generated for the individual, for family doctors and for other staff.

8.9 Genetics and fetal medicine centres offer ongoing support to women throughout their pregnancies. Support is available through lay organisations such as ARC (formerly known as SAFTA) or through groups with an interest in a specific condition. When a termination of pregnancy is carried out, many hospitals have a bereavement support group with a named individual as a contact person.

8.10 As much of the long-term support and follow-up devolves to primary health care teams it is important that they have the mechanisms to cope with this duty. Such mechanisms include suitable record keeping of genetic tests taken and family history data.

8.11 The cost of genetic counselling and related measures should be costed in addition to and separately from the laboratory aspects of a prenatal genetic test. Some early prenatal genetic tests may avoid other later, costly, and for the woman potentially risky investigations. The potential effects of prenatal genetic test results in terms of long term support and treatment also need to be considered when the likely overall benefit of the test is being assessed.

Recommendations

Appropriate support in preparation for and subsequent to genetic testing should be part of the prenatal genetic testing process.

Consideration should be given to the cost of the potential support needed by families in addition to the genetic tests when evaluating and commissioning prenatal genetic and fetal medicine services.

Full information should be supplied to the woman in an appropriate form giving details of the tests. The information should enable the woman to understand the nature of the test, its scope and limitations, and the accuracy, significance and use of the result, and, where appropriate, its possible implications for family members. Information should also be provided on appropriate professional and voluntary bodies able to offer support, as they may be able to provide advice about information materials.

Pre-test genetic counselling and post-test consultation opportunities should be provided to women, and if appropriate to their partners, by suitably qualified and experienced professionals.

The general medical practitioner or other professionals who continue the care of the woman and, where appropriate, her family should be provided with appropriate information pre and post test.

CHAPTER 9

OUTCOMES

Discussion

- 9.1 Women undergoing prenatal tests should be informed clearly of the possible outcomes of the test. Information should include any risks inherent in the testing procedures and the potential for false positive and false negative results. The options available to the woman following the test should be clearly discussed.
- 9.2 For any test undertaken there are different possible outcomes and for each there are decisions which can be made.
- (i) A normal result for the condition being tested:
 - continue with the pregnancy that is now known to be at low risk for that specific disorder.
 - (ii) An abnormal result indicating the presence of the condition being tested:
 - continue with the pregnancy free from uncertainty, able to plan any pre- or postnatal treatment which may be available, meet appropriate specialists, arrange antenatal transfer to appropriate unit if necessary. Referral may be made to the appropriate support groups who may provide helpful literature;
 - termination of pregnancy (subject to the provisions of the Abortion Act 1967 (the 1967 Act) see paragraph 7.9).
 - (iii) An equivocal result or one of uncertain significance e.g. chromosomal mosaicism on an amniocentesis result.
 - (a) further testing to clarify diagnosis possible, for example fetal blood sampling:
 - further testing may be undertaken or declined.

- (b) no further testing possible/undertaken:
 - continue with pregnancy whilst planning for the birth of a child potentially affected with that genetic condition;
 - terminate the pregnancy (subject to the provisions of the Abortion Act 1967 (the 1967 Act)).

(iv) Diagnostic ultrasound.

- (a) When single malformation found by initial ultrasound study:
 - detailed scan to look for other anomalies and consider further tests, for example amniocentesis;
 - refer to appropriate clinical specialist, for example, neonatal surgeon and appropriate delivery unit;
 - continue pregnancy;
 - terminate the pregnancy (subject to the provisions of the 1967 Act).
- (b) When multiple malformations found consider further tests, for example amniocentesis:
 - refer to appropriate specialist for example, clinical geneticist, neonatal surgeon and appropriate delivery unit;
 - continue pregnancy;
 - terminate the pregnancy (subject to the provisions of the 1967 Act).

9.3 Ongoing support should be provided throughout the pregnancy for those who continue with the certainty or uncertainty of a baby with a genetic abnormality. Discussion with healthcare professionals who may be involved with the care of the baby or meeting parents of similarly affected children may be helpful to prepare the parents for the birth of the child.

