Genetics in Family Medicine:
The Australian Handbook for General Practitioners

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Australian College of Rural and Remote Medicine (ACCRM)

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Rapid advances in genetics have led to major impacts upon general practitioners' (GPs) needs to better understand and provide information and referrals on genetic conditions to patients and their families.

In late 2004, the Australian Government Agency, Biotechnology Australia initiated a project to develop a national educational resource on genetic medicine for Australian GPs. The outcome of this project is the *Genetics in Family Medicine: The Australian Handbook for General Practitioners*.

The major work in developing this was undertaken by the Genetics Education in Medicine (GEM) Consortium, whose work was informed by a nationwide GPs’ needs assessment, consumer input, and a mapping exercise of current Australian resources. *Genetics in Family Medicine: The Australian Handbook for General Practitioners* aims to support GPs dealing with genetic medicine in their everyday practice. The handbook includes information aimed predominantly for use by general practitioners and other primary healthcare professionals; with relevant consumer information making up the Patient and family fact sheets.

*Genetics in Family Medicine: The Australian Handbook for General Practitioners* represents a culmination of previous efforts, building on existing resources, to meet the current and future needs of GPs in the area of genetic medicine. In developing this handbook two existing publications have been largely referred to:

- *The Genetics File – A resource for GPs* (2003), Genetics Education, Murdoch Childrens Research Institute, Victoria

Responding to identified current needs, we have produced new sections on clotting and bleeding conditions, cardiovascular conditions, diabetes and consumer support groups. The support and input from the National Advisory Group on Genetics Education for General Practitioners, appointed by Biotechnology Australia to steer the development of the resources, has been invaluable, and the quality of this resource reflects the calibre and dedication of all involved, to improve genetic resources for GPs, and their patients and families.

We would also like to thank and acknowledge all the contributors and organisations who have provided their expert knowledge in reviewing this resource.

---

**Australian Government**

**Biotechnology Australia**

Biotechnology Australia is the Australian Government body responsible for coordinating all non-regulatory biotechnology issues. Biotechnology Australia’s Communications and Engagement Program aims to increase the public’s general awareness of biotechnology and its uses, through the provision of balanced and factual information explaining the technology, its applications, and regulations to safeguard people and the environment.

We work with a wide range of experts and government authorities including the Office of the Gene Technology Regulator, Food Standards Australia New Zealand, State and Territory Governments, local councils, Cooperative Research Centres, Universities, various teachers associations and community groups; to provide factual information across a broad range of issues to enable the community to make informed choices on the applications of biotechnology.
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Cancer Council SA
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Familial Cancer Register SA
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Familial Cancer Register VIC
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Familial Cancer Service SA
Familial Cancer Service VIC
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Royal College of Surgeons of Australia
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  What is a gene?
  How do genetic conditions occur?
  Talking with doctors
  Your family history
GP’s role

- Consult with, and refer, to Genetics Services for clarification of genetic issues, risk assessment, counselling, diagnosis, testing and support when needed.
- Be aware of relevant support groups that may be useful regarding specific conditions, promote their service, and promote patients to make contact with them.
- The GP’s role in ordering specific genetic tests will vary according to the condition.
- Be aware that the patient’s ethnicity or cultural background can guide the ordering of specific genetic tests.
- Inform the patient about the purpose, personal, and family implications, of a genetic test prior to obtaining consent.
- Be aware that patients who have had a predictive or pre-symptomatic genetic test have a duty to inform life insurers of the test result when applying for a new, or altering an existing, policy.
- A GP has no duty to inform the relatives of a patient about a positive genetic test result. Encourage and support the patient to share the information with their relatives.

Australian Genetics Services

- These services provide specialist genetic risk assessment, counselling, diagnosis and testing services, including those for familial cancer and prenatal testing, and work closely with genetic testing laboratories and education services.
- Professionals within Genetics Services include:
  - Clinical geneticists – physicians (FRACP) with sub-specialty training in clinical genetics. Their role is in diagnosis, management for some conditions and the provision of genetic counselling and appropriate genetic testing
  - Genetic counsellors - health professionals with specialist training in genetics and counselling, certified by the Human Genetics Society of Australasia (HGSA). They have a primary role in the provision of genetic counselling
  - Social workers - health professionals with a special interest in genetics and particular conditions, work closely with clinical geneticists, genetic counsellors and support groups, offering counselling and practical resources for families and individuals
  - Related medical specialists - specialist medical practitioners with expertise in areas such as prenatal diagnosis, familial cancers and neurology work closely with clinical genetics services
  - Scientists and pathologists working in diagnostic laboratory services
- Contacts for general Genetics Services, Medications in Pregnancy and Lactation Services and Birth Defects Registers available in each State and Territory are listed below.
- See Cancer in the family and Testing and pregnancy for details of familial cancer and prenatal testing services where available in each State and Territory.
## Australian Capital Territory

### Metropolitan and outreach

<table>
<thead>
<tr>
<th>Canberra</th>
<th><strong>The Canberra Hospital</strong></th>
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<tbody>
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<td>PO Box 11, Woden, ACT 2605</td>
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<td>Ph: (02) 6244 4042 Fax: (02) 6244 3422</td>
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</tbody>
</table>
# New South Wales

## Metropolitan centres

<table>
<thead>
<tr>
<th>Location</th>
<th>Address</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
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<td>Missenden Rd, Camperdown, NSW 2050  &lt;br&gt; Ph: (02) 9515 5080  Fax: (02) 9515 7595</td>
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<tr>
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<td>St George Hospital</td>
<td>Kogarah, NSW 2217  &lt;br&gt; Ph: (02) 9350 3635  Fax: (02) 9350 3901</td>
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<tr>
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## Regional centres

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No NT based or outreach genetics services
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Herston Rd, Herston, QLD 4029  
Ph: (07) 3636 1686 Fax: (07) 3636 1987 |

### Regional centres

<table>
<thead>
<tr>
<th>Town</th>
<th>Address</th>
</tr>
</thead>
</table>
| Bundaberg  | Associate Genetic Counsellor  
Bundaberg Base Hospital  
Bourbong St, Bundaberg, QLD 4670  
Ph: (07) 4150 2794 Fax: (07) 3636 1987 |
| Cairns     | Associate Genetic Counsellor  
Cairns Base Hospital  
2nd Floor, Block B, Cairns, QLD 4870  
Ph/Fax: (07) 4050 6247 |
| Nambour    | Associate Genetic Counsellor  
Nambour General Hospital  
Cnr Hospital and Mapleton Rd, Nambour, QLD 4560  
Ph/Fax: (07) 5441 7167 |
| Southport  | Genetic Counsellor Gold Coast Hospital  
Queensland Clinical Genetics Service  
Quarters 1, Rm1-28, 108 Nerang St, Southport QLD 4215  
Ph/Fax: (07) 5571 8741 |
| Toowoomba  | Associate Genetic Counsellor  
Toowoomba Base Hospital  
Private Mail Bag 2, Toowoomba, QLD 4350  
Ph/Fax: (07) 4616 6995 |
| Townsville | Clinical Geneticist And Associate Genetic Counsellor  
The Townsville Hospital  
Angus Smith Rd, Douglas, Townsville, QLD 4810  
Ph/Fax: (07) 4796 1463/1461 |