Termination of Pregnancy

9.4 Those who undergo prenatal diagnosis have the wish to have a healthy child. Thus, when a fetus is found to have a genetic, chromosomal or structural abnormality, some may, when provided with information on the effects of the abnormality, choose to seek a termination of the pregnancy if the grounds of the Abortion Act are met.

9.5 ACGT draws attention to the guidelines in the report from the Royal College of Obstetricians and Gynaecologists "Termination for fetal abnormality in England, Wales and Scotland".

9.6 The unit where the termination is to be carried out should have the appropriate experience in both the methods of termination and the care of families in this situation.

9.7 ACGT notes that the report says:

"Agreement to have an abortion if the fetus is seriously abnormal should not be a precondition for definitive antenatal investigation".

"The purpose of [definitive testing] is to ensure, as far as possible, the woman, and usually her partner, have accurate information about the fetus so that she has a choice of giving birth to a seriously handicapped child or having a termination".

Fetal Examination after Termination

9.8 Ideally, a paediatric/fetal pathologist should carry out a post-mortem examination, with parental consent. For fetuses with multiple malformations, external examination by a clinical geneticist may also be helpful. If a post mortem examination is declined, an external or limited examination, possibly with x-rays, may be acceptable.

9.9 Samples of fetal material may be required post-termination for confirmation of the prenatal test. This may enable a definitive syndrome diagnosis to be made or an existing diagnosis to be modified. This then allows accurate genetic information to be made available to the family.

9.10 A photographic record of the fetus may be valuable for two purposes:

- as a record for completion of the examination and for possible later consultation; and
- as a memento for the family.

The style of photography should differ for these two purposes.

Support after Termination

- 9.11 Support after termination may be provided by a number of professionals, in the immediate period following termination mainly the general practitioner, midwife and obstetrician.
- 9.12 Lay organisations such as ARC (formerly SATFA) also provide valuable ongoing support for the family for some time after the termination.
- 9.13 In most cases where the local genetics department knows the family, there is opportunity for ongoing follow-up and support.
- 9.14 In some cases, the index pregnancy may be the first instance of a genetic condition in the family. Follow-up of the immediate family and, where appropriate, the offer of genetic counselling and testing to both them and other family members can be made. Where a new or modified diagnosis is made, this should be discussed with the family. If possible and appropriate, recurrence risks and management and options in future pregnancies should be discussed.

Recommendations

Where diagnosis is unknown or uncertain, facilities should be available for further assessment by a paediatric/fetal pathologist and/or clinical geneticist to enable accurate information to be available to the parents.

CHAPTER 10

QUALITY ASSESSEMENT

Discussion

10.1 Cytogenetics

10.1.1 All UK cytogenetics laboratories belong to the National External Quality Assessment Scheme (NEQAS). This undertakes retrospective assessment of work undertaken in diagnostic laboratories on samples of amniotic fluid, chorion villus biopsies, blood and solid tissues. The assessments take into consideration reporting times, success rates, abnormality rates, slide preparation quality and the information provided in reports of abnormal cases.

10.1.2 The reporting time guidelines represent the upper limit for an acceptable reporting time for a successful case. These times are reviewed and amended to improve the quality of service. For 1997/8, the reporting guideline times for prenatal samples was reduced to 17 days. Overall in the UK, 86.9% of amniocenteses and 81.1% of chorionic villus samples were within this reporting time. There was considerable variation between centres and in many cases, the reports were well within the suggested reporting times.

10.1.3 All the UK laboratories performing prenatal diagnosis by CVS contribute their data to European Collaborative Research on Mosaicism in Chorionic Villus Sampling (EUCROMIC). Quality guidelines and standards for genetic laboratories, both cytogenetic and molecular genetic, for prenatal diagnosis on fetal samples obtained by invasive procedures have also been stated by EUCROMIC to establish a common European framework for quality assessment. This document deals with a wide range of issues governing minimum quality standards.

Molecular Genetics

External quality assessment schemes are provided through NEQAS or the European Molecular Genetics Quality Network and are relevant to most genetic tests where prenatal genetic testing is likely. Guidelines for laboratories relevant to internal quality assurance and best practice are published through the Clinical Molecular Genetics Society (<http://www.cmgs.org>)

10.3 Ultrasound

Equipment should be of appropriate resolution and specification and regularly serviced. Staff should have relevant training and qualifications and should go on regular updating courses. Outcomes should be monitored by audit and by fetal pathology meetings.

Recommendations

ACGT confirms that its advice in earlier reports remains valid. In particular;

All laboratories undertaking prenatal genetic testing should be appropriately staffed and equipped, and:

- (i) be registered with a National Accreditation Body and conform to the requirements of BS 5750 (ISO9002). Continued registration is dependent on satisfactory audits that are performed every six months by the Accreditation Body to ensure compliance with the appropriate standards;*
- (ii) be accredited by the Clinical Pathology Accreditation (UK) Ltd (CPA). Accreditation by CPA involves external audit to standards reflecting best professional practice for clinical laboratories;*
- (iii) perform adequate internal quality control;*
- (iv) undertake regular audit to identify areas where improvements in practice are possible and participate in all relevant external quality assessment schemes.*

All equipment, reagents and procedures used in testing laboratories should reflect current best practice and provide assured levels of accuracy and reliability as a prerequisite of good practice.

Some sampling devices and testing equipment may be required to comply with relevant UK Regulations and European Directives. In such cases the quality requirements set out in the General Product Safety Regulations 1994, the Medical Devices Regulations 1994 (the Medical Devices Directive (93/42/EEC)) and the In Vitro Diagnostic Medical Devices Regulations 2000 (Directive 98/79/EC) should be the minimum adopted.

Staff involved in prenatal diagnosis in regional genetic centres and fetal medicine centres should ensure their continued professional development. Clinicians should be able to demonstrate regular audit of their services.

CHAPTER 11

RESEARCH

Discussion

- 11.1 Most genetic studies leading to isolation of a disease-related gene have involved analysis of affected and unaffected family members. Stored DNA samples may be available for testing long after the original study has been completed. During the course of the research, by using samples to define a gene location, there is a possibility of important results being generated about the individual's status of which they may be unaware. The ACGT has issued a report which gives advice to research ethics committees assessing genetic research proposals.
- 11.2 Research studies that generate identifiable genetic test results on individuals should only be done with appropriate consent and following approval of a designated research ethics committee. Safeguards of this nature are particularly important since the stability of DNA enables samples collected originally for a study with no individual implications being used subsequently to generate sensitive genetic information. Where there is a possibility of this, new consent and new research ethics committee permission should be obtained, or the samples should be made completely anonymous. There may be exceptional situations where research information needs to be used, as when an individual is deceased and no further material is available, or when no service is available outside a research setting.
- 11.3 Individual genetic test information resulting from research studies should not be given to participants unless a clear and specific arrangement has been made at the outset; nor should it be placed in the individual's medical record without consent. Those giving consent to participation in research should be made aware that they would not normally receive genetic test information that forms part of research. In some cases, while a test may be available on a research basis to define the risk in an individual, the researchers may be reluctant to undertake prenatal diagnosis, even though it is technically possible. This should be stated to the patients.

11.4 Research information is, by its nature, provisional and the way material is collected and analysed may make it unsuitable for service use. Where a research participant wishes to have genetic testing as a service this preferably should be done using a separate sample and following appropriate laboratory and clinical service standards. There may be exceptional situations when no service is available outside a research setting.

Recommendations

Research should only be performed when approved by an appropriate Research Ethics Committee.

Prenatal genetic tests undertaken for research purposes should only take place after the individuals participating have given their consent. Such consent should be recorded.

All test results obtained through research are confidential and should not be given to anyone without the consent of the participant.

Women taking part in genetic research should be fully aware of the use of their sample. No further tests should be undertaken on identifiable samples without explicit explanation to, and consent from, the woman.

It should be made clear to women that in some cases a test that is available on a research basis to individuals is not suitable or available for prenatal testing.