### Birth Defects Register (QLD)

<table>
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<tr>
<th>Dept</th>
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</table>
| Perinatal Data Collection | Data Services Unit  
Queensland Health  
PO Box 48, QLD 4001  
Ph: (07) 3234 1885 Fax: (07) 3234 0279 |
## South Australia

### Metropolitan centres

| North Adelaide | South Australian Clinical Genetics Service  
|---------------|---------------------------------------------|
|               | Women’s and Children’s Hospital  
|               | 72 King William Rd, North Adelaide, SA 5006  
|               | Ph: (08) 8161 7375 or (08) 8161 7010  
|               | Fax: (08) 8161 6088  

Outreach clinics held in  
Flinders Medical Centre,  
Lyell McEwin Health Service,  
Royal Adelaide Hospital,  
The Queen Elizabeth Hospital.

| Outreach clinics held in  
| South Australian Clinical Genetics Service  
| Mount Gambier,  
| Port Augusta, Whyalla  
| C/O South Australian Clinical Genetics Service  
| Ph: (08) 8161 7375 or (08) 8161 7010  
| Fax: (08) 8161 6088  

### Regional centres

| Outreach clinics held in  
| South Australian Birth Defects Register  
| Mount Gambier,  
| Port Augusta, Whyalla  
| C/O South Australian Clinical Genetics Service  
| Ph: (08) 8161 7375 or (08) 8161 7010  
| Fax: (08) 8161 6088  

### Birth Defects Register (SA)

| South Australian Birth Defects Register  
| South Australian Clinical Genetics Service  
| Women’s and Children’s Hospital  
| 72 King William Rd, North Adelaide, SA 5006  
| Ph: (08) 8161 7368  
| Fax: (08) 8161 6049  

Birth Defects Register (SA)
## Tasmania

<table>
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<tr>
<th>Location</th>
<th>Service Name</th>
<th>Contact Information</th>
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</table>
| Hobart   | Tasmanian Clinical Genetics Service | Royal Hobart Hospital  
PO Box 1061L, Hobart, TAS 7001  
Ph: (03) 6222 8296 Fax: (03) 6222 7961 |
| Launceston | Tasmanian Clinical Genetics Service | Launceston General Hospital  
C/O Royal Hobart Hospital  
Ph: (03) 6222 8296 Fax: (03) 6222 7961 |
| Burnie  | Tasmanian Clinical Genetics Service | North West Regional Hospital, Burnie Campus  
C/O Royal Hobart Hospital  
Ph: (03) 6222 8296 Fax: (03) 6222 7961 |

## Birth Defects Register (TAS)

<table>
<thead>
<tr>
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<tr>
<td>Perinatal Data Collection</td>
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</tr>
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</table>
PO Box 125L  
Hobart, TAS 7000  
Ph: (03) 6233 4016 Fax: (03) 6233 3550 |
## Victoria

### Metropolitan centres

<table>
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<tr>
<th>Location</th>
<th>Organisation</th>
<th>Address</th>
<th>Phone</th>
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<tbody>
<tr>
<td>Parkville</td>
<td>Genetic Health Services Victoria (GHSV)</td>
<td>Royal Children’s Hospital</td>
<td>(03) 8341 6270</td>
<td>(03) 8341 6390</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flemington Rd, Parkville, VIC 3052</td>
<td></td>
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</tr>
<tr>
<td>Clayton</td>
<td>Genetic Health Services Victoria</td>
<td>Monash Medical Centre</td>
<td>(03) 9594 2026</td>
<td>(03) 9594 6022</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clayton Rd, Clayton, VIC 3168</td>
<td></td>
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</tr>
<tr>
<td>Melbourne</td>
<td>Melbourne Health/Genetic Health Services Victoria</td>
<td>Royal Melbourne Hospital</td>
<td>(03) 9342 7151</td>
<td>(03) 9342 4267</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parkville, VIC 3052</td>
<td></td>
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</tr>
<tr>
<td>Heidelberg</td>
<td>Genetic Health Services Victoria/Austin and Repatriation Medical Centre</td>
<td>Austin Hospital</td>
<td>(03) 9496 5000</td>
<td>(03) 9458 4779</td>
</tr>
<tr>
<td></td>
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<td>Burgundy St, Heidelberg, VIC 3084</td>
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### Non-metropolitan and regional centres

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<tbody>
<tr>
<td>Albury/Wodonga</td>
<td>Genetic Health Services Victoria</td>
<td>78 Vermont St, Wodonga, VIC 3690</td>
<td>(02) 6056 0451</td>
<td></td>
</tr>
<tr>
<td>Ballarat</td>
<td>Genetic Health Services Victoria</td>
<td>Non-Metropolitan Genetics Services</td>
<td>(03) 8341 6201</td>
<td>(03) 8341 6390</td>
</tr>
<tr>
<td>Bendigo</td>
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### Medications in Pregnancy and Lactation Service (VIC)

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<th>Organisation</th>
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<th>Phone</th>
<th>Fax</th>
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<tbody>
<tr>
<td>Mothersafe</td>
<td>Medications in Pregnancy and Lactation Service</td>
<td>Royal Children’s Hospital</td>
<td>(03) 9345 6987 or (03) 9345 4702</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flemington Rd, Parkville, VIC 3052</td>
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### Birth Defects Register (Vic)

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Address</th>
<th>Phone</th>
<th>Fax</th>
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<tbody>
<tr>
<td>Victorian Birth Defects Register</td>
<td>Victorian Perinatal Data Collection Unit</td>
<td>PO Box 4003, Melbourne, VIC 3001</td>
<td>(03) 9616 2695 or 1300 858 505</td>
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## Western Australia

### Metropolitan centres

| Subiaco | Genetics Services of Western Australia  
|---------|----------------------------------------|
|         | King Edward Memorial Hospital  
|         | 374 Bagot Rd, Subiaco, WA 6008  
|         | Ph: (08) 9340 2222 Fax: (08) 9340 1678 |

| Subiaco | Genetics Services of Western Australia  
|---------|----------------------------------------|
|         | Princess Margaret Hospital for Children  
|         | Roberts Rd, Subiaco, WA 6008  
|         | Ph: (08) 9340 2222 Fax: (08) 9340 7058 |

### Regional centres

<table>
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<th>Albany</th>
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<tbody>
<tr>
<td>Bunbury</td>
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<td>Geraldton</td>
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<tr>
<td>Joondalup</td>
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<tr>
<td>Kalgoorlie</td>
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<tr>
<td>Port Hedland</td>
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<td>Rockingham</td>
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| C/O Genetics Services of Western Australia  
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</thead>
<tbody>
<tr>
<td>Ph: (08) 9340 2222 Fax: (08) 9340 1678</td>
</tr>
</tbody>
</table>

### Birth Defects Register (WA)

| Western Australian Birth Defects Registry  
|---------------------------------------------|
| King Edward Memorial Hospital  
| 374 Bagot Rd, Subiaco, WA 6008  
| Ph: (08) 9340 2735 Fax: (08) 9340 2636 |
Professional genetic counselling

- Genetic counselling is a communication process that aims to provide information and supportive counselling to members of families regarding problems in growth, development and health that may have a genetic basis.