CHAPTER 12

RARE DISORDERS

Background

12.1 Rare disorders are defined as those where the current UK genetic testing workload is less than 100 tests per year. Although individually rare, collectively these conditions add up to a substantial part of the clinical workload of genetics services. The individuals who request prenatal testing for these disorders usually have a very high risk of having an affected child. There is likely to be a substantial unmet need for testing for genetic disorders, particularly as many more of the individual causative genes are identified and diagnostic technology improves.

Issues

- 12.2 The diagnostic services available for rare disorders should be comprehensive and their availability equitable; not dependent on the area of residence of the patient/family concerned. As relatively few of these tests are undertaken, there would be insufficient demand within a single region to justify setting up a laboratory service. The cost of the appropriate reagents would be relatively high and little experience would be gained in carrying out or interpreting these tests.
- 12.3 In some cases, testing may have been available as part of a research study but later withdrawn due to lack of funding or infrastructure. This problem has been recognised by the House of Commons Science and Technology Committee in its report Human Genetics: the science and the consequences 1994/5- paragraph 135. "It is particularly distressing that diagnosis for a rare inherited condition can be offered on one occasion since it is part of a research project, and withheld on another." In other instances, ongoing research may enable testing of family members but prenatal testing will not be offered.
- 12.4 Recommendations for setting up services for these conditions have been suggested in a report by a working party of the British Society of Human Genetics (1998). The report entitled "Co-ordinated arrangements for genetic testing for rare disorders" proposed that clinical need for tests in specific rare disorders and recommendations for areas of service development could be assessed by the Joint Genetics Committee of the Royal Colleges of Physicians and Pathologists and the BSHG.

Recommendations

Prenatal genetic testing for rare disorders should be organised on a supra-regional or national level.

Appropriate funding for such testing should be identified.

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Diagnostics, Abingdon, Oxfordshire.

* resigned 1998 ** appointed 1998

MEMBERS OF THE ACGT PRENATAL SUBGROUP

CHAIRMAN:

Professor Sally Macintyre (until January 1999)	Director, MRC Medical Sociology Unit, University of Glasgow.
Mr Philip Webb (from February 1999)	General Manager, AstraZeneca Diagnostics, Abingdon, Oxfordshire

MEMBERS:

Professor Dian Donnai	Medical Genetics, St Mary's Hospital, Manchester
Professor Marcus Pembrey	Retired Mothercare Professor of Paediatric Genetics, Institute of Child Health, London
Professor Sheila McLean	School of Law, University of Glasgow
Professor Charles Rodeck	University College London Medical School
Dr Hilary Harris	General Practitioner, Manchester
Miss Wendy Johnston	Specialist Health Visitor in Genetics, Belfast City Hospital
Mrs Christine Lavery	Director of the Society for Mucopolysaccharide Diseases and founding trustee of the Genetic Interest Group

USEFUL ADDRESSES

FETAL MEDICINE CENTRES

Department of Obstetrics &
Gynaecology
Aberdeen Maternity Hospital
Forester Hill
Aberdeen AB25 2ZN

Department of Obstetrics &
Gynaecology
Royal Maternity Hospital
Grosvenor Road
Belfast BT12 6BJ

Department of Fetal Medicine
Birmingham Women's Hospital
Metchley Park Road
Edgbaston
Birmingham B15 2TG

Department of Maternal/Fetal
Medicine
St Michael's Hospital
Southwell Street
Bristol BS2 8EG

Department of Obstetrics &
Gynaecology
University of Edinburgh
37 Chalmers Street
Edinburgh EH3 9EW

Department of Obstetrics &
Gynaecology
Glasgow Royal Infirmary
Queen Elizabeth Building
10 Alexandra Parade
Glasgow G31 2ER

University Department of Obstetrics &
Gynaecology
St James's University Hospital
Beckett Street
Leeds LS9 7TF

Department of Obstetrics &
Gynaecology
Clinical Sciences Building
University of Leicester
Leicester Royal Infirmary
Leicester LE2 7LX

Department of Obstetrics
2nd Floor New Guy's House
Guy's Hospital
St Thomas' Street
London SE1 9RT