- The process of professional genetic counselling involves assisting patients to:
  > Comprehend the medical facts regarding a genetic condition, including the diagnosis, probable course of the condition and the available management
  > Appreciate the way heredity contributes to the condition and the risk of occurrence in relatives
  > Understand the options for dealing with the risk of recurrence
  > Choose the course of action that seems appropriate in view of their situation, risk, and values, and act in accordance with that decision
  > Make the best possible adjustment to the condition in an affected family member and/or to the risk of recurrence of that condition

- During a consultation the following may be discussed:
  > Information about the condition including:
    - Key clinical features
    - The genetic contribution to its cause, including the gene(s) involved, the inheritance pattern, the likelihood that a person who inherits the genetic susceptibility will develop the condition
    - Interactions between genes and the interplay between genes and environment
  > Genetic testing:
    - Availability of testing
    - Helping patients to decide whether to undergo genetic testing
    - Helping patients understand and use genetic test results
  > Implications for family members:
    - Depending on the particular condition and the information provided, there may be profound medical and psychological implications for blood relatives
    - There may be implications for future reproductive choices, employment or insurance, and issues concerning the privacy and confidentiality of genetic information

Preparing families for a professional genetics consultation

- Patients should gather information about their family’s health history (including age of diagnosis, causes and age of death). There is usually a pre-clinic contact (either phone call or questionnaire) where family information will be requested prior to the consultation.

- Photos of relatives can sometimes help with diagnosis.

- Patients should make a list of questions they wish to ask before the appointment and take it with them.

- Consultations usually last about an hour. If tests are required, the family may be at the service for longer.

- Patients should be aware that the consultation may not provide definitive information, eg in relation to diagnosis or risk for future children.

- Other family members may need a physical examination or investigation, eg the parents of a child.

- Blood tests may be required.

- The presence of another family member or friend can provide moral support and help recall.

- Health care interpreter services are usually available.

- A letter is sent to the family and referring doctor after a consultation, documenting what was said and the findings.
At a genetics consultation session

- Whilst each genetics consultation session will differ depending on the patient and their particular situation, in general terms the following is likely to take place:
  - Confirmation of family history
  - Clinical examination
  - Diagnosis (if appropriate)
  - Provision of genetic information
  - Discussion and possible provision of genetic testing
  - Discussion surrounding the implications for the individual and other family members
  - Provision of support and counselling

Related genetics services

Prenatal genetics services

- Prenatal services, including fetal medicine services and associated professional genetic counselling, provide prenatal screening and diagnostic tests, pre- and post-test counselling and, if appropriate, discussion of pre-implantation genetic diagnosis.
- Pregnant women are often referred to a prenatal genetics service to discuss issues surrounding:
  - Advanced maternal age
  - A family history of a heritable condition – the risk of it recurring in the couple’s children, tests to clarify the risk and screening tests or diagnostic tests during pregnancy to assess whether the fetus is affected
  - A history of infertility, miscarriages, stillbirths or early infant deaths
  - Concern about the effects of drugs and infections during early pregnancy
- Genetic counselling is essential before prenatal diagnosis, to ensure that screening or testing is undertaken with informed consent.
- Where an abnormality is detected, genetic counselling provides current information and support for those making decisions about the continuation of the pregnancy.
- See Testing and pregnancy for further information on testing and pregnancy as well as for contact details of prenatal services in each Australian State and Territory.

Medications in pregnancy and lactation services

- These are specialist services providing information and counselling for women and their health care providers regarding pregnancy and lactation exposure to:
  - Chemicals
  - Drugs
  - Radiation or
  - Other environmental agents
- See contact list for details of these services in NSW and Victoria, or Genetics Services for other States and Territories.
Paediatric genetics services

- These services specialise in syndrome diagnosis for conditions including:
  - Connective tissue conditions, eg Marfan syndrome
  - Dental, eg ectodermal dysplasia
  - Developmental disabilities, eg fragile X syndrome
  - Eye conditions, eg retinoblastoma
  - Metabolic conditions, eg enzyme deficiencies
  - Muscle conditions, eg muscular dystrophy
  - Neurogenetic, eg neurofibromatosis
  - Skeletal dysplasias, eg short stature conditions

Familial cancer services

- Patients are referred to familial cancer services following their identification as potentially high risk based on their family history to discuss familial cancers such as:
  - Breast and/or ovarian cancer
  - Bowel cancer, including familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC)
  - Syndromes with cancer as a feature, eg Von-Hippel-Lindau syndrome and multiple endocrine neoplasia

- These multidisciplinary clinics perform a wide range of important functions including:
  - Extended family history collection
  - Verification of diagnoses through death and cancer registers and pathology results
  - Risk estimation
  - Collection of blood and tissue samples from family members when appropriate
  - Liaison with other relevant health professionals and registers within the state, interstate and internationally
  - Educational support and counselling, including prevention and surveillance options
  - Discussion concerning surveillance and prophylactic strategies
  - Identification of at-risk relatives
  - Genetic counselling before and after testing to identify the family-specific mutation in an affected person or predictive testing for unaffected family members
  - Documentation of follow-up in the extended family with consent

- See Cancer in the family for further information on familial cancers and for contact details of familial cancer services in each Australian State and Territory.

Other genetics specialty services

- Clinical genetics centres sometimes work in conjunction with clinical services in hospitals that provide treatment. The specialty Genetics Services can provide the essential counselling associated with risk assessment, management advice for specific conditions, and carrier and pre-symptomatic genetic testing where it is available.

- Information regarding the availability of clinics which specialise in diagnosis, management and genetic counselling for particular conditions or syndromes such as those listed below, is available from Genetics Services:
  - Blood conditions, eg thalassaemia
  - Cancer, eg breast, colon, melanoma
  - Adult-onset neurological conditions
Contacts, support and testing

**Registers**
- Birth defects registers that have been established in each State and Territory are population-based surveillance systems. Data collection policies and the periods of collection vary between the registers.
- See contact list for details for the Birth Defects Registers (where available) in each State and Territory.
- Registers for a range of familial cancers have been established to assist in the management of people with an inherited predisposition to develop specific cancers. Registration allows patients and their family members to be followed and monitored with respect to cancer screening, prevention and the early detection of symptoms. Individuals opting for registration have been shown to have a reduced risk, for example, for colorectal cancer as patients are educated about their condition, advised and reminded about screening procedures, and advised when prophylactic surgery should be considered.

**Laboratory genetics services**
- Laboratory services refer to the range of chromosomal, biochemical and DNA testing that can be undertaken to diagnose a particular genetic condition, to determine whether an individual is a ‘carrier’ of a mutation for a particular condition even though he/she may be unaffected, or to assess whether a person will, or is likely to, develop a condition later in life.
- Laboratory services include newborn screening, maternal serum screening, cytogenetic, biochemical and molecular testing, including carrier, predictive and pre-symptomatic genetic testing.
- For information regarding laboratory services please contact Genetics Services.