Department of Obstetrics &
Gynaecology
Homerton Hospital
Homerton Row
London E9 6SR

Harris Birthright Research Centre for Fetal
Medicine
King's College Hospital Medical School
Denmark Hill
London SE5 8RX

Institute of Obstetrics & Gynaecology
Queen Charlotte's Hospital
Goldhawk Road
London W6 0XG

Department of Obstetrics & Gynaecology
St George's Hospital Medical School
Cranmer Terrace
London SW17 0RE

Department of Obstetrics &
Gynaecology
University College Hospital
86-96 Chenies Mews
London WC2E 6HX

Department of Obstetrics &
Gynaecology
St Mary's Hospital
Whitworth Park
Manchester M13 0JH

Department of Fetal Medicine
Leazes Wing
Queen Victoria Road
Newcastle Upon Tyne NE1 4LP

Royal Victoria Infirmary
Department of Feto-Maternal Medicine
University Hospital of Nottingham
Queens Medical Centre
Clifton Boulevard
Nottingham NG7 2UH

Department of Obstetrics &
Gynaecology
The John Radcliffe Hospital
Headley Way
Headington
Oxford OX3 9DU

Department of Fetal Medicine
The Princess Anne Hospital
Coxford Road
Southampton SO16 5YA

REGIONAL GENETICS CENTRES

Northern Ireland Regional Genetics Centre
Floor A Tower Block
West Podium Extension
Belfast City Hospital
51 Lisburn Road
Belfast BT9 7AB

Clinical Genetics Unit
Birmingham Women's Hospital
Edgbaston
Birmingham B15 2TG

Clinical Genetics Department
Royal Hospital for Sick Children
St Michael's Hill
Bristol BS5 5BJ

Department of Medical Genetics
Box 134 Addenbrooke's Hospital
Hills Road
Cambridge CB2 2QQ

Wales Medical Genetics Service
Institute of Medical Genetics
University Hospital of Wales
Heath Park
Cardiff CF4 4XW

Department of Clinical Genetics
Moston Lodge
Countess of Chester Hospital
Liverpool Road
Chester CH2 1UL

Human Genetics Laboratories
Department of Pathology
Ninewells Hospital and Medical School
Dundee DD1 9SY

Clinical Genetics Unit
Western General Hospital
Crewe Road
Edinburgh EH4 2XU

Clinical Genetics Service
Department of Child Health
Royal Devon and Exeter Hospital
Barrack Road
Exeter EX2 5DW

West of Scotland Regional Genetic Service
Institute of Medical Genetics
Yorkhill Hospital
Glasgow G3 8SJ

Regional Genetics Services
Department of Clinical Genetics
Ashley Wing, St James Hospital
Leeds LS9 7TF

Department of Clinical Genetics
Leicester Royal Infirmary
Leicester LE1 5WW

Clinical Genetics Services
Alder Hey Children's Hospital
Eaton Road, West Derby
Liverpool L12 2AP

Kennedy-Galton Centre for Clinical Genetics
Level 8V, Northwick Park Hospital
Harrow, London HA1 3UJ

Clinical Genetics Unit
Royal Free Hospital
Pond Street, Hampstead
London NW3 2QG

Division of Medical and Molecular Genetics
8th Floor, Guy's Tower, Guy's Hospital
London SE1 9RT

Regional Genetic Services
St George's Hospital, Cranmer Terrace
London SW17 0RE

Clinical Genetics Unit
Institute of Child Health
30 Guilford Street
London WC1N 1EH

Department of Clinical Genetics
St Mary's Hospital
Manchester M13 0JH

Regional Genetics Service
Manchester Children's Hospital
Pendlebury
Manchester M27 4HA

Northern Genetics Service
Royal Victoria Infirmary and Associated
Hospitals NHS Trust
19/20 Claremont Place
Newcastle upon Tyne NE2 4LP

North of Scotland Regional Genetics Service

- Aberdeen Royal Hospitals
Forester Hill
Aberdeen AB9 2AL
- Raigmore Hospital
Inverness IV2 3UJ