**Education and health promotion**
- Programs of education and health promotion coordinated by Genetics Services have been designed to raise awareness amongst health, education, welfare professionals and the community of the importance of the contribution of genetics to family health.
- Genetics Services support programs that help reduce the occurrence of birth defects, e.g., folate prevention of spina bifida and screening programs that help identify individuals or pregnancies at risk of birth defects, e.g., first and second trimester prenatal screening and newborn screening programs.
- Condition-specific education programs, for example related to particular cancers or haemochromatosis, have been established in many areas.
- Many support groups for particular genetic conditions are active in raising community awareness through a combination of family and genetic health professional involvement.
Support groups

Community perspective

In the development of the Genetics in Family Medicine handbook, a focus group study was conducted exploring Australian consumers’ views regarding the management of genetic conditions by GPs. This was an exploration of how people living with genetic conditions view GPs as unique health care providers: what is done well and what could be improved upon regarding management of genetic conditions. The following points have been drawn from the study’s results as being specific to the GP’s role regarding support groups.

GPs play a unique role:

- As the first point of contact for patients, GPs fill a certain ‘gate-keeping’ role. In this sense, their direction regarding specialist and support interventions is very important.
- GPs are expected to treat patients and their families in a holistic manner – covering specific genetic, other medical and psychosocial issues. Referral to support groups is part of such holistic treatment, promoting overall wellbeing in the patient and family.

GPs could improve their use of support groups:

- Overall it was considered that GPs need to be more aware of support groups and networks that could benefit their patients and have relevant information on hand to refer patients and their families to relevant groups.
- Through being aware of the wider community it is hoped that GPs are able to include and appreciate the benefits of support groups as part of their everyday practice.

The importance and value in referring to genetics support groups

- In addition to support from the GP, Genetics Services and professional counselling, referral to support organisations can be beneficial and, in some cases, necessary for the wellbeing of the patient and/or their family.
- All people who live with a genetic condition (either personally or in their family) should have access to appropriate, up-to-date and accurate information. Additionally, they should have available the necessary support to assist them to manage the challenges to their health and wellbeing and to enable them to reach their full potential.
- Support groups can be an important source of peer support and empowerment, practical information and advice about living with a genetic condition. Families can benefit from contact with other people in similar situations, regardless of their level of coping or need for support.
- Genetics support groups can be state, national or international, allowing families to appreciate that they are not alone in the challenges they may face living with a particular genetic condition.
• **Genetics support group meetings**

  - For each genetics support group, there is usually a chair or coordinator, who arranges and facilitates the discussion or activities at a meeting. They may host the meeting in their home, or at a central meeting venue such as the office of the local AGA Peak Body (see 'Australasian Genetic Alliance' below).

  - Different genetics support groups will conduct their meetings in different ways. Some may meet over a lunchtime period and offer a casual arena for open-ended discussion. Other groups may provide more structured events and activities, and may invite guest speakers to attend their meeting.

  - Genetics support groups often distribute a newsletter at regular intervals to update their members on news, upcoming events and share experiences that are relevant to their group.

  - Whilst not all people will want to, or be able to attend support group meetings, they may benefit from accessing the written, telephone or online options offered by some groups, in order to discuss interests and concerns with others in similar circumstances.

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**Australasian Genetic Alliance**

http://www.australasiangeneticalliance.org.au

- The Australasian Genetic Alliance (AGA) is a network of Peak Bodies which includes:
  - Association of Genetics Support of Australasia (AGSA)
  - Genetics Support Council Western Australia (GSCWA)
  - Genetic Support Network Victoria (GSNV)
  - New Zealand Organisation for Rare Conditions (NZORD)
  - Self-Help Organisations United Together in the Australian Capital Territory (SHOUT)
  - Self Help Queensland (SHQ).

- The AGA aims to work collectively in supporting people living with a genetic condition and genetics support groups, as well as to increase community awareness through networking, sharing resources and representing common interests.

- The Peak Bodies of the AGA facilitate an exchange of information, resources and assistance in order to support a number of existing genetics support groups and aid the development of new groups. They are able to support many groups that provide a point of contact for parents and people with the same genetic condition. Furthermore, they also serve as an excellent ‘sign post’ for direction to relevant support for those faced with rare genetic conditions for which there is not always an established support group.

- The following is a contact list for the Peak Bodies currently in place under the umbrella of the AGA. It is important to note that these bodies work as a collaborative and consultative network and, as such, work as a team to find the appropriate service for particular individual/family needs. Whilst there is currently not a Peak Body in the Northern Territory, South Australia, or Tasmania, it is hoped this can be addressed in due course. Other Peak Bodies can be contacted to find information pertaining to these States and Territories.
Table 1: Peak Bodies of the Australasian Genetic Alliance (AGA)

Australasian Genetic Alliance
Email: info@australasiangeneticalliance.org.au
Website: http://www.australasiangeneticalliance.org.au

<table>
<thead>
<tr>
<th>State / Territory</th>
<th>AGA Peak Body</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td>Australian Capital Territory</td>
<td><strong>Self-Help Organisations United Together (SHOUT)</strong></td>
<td>PO Box 717, Mawson, ACT 2607</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph: (02) 6290 1984</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fax: (02) 6286 4475</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Email: <a href="mailto:admin@shout.org.au">admin@shout.org.au</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Website: <a href="http://www.shout.org.au">www.shout.org.au</a></td>
</tr>
<tr>
<td>New South Wales</td>
<td><strong>Association of Genetic Support of Australasia (AGSA) Inc.</strong></td>
<td>66 Albion Street, Surry Hills, NSW 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph: (02) 9211 1462</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fax: (02) 9211 8077</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Email: <a href="mailto:info@agsa-geneticsupport.org.au">info@agsa-geneticsupport.org.au</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Website: <a href="http://www.agsa-geneticsupport.org.au">www.agsa-geneticsupport.org.au</a></td>
</tr>
<tr>
<td>New Zealand</td>
<td><strong>New Zealand Organisation for Rare Conditions (NZORD)</strong></td>
<td>PO Box 38-538, Petone, NZ 6008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph: (+ 64) (0)4 566 7707</td>
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<tr>
<td></td>
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<td>Fax: (+64) (0)4 566 7717</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Email: <a href="mailto:exec.director@nzord.org.nz">exec.director@nzord.org.nz</a></td>
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<td>Website: <a href="http://www.nzord.org.nz">www.nzord.org.nz</a></td>
</tr>
<tr>
<td>Queensland</td>
<td><strong>Self Help Queensland (SHQ) Inc</strong></td>
<td>PO Box 353, Sunny Bank, QLD 4109</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph/Fax: (07) 3344 6919</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Email: <a href="mailto:selfhelp@gil.com.au">selfhelp@gil.com.au</a></td>
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<td>Website: <a href="http://www.selfhelpqld.org.au">www.selfhelpqld.org.au</a></td>
</tr>
<tr>
<td>Victoria</td>
<td><strong>Genetic Support Network Victoria (GSNV)</strong></td>
<td>Royal Children’s Hospital, Parkville, VIC 3052</td>
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<td>Ph: (03) 8341 6315</td>
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<td>Fax: (03) 8341 6390</td>
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<td>Email: <a href="mailto:info@gsnv.org.au">info@gsnv.org.au</a></td>
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<td>Website: <a href="http://www.gsnv.org.au">www.gsnv.org.au</a></td>
</tr>
<tr>
<td>Western Australia</td>
<td><strong>Genetic Support Council WA (GSCWA)</strong></td>
<td>Level 1, Oasis Lotteries House</td>
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<tr>
<td></td>
<td></td>
<td>37 Hampden Rd, Nedlands, WA 6009</td>
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<td>Ph: (08) 9389 6722</td>
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<td>Fax: (08) 9389 9377</td>
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<td>Email: <a href="mailto:info@geneticsupportcouncil.org.au">info@geneticsupportcouncil.org.au</a></td>
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</table>
Conditions for which there are genetics support groups

- Table 2 is a list of conditions for which there are genetics support groups in Australasia.
- Whilst this gives an idea of the broad scope of genetic conditions for which there are support groups, it is important to note that this is by no means an exhaustive list.
- The AGA Peak Bodies will be able to direct individuals and/or their families to a relevant group, or assist if a particular support group does not exist in a given State or Territory.

Rare conditions

- While individuals with rare conditions do not commonly present to GPs, collectively there are probably about 1.2 million Australians who have a rare condition.
- GPs may be the first point of call and it is acknowledged that management can be challenging.
- Individuals and their families have similar experiences despite their different diagnoses and GPs are well placed to help with these problems.
- The patient and their family as well as support groups can be an important source of information for GPs about the specific condition.
- Peer support can be helpful for individuals when a support group is not available.

Table 2: Conditions for which there are genetics support groups in Australia

<table>
<thead>
<tr>
<th>A</th>
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<tbody>
<tr>
<td>Acoustic neuroma</td>
<td>Ankylosing spondylitis</td>
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<td>Arthritis</td>
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<td>Alopecia areata</td>
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<td>Alpha-1-antitrypsin deficiency</td>
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<td>Alzheimer disease</td>
<td>Asthma</td>
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<tr>
<td>Androgen insensitivity syndrome</td>
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<td>Angelman syndrome</td>
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<tr>
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<tbody>
<tr>
<td>Bardet-Bied/Laurence-Moon syndrome</td>
<td>Bi-polar affective disorder</td>
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<tr>
<td>Batten disease</td>
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<td>Beckwith-Wiedemann syndrome</td>
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<tr>
<td>Cancer</td>
<td>Congenital adrenal hyperplasia</td>
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<tr>
<td>Cardiac conditions</td>
<td>Cornelia de Lange syndrome</td>
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<tr>
<td>Cardiomyopathy</td>
<td>Costello syndrome</td>
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<td>Charcot-Marie-Tooth disease</td>
<td>Cranio-facial disorders</td>
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<tr>
<td>Choanal atresia</td>
<td>Cri du chat syndrome</td>
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<tr>
<td>Chromosomal conditions</td>
<td>Crohn disease and colitis</td>
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<tr>
<td>Cleft palate and/or cleft lip</td>
<td>Cushing disease</td>
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<td>Coeliac disease</td>
<td>Cystic fibrosis</td>
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<td>Dementia</td>
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<td>Di George syndrome</td>
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<td>Diabetes mellitus</td>
<td>Dystonia</td>
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<td>Ectodermal dysplasia</td>
<td>Epidermolysis bullosa</td>
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<tr>
<td>Ehlers-Danlos Syndrome</td>
<td>Epilepsy</td>
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<td><strong>F</strong></td>
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<tr>
<td>Fabry disease</td>
<td>Friedreich ataxia</td>
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<td>Fragile X syndrome</td>
<td>Fucosidosis</td>
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<td>Growth disorders</td>
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<td>Galactosaemia</td>
<td>Guillain-Barre syndrome</td>
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<tr>
<td>Gaucher disease</td>
<td>Hydrocephalus</td>
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<td>Haemochromatosis</td>
<td>Homocystinuria</td>
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<td>Hunter disease</td>
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<td>Hearing impairment</td>
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<td>Hemorrhagic telangiectasia</td>
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<td>Hirschsprung syndrome</td>
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<td><strong>I</strong></td>
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<td>Immunodeficiency disorders</td>
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<tr>
<td>Kidney disorders</td>
<td>Klippel-Feil syndrome</td>
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<td>Klinefelter syndrome</td>
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<tr>
<td>Landau-Kleffner syndrome</td>
<td>Lissencephaly</td>
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<tr>
<td>Learning difficulties/disabilities</td>
<td>Long QT syndrome</td>
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<tr>
<td>Leigh syndrome</td>
<td>Lupus</td>
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<tr>
<td>Leukodystrophy</td>
<td>Lymphoedema</td>
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<td>Limb deficiency</td>
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<td><strong>M</strong></td>
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<tr>
<td>Macular degeneration</td>
<td>Motor neurone disease</td>
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<td>Manic depressive/mood disorders</td>
<td>Mucolipidosis</td>
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<tr>
<td>Marfan syndrome</td>
<td>Mucopolysaccharide disease</td>
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<td>Meniere disease</td>
<td>Multiple epiphyseal dysplasia</td>
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<td>Maroteaux-Lamy disease</td>
<td>Mullerian aplasia syndrome</td>
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<td>Mental illness</td>
<td>Muscular dystrophy/neuromuscular disorders</td>
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<td>Metabolic disorders</td>
<td>Myasthenia gravis</td>
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<td>Miller syndrome</td>
<td>Myotonia congenita</td>
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<td>Mitochondrial disorders</td>
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<td>Moebius syndrome</td>
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<td>Nager syndrome</td>
<td>Neurofibromatosis</td>
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<tr>
<td>Narcolepsy</td>
<td>Neuronal intestinal dysplasia (NID)</td>
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<tr>
<td>Neural tube defects</td>
<td>Noonan syndrome</td>
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<tr>
<td>Obsessive compulsive disorder</td>
<td>Osteoporosis</td>
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<td>Osteogenesis imperfecta</td>
<td>Ovarian cancer</td>
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<td>Paget disease</td>
<td>Poland syndrome</td>
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<td>Periodic paralysis</td>
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<td>Prader-Willi syndrome</td>
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<td>Pseudoxanthoma elasticum</td>
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<td>Pituitary disorders</td>
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<td>Raynaud syndrome</td>
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<td>Retinoblastoma</td>
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<td>Smith Magenis syndrome</td>
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<td>Sanfilippo disease</td>
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<td>Schizophrenia</td>
<td>Spina bifida</td>
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<td>Scleroderma</td>
<td>Spinal muscular atrophy</td>
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<td>Short stature</td>
<td>Spino cerebellar ataxia</td>
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<td>Shwachman syndrome</td>
<td>Stickler syndrome</td>
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<td>Sialic acid diseases</td>
<td>Stillbirth, neonatal death, miscarriage</td>
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<td>Sickle cell disease</td>
<td>Stuttering</td>
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<td>Sleep apnea</td>
<td>Sudden infant death syndrome</td>
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<td>Usher Syndrome</td>
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<td>VATER syndrome</td>
<td>Von Hippel-Lindau syndrome</td>
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<td>Velo-cardio facial syndrome</td>
<td>Von Recklinghausen disease</td>
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<td>Visual impairment</td>
<td>Von Willebrand disorder</td>
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<td>Williams syndrome</td>
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<td>XO syndrome</td>
<td>XYY syndrome</td>
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<td>XXXY syndrome</td>
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Genetic information