Department of Clinical Genetics
City Hospital
Hucknall Road
Nottingham NG5 1PB

Department of Clinical Genetics
The Churchill Oxford Radcliffe Hospital
Old Road, Headington
Oxford OX3 7LJ

Centre for Human Genetics
117 Manchester Road
Sheffield S10 5DN

Wessex Regional Genetics Service
Princess Anne Hospital
Coxford Road
Southampton SO16 5YA

OTHER USEFUL ADDRESSES

Advisory Committee on Genetic Testing

Department of Health
Room 401, Wellington House
133-155 Waterloo Road
London SE1 8UG
Telephone: 0171 972 4017

Antenatal Results and Choices

73 Charlotte Street
London W1P 1LB
Telephone: 0171 631 0280

British Society for Human Genetics

Clinical Genetics Unit
Birmingham Women's Hospital
Edgbaston
Birmingham B15 2TG
Telephone: 0121 627 2630

The main academic and professional society for human geneticists. Includes all members of ACC, AGNC, CGS and CMGS (see below), plus others.

Association of Clinical Cytogeneticists (ACC)

c/o Oxford Medical Genetic Laboratories
The Churchill, Headington
Oxon OX3 7LJ
Telephone: 01865 226022

The ACC promotes the science and service of clinical cytogenetics, to ensure the development and maintenance of professional standards and to act as an advisory body on behalf of the profession.

Association of Genetic Nurses and Counsellors (AGNC)

Department of Clinical Genetics
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
Telephone: 0131 651 1012

The AGNC is one of the founding groups of the British Society for Human Genetics. Its role is to represent the interests of nurses and counsellors working in the field of genetics.

Clinical Genetics Society (CGS)

Clinical Genetics Unit
Birmingham Maternity Hospital,
Edgbaston
Birmingham B15 2TG
Telephone: 0121 627 2630

Clinical Molecular Genetics Society (CMGS)

Regional Molecular Genetics Laboratory
St Mary's Hospital, Hathersage Road
Manchester M13 0JH
Telephone: 0161 276 6129

Clinical Molecular Genetics Society - part of the federated BSHG representing diagnostic molecular geneticists mostly working in NHS Regional Genetics Centres.

Clinical Pathology Accreditation (UK) Limited

45 Rutland Park
Botanical Gardens
SHEFFIELD S10 2PB
Telephone: 0114 268 6151

CPA (UK) Ltd accreditation programme provides peer review inspection of pathology departments to assess the quality of service provided.

Contact a Family

170 Tottenham Court Road
London W1P 0HA
Telephone: 0171 383 3555

Provides advice and information to families caring for children with disabilities, including inherited disorders.

Genetic Interest Group

29-35 Farringdon Road
London EC1M 3JB
Telephone: 0171 430 0090

GIG is the UK alliance of charities and support groups for people who are affected by genetic disorders.

Human Genetics Commission

Department of Health
Room 401, Wellington House
133-155 Waterloo Road
London SE1 8UG
Telephone: 0171 972 4017

Royal College of General Practitioners

14 Princes Gate
Hyde Park
London SW7 1PU
Telephone: 0171 581 3232

Royal College of Obstetricians and Gynaecologists

27 Sussex Place
Regents Park
London NW1 4LE
Telephone: 0171 772 6263

Royal College of Pathologists

2 Carlton House Terrace
London SW1Y 5AF
Telephone: 0171 930 5861

Promotes the science and practice of pathology - the study of the cause and effect of disease - aims to increase public awareness of the broad scope of pathology and its role in saving and protecting lives.

Royal College of Physicians

(College Committee on Clinical Genetics)
11 St Andrew's Place
London NW1 4LE

Further copies of this report can be obtained from:

Genetics Secretariat
Department of Health
Room 401, Wellington House
133-155 Waterloo Road
LONDON SE1 8UG

Tel: 0171-972-4017
Fax: 0171-972-4196
Email: genetics-policy@doh.gov.uk

For more information about ACGT see the Department of Health Homepage:

<http://www.open.gov.uk/doh/genetics/htm>

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