- Genetic information may be obtained from:
  - The examination of a person's family medical history
  - A clinical examination that diagnoses a genetic condition
  - A genetic test

Genetic tests

- There are several types of tests generally described as ‘genetic’ and include:
  - **Direct analysis of a genetic sequence** where a segment of DNA or RNA is targeted using a process known as polymerase chain reaction (PCR). This process enables the DNA, even from a single cell, to be reproduced in large amounts (ie amplified) for testing (molecular genetic testing)
  - **Linkage testing** (indirect gene tracking) when mutation(s) in a gene have not yet been defined or where the DNA region containing the gene is known but the gene itself has not been precisely located. This test involves tracking polymorphic markers located close to the gene in question
  - **Analysis of the chromosomes** (cytogenetic testing). Molecular genetic techniques are increasingly used in cytogenetic analyses
  - **Analysis of the biological products of particular genes**, eg: HbS in sickle cell disease (see Haemoglobinopathies); abnormal metabolites resulting from gene mutations such as high phenylalanine levels in phenylketonuria (PKU) in newborn screening (see Newborn screening); analysis of the protein produced by the BRCA gene (protein truncation testing – PTT) when testing for inherited predisposition to breast and ovarian cancer (see Cancer in the family)
  - **Biochemical tests of substances** that may be under multifactorial control may also reveal genetic information. For example, a positive test for high cholesterol or faecal occult blood may be the consequence of mutations in the genes conferring susceptibility to heart disease or colon cancer. In an appropriate clinical setting, results of these biochemical tests may provide strong indicators of particular genetic conditions

Genetic testing in general practice

- The same genetic test can be used clinically for different purposes. The types of molecular genetic tests have been classified according to their purpose (Table 3) in the 2006 guidelines for Nucleic Acid Detection by the National Pathology Accreditation Council (NPAAC) used for laboratory accreditation:
  - Level 1 (standard DNA test)
  - Level 2 (DNA test with potential complex issues)
• The distinction between the two levels would usually be made by the doctor ordering the test, since that individual will be best placed to appreciate the short-term and long-term implications of the test for the patient and other family members. Within these levels are tests that are used for a range of purposes:

> **Diagnostic testing** is done to make or confirm a diagnosis of a specific condition in a person who generally already has signs or symptoms of that condition. This may involve molecular, cytogenetic or biochemical genetic testing.

> **Linkage testing** is used when the mutation causing the condition is unknown and involves examination of multiple DNA markers close to the DNA loci associated with the condition. Linkage testing can be used for a number of purposes such as predictive or prenatal testing. For example, in families who have a child with cystic fibrosis, in whom the mutation causing the condition is unknown, linkage testing may be useful for prenatal testing in future pregnancies. DNA markers located close to the CFTR gene are examined for the child with cystic fibrosis, who has both copies of the mutated CFTR gene, and for the parents, who each have a correct and a mutated CFTR gene copy. These are then compared to DNA markers from the baby to see if the baby has the same markers as his/her sibling with cystic fibrosis. If the markers are the same, the mutated gene copies are likely to be there too.

> **Mutation searching** is done to find the genetic basis of a condition that appears clinically to be inherited or involve inherited susceptibility, e.g. breast cancer genetic testing in a person who has or had breast cancer and meets the criteria of potential inherited susceptibility. It is necessary to identify the mutation in the family (the family-specific mutation) before predictive testing can be offered (see below).

> **Predictive testing** is done to determine if a person, who generally has no signs or symptoms of a specific condition at the time of testing, has the specific genetic mutations that increase the likelihood that he or she may, or will, develop the condition in the future. Predictive testing is often performed in relation to genetic conditions that are not evident at birth but have their onset during adulthood, such as some cancers. Predictive genetic testing in conditions such as familial cancer can only be done when the family-specific genetic mutation is known. Hence, genetic testing must first be done on a family member affected with cancer, as they are the most likely to carry the genetic mutation.

> **Pre-symptomatic testing** is done to determine if a person will develop the condition if they live long enough but symptoms of the condition have not yet manifested, e.g. Huntington disease.

> **Carrier testing** is done to determine whether or not a person carries a genetic mutation or chromosomal alteration that does not generally affect the person’s health but increases his or her chance of having children with the condition in question (depending upon their partner’s genotype). The outcome of such testing can influence future reproductive decisions.

  – Studies have shown that using the term ‘carrier of a genetic condition’ has the potential to be confused with being a carrier of an infectious condition, e.g. HIV carrier, hepatitis C carrier (see Genetics in practice). For example, a person who has a positive carrier test result for a mutation in the CFTR gene is **not a CF carrier** but is a carrier for a CF mutation or a **carrier for CF**.

  – **Carrier screening** is performed on people who are not necessarily known to be at increased risk for a particular genetic condition. Screening tests can be conducted on individuals, groups such as those from a common ethnic background (see below ‘Screening in multicultural Australia’) and entire populations, such as with newborn screening.

  – **Cascade testing** is a form of screening that is triggered by a heightened risk suggested by family medical history information or genetic testing of other family members. In some cases cascade testing is an extension of carrier screening since it allows asymptomatic individuals in the community to be tested to see if they carry a genetic defect. This information might be helpful in family planning, and would also be helpful if it enabled preventive measures to be implemented to avoid disease.

> Prenatal testing is performed on a sample of fetal cells (see Testing and pregnancy). Testing may be cytogenetic, with or without molecular testing.

> Pre-implantation genetic diagnosis (PGD) is cytogenetic testing, with or without molecular testing, performed on embryos used in assisted reproductive technology procedures (see Testing and pregnancy). Prenatal testing of successful pregnancies may be recommended for confirmation of the test result.

> Identification testing (parentage/kinship testing) is performed on non-coding DNA, with respect to a number of agreed core loci, to construct a unique DNA profile for identification purposes. Clinically it is used in searches for missing persons; in the identification of deceased persons; and in establishing kinship for various purposes, including family law proceedings and immigration.
Table 3. Classification of types of genetic tests by the National Pathology Accreditation Council (NPAAC - 2006) in guidelines for laboratory accreditation

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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</table>
| Level 1 DNA test (standard)                          | Included here would be:                                                                                      a) DNA testing for diagnostic purposes (eg the patient has clinical indicators or a family history of an established inherited condition, and DNA testing is being used to confirm the condition) or any other DNA test that doesn’t fall into level 2  
  b) Newborn screening programs                       |
| Level 2 DNA test (ie the test has the potential to lead to complex clinical issues) | DNA testing for which specialised knowledge is needed for the DNA test to be requested, and for which professional genetic counselling should precede and accompany the test. Predictive or pre-symptomatic DNA testing for conditions for which there is no simple treatment would usually be included in this grouping. Specific written consent and counselling issues are associated with this grouping. |

Applications of genetic testing and screening in multicultural Australia

- Table 4 lists the more common conditions for which diagnostic, predictive or carrier molecular genetic testing would be used, given clinical indications in the patient or a family history that meet criteria for access to testing.
- Table 5 lists conditions for which carrier screening may be appropriate based on the ethnic and cultural background of the patient even in the absence of a personal family history.
- Very little is known about the specific genetic issues pertaining to Indigenous Australians. However, the rare genetic condition called Machado-Joseph syndrome or Groote Eylandt syndrome (spinal cerebellar ataxia 3) is more prevalent in aboriginal communities particularly in North Eastern Arnhem land (see Genetics in practice).
Table 4. Conditions for which diagnostic, predictive/pre-symptomatic or carrier genetic testing may be used. MBS indicates those tests that are available on Medicare Benefits Schedule. Detailed information provided in the sections under which the conditions are listed (AR = autosomal recessive, AD = autosomal dominant, XL = X-linked)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pattern of inheritance and prevalence</th>
<th>Gene(s) in which mutations cause the condition</th>
<th>Clinical indications</th>
<th>Type of testing</th>
<th>Prevention/surveillance for early detection</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer in the family</strong></td>
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<tr>
<td>FAP (familial adenomatous polyposis)</td>
<td>AD 1 in 3,500</td>
<td>APC</td>
<td>Clinical symptoms. Family history. Onset in 20s, 30s or 40s - sometimes even earlier.</td>
<td>Mutation search. Predictive - where a family-specific mutation has been identified.</td>
<td>Surveillance by sigmoidoscopy from 10 - 15 years. Surgery to remove colon after polyps appear.</td>
<td>Standard treatment for bowel cancer if it develops.</td>
</tr>
<tr>
<td>HNPCC (hereditary non-polyposis coli)</td>
<td>AD Between 5-10% of all cases of bowel cancer.</td>
<td>MLH1, MSH2, MSH6, PMS1, PMS2</td>
<td>Clinical symptoms. Family history of bowel and related cancers. Onset is very variable (from 20s-80s).</td>
<td>Mutation search. Predictive - where a family-specific mutation has been identified.</td>
<td>Colonoscopy, surgical removal of the colon (colectomy) once cancer develops, endometrial and ovarian cancer surveillance.</td>
<td>Standard treatment if cancer develops.</td>
</tr>
<tr>
<td>Inherited susceptibility to breast cancer and ovarian cancer</td>
<td>AD About 5% of all cases of breast and ovarian cancer.</td>
<td>BRCA1, BRCA2</td>
<td>Clinical symptoms. Family history of breast, ovarian and related cancers. Onset is very variable (from 20s-80s).</td>
<td>Mutation search. Predictive where a family-specific mutation has been identified.</td>
<td>Breast examination, mammography, prophylactic breast or ovary removal, and ovarian cancer surveillance.</td>
<td>Standard treatment if cancer develops.</td>
</tr>
<tr>
<td>MUTYH – associated polyposis (MAP)</td>
<td>AR 1 in 50 - 100</td>
<td>MUTYH</td>
<td>Clinical symptoms. Family history of bowel cancer consistent with an autosomal recessive inheritance pattern.</td>
<td>Mutation search. Predictive where a family-specific mutation has been identified.</td>
<td>Under investigation.</td>
<td>Under investigation.</td>
</tr>
</tbody>
</table>
### Table 4. Continued

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pattern of inheritance and prevalence</th>
<th>Gene(s) in which mutations cause the condition</th>
<th>Clinical indications</th>
<th>Type of testing</th>
<th>Prevention/surveillance for early detection</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td><strong>Neurological conditions</strong></td>
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</tr>
<tr>
<td>Huntington disease</td>
<td>AD</td>
<td>HD</td>
<td>Clinical symptoms. Family history. The typical age of onset is between 30 and 55 years.</td>
<td>Diagnostic. Pre-symptomatic.</td>
<td>None</td>
<td>Supportive</td>
</tr>
<tr>
<td>Alzheimer disease - early onset</td>
<td>AD</td>
<td>PS1, PS2, APP</td>
<td>Clinical symptoms. Family history. This form occurs in at least 10% of cases. Onset in 40s -50s.</td>
<td>Diagnostic. Pre-symptomatic.</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Cystic fibrosis</strong></td>
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<tr>
<td><strong>Fragile X syndrome and other causes of development delay</strong></td>
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</tr>
<tr>
<td>Condition</td>
<td>Pattern of inheritance and prevalence</td>
<td>Gene(s) in which mutations cause the condition</td>
<td>Clinical indications</td>
<td>Type of testing</td>
<td>Prevention/surveillance for early detection</td>
<td>Treatment</td>
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<td>---------------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------</td>
<td>----------------</td>
<td>------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Hereditary haemochromatosis</td>
<td>AR ≤ 1 in 250</td>
<td>HFE (for &gt;95% of Australians)</td>
<td>When untreated, accumulation of iron in various body organs leads to conditions such as cirrhosis, cardiomyopathy and diabetes.</td>
<td>Diagnostic. Predictive testing in relatives of affected.</td>
<td>Surveillance for excess iron (iron overload).</td>
<td>Blood donation (venesection).</td>
</tr>
<tr>
<td>Haemoglobinopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-thalassaemia</td>
<td>AR Various depending on ethnic background.</td>
<td>HBB (β-globin)</td>
<td>Severe anaemia that onsets after birth.</td>
<td>Diagnostic. Carrier testing in relatives of affected or in high risk ethnic groups.</td>
<td>None</td>
<td>Blood transfusion, chelation therapy to remove iron build-up from transfusions.</td>
</tr>
<tr>
<td>α-thalassaemia</td>
<td>AR Various depending on ethnic background.</td>
<td>HBA1, HBA2 (α-globin)</td>
<td>Hydrops fetalis or mild to severe anaemia</td>
<td>Diagnostic. Carrier testing in relatives of affected or in high risk ethnic groups.</td>
<td>None</td>
<td>Blood transfusion, chelation therapy to remove iron build-up from transfusions.</td>
</tr>
<tr>
<td>Sickle cell disease (HbS disease)</td>
<td>AR Various depending on ethnic background.</td>
<td>HBB (β-globin)</td>
<td>Anaemia, failure to thrive, repeated infections, painful swelling of the hands or feet, infarction, asplenia, abdominal and chest pain.</td>
<td>Diagnostic. Carrier testing in relatives of affected or in high risk ethnic groups.</td>
<td>None</td>
<td>Management of sickling effects by IV fluids, pain relief and other treatment as indicated.</td>
</tr>
</tbody>
</table>
### Table 4. Continued

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pattern of inheritance and prevalence</th>
<th>Gene(s) in which mutations cause the condition</th>
<th>Clinical indications</th>
<th>Type of testing</th>
<th>Prevention/surveillance for early detection</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clotting and bleeding conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>XL&lt;br&gt;1 in 10,000 boys</td>
<td>Factor VIIIC</td>
<td>A condition in which the blood clotting process is defective resulting in a tendency towards prolonged bleeding. Symptoms appear in the first few months of life when severe.</td>
<td>Diagnostic. Predictive and carrier testing in relatives of affected.</td>
<td>Not relevant.</td>
<td>Factor VIII</td>
</tr>
<tr>
<td>Factor V Leiden MBS</td>
<td>AR&lt;br&gt;Various depending on ethnic background.</td>
<td>Factor V</td>
<td>A weak thrombophilic condition (6% of individuals will develop thrombosis by age 65 years).</td>
<td>Diagnostic. Carrier testing in relatives of affected.</td>
<td>Screening for individuals at high risk.</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial hypercholesterolaemia</td>
<td>AD&lt;br&gt;Various depending on ethnic background.</td>
<td>LDLR</td>
<td>Lifelong marked hypercholesterolaemia leads to tissue cholesterol deposition. Atherosclerosis begins in early childhood. Carotid atherosclerosis rapidly progresses during childhood. Family history.</td>
<td>Diagnostic. Predictive testing in relatives of affected.</td>
<td>Children of an affected parent should be screened after the age of 2-3 years.</td>
<td>Cholesterol-lowering diet, lifestyle modifications and statins.</td>
</tr>
<tr>
<td>Condition</td>
<td>Pattern of inheritance and prevalence</td>
<td>Gene(s) in which mutations cause the condition</td>
<td>Clinical indications</td>
<td>Type of testing</td>
<td>Prevention/surveillance for early detection</td>
<td>Treatment</td>
</tr>
<tr>
<td>-----------</td>
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<td>-----------------------------------------------</td>
<td>---------------------</td>
<td>----------------</td>
<td>------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Metabolic conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase (G6PD) deficiency</td>
<td>XL Various depending on ethnic background, eg 1 in 5 in some Africans.</td>
<td>G6PD</td>
<td>G6PD deficiency may result in an acute haemolytic anaemia. Occurs after an affected individual is exposed to certain medications or chemicals (eg aspirin, naphthalene), infections, and/or inhales the pollen of, or consumes, fava beans (favism).</td>
<td>Diagnostic enzyme testing is available in affected individuals. Carrier testing is not readily available.</td>
<td>Babies, particularly boys, may be screened after birth where there is a family history.</td>
<td>Preventive measures used. Avoidance of agents causing haemolytic anaemia in affected individuals.</td>
</tr>
</tbody>
</table>
### Table 5. Carrier screening based on ethnic and cultural background

(AR = autosomal recessive, AD = autosomal dominant, XL = X-linked)

<table>
<thead>
<tr>
<th>Ethnic or cultural background</th>
<th>Condition and inheritance pattern of the mutated gene</th>
<th>Clinical features</th>
<th>Overall carrier frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish (Central and Northern European Jewish)</td>
<td>Tay-Sachs disease (hexosaminidase deficiency), AR</td>
<td>Degenerative neurological condition leading to early childhood death.</td>
<td>1 in 25</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis, AR</td>
<td>See <em>Cystic fibrosis</em></td>
<td>1 in 25</td>
</tr>
<tr>
<td></td>
<td>Familial dysautonomia (IB kinase complex-associated protein family deficiency), AR</td>
<td>Affects gait, hearing, tasting, impacts control of body functions, eg temperature and blood pressure. About 30% survival to 20 years.</td>
<td>1 in 30</td>
</tr>
<tr>
<td></td>
<td>Canavan disease, AR</td>
<td>Degenerative neurological condition leading to early childhood death.</td>
<td>1 in 40</td>
</tr>
<tr>
<td></td>
<td>Fanconi anaemia, AR</td>
<td>Severe anaemia, failure of immune system, problems with growth and kidneys, increased susceptibility to aplastic anaemia, acute myeloblastic leukaemia or squamous cell carcinoma.</td>
<td>1 in 100</td>
</tr>
<tr>
<td></td>
<td>Familial breast and ovarian cancer predisposition, AD</td>
<td>See <em>Cancer in the family</em></td>
<td>1 in 40</td>
</tr>
<tr>
<td>Northern European (includes UK)</td>
<td>Cystic fibrosis, AR</td>
<td>See <em>Cystic fibrosis</em></td>
<td>1 in 25</td>
</tr>
<tr>
<td></td>
<td>Haemochromatosis, AR</td>
<td>See <em>Hereditary haemochromatosis</em></td>
<td>1 in 8</td>
</tr>
<tr>
<td>Middle-Eastern, Mediterranean, African, South East Asian, African and New Guinea</td>
<td>Glucose-6-phosphate dehydrogenase (G6PD) deficiency, XL</td>
<td>See Metabolic conditions in Table 4</td>
<td>1 in 20 - 1 in 4</td>
</tr>
<tr>
<td>Middle Eastern, Southern Europe, Indian subcontinent, Central and South East Asian and Africa</td>
<td>β–thalassaemia, AR</td>
<td>See <em>Haemoglobinopathies</em></td>
<td>1 in 5 - 1 in 12</td>
</tr>
<tr>
<td>Chinese, South East Asian (also Southern European, Middle Eastern, Indian subcontinent, Pakistan, Africa, the Pacific Islands and Maori)</td>
<td>α-thalassaemia, AR</td>
<td>See <em>Haemoglobinopathies</em></td>
<td>1 in 20</td>
</tr>
<tr>
<td>Lebanese (Christian), Dutch descent (cf Afrikaans), French Canadian</td>
<td>Familial hypercholesterolaemia, AD</td>
<td>See <em>Cardiovascular conditions</em></td>
<td>1 in 70</td>
</tr>
</tbody>
</table>
Considerations in genetic testing

- Genetic testing has distinct advantages, disadvantages and limitations and should only be used after the person being tested has given full consideration to the relevant issues.
- Genetic conditions by their nature run in families, so that a diagnosis in one member has implications for other family members.
- Testing may benefit individuals and families in a number of ways but it may also create dilemmas which need sensitive management, making genetic counselling an essential element of genetic testing.
- All testing should be carried out with the informed consent of the person being tested.
- It is important for health professionals requesting tests and potential test users to become familiar with the context in which the tests are used.
- Mutation searching can be an expensive and lengthy process. The results can be complex and hard to interpret.

  > A positive genetic test result means that a mutation has been found in the gene being tested. This result may confirm a diagnosis, confer a higher risk of developing a disease, or be an indication for further testing.

  > A negative genetic test result means that no mutation was found. However, the result is uninformative as it is possible that the genetic testing may not be sensitive enough to identify all the disease causing genetic mutations in that gene. This may occur in, for example, familial cancer mutation searching (not predictive testing for familial cancers) or where there are multiple different mutations in a gene such as in genetic testing for cystic fibrosis.

  > The test may find a gene change of unknown significance. This may be referred to in the laboratory report as 'unclassified variant', a 'variant of unknown significance' or a polymorphism. The test result is considered uninformative.

- Predictive genetic testing involves testing for the known family-specific genetic mutation, so it usually results in a definitive positive or negative result for that mutation. It is less expensive and can be done in much less time than mutation searching.
- Pre-symptomatic testing of triplet repeat conditions can be done without the genetic testing of other family members.
- Genetic test results that are uninformative cannot confirm or rule out a diagnosis, or give any indication as to whether the individual has an increase risk of the condition (see later under 'Interpreting genetic test results').

  > For example, in a condition such as Huntington disease where the result is provided as the number of triplet repeats detected in a specific part of the gene (see Neurological conditions), there is an intermediate range in the number of repeats where it is unclear if the person will develop the condition or not.

  > Residual risk may be present when no mutation is found (a ‘normal’ test result) where there are multiple known mutations in a gene if the panel of mutations tested for in that gene is limited, for example cystic fibrosis genetic testing in newborn screening (see Newborn screening).
Pre- and post-test genetic counselling

- Testing should be accompanied by pre- and post-test genetic counselling that addresses:
  > The genetic condition being tested including, where appropriate, clinical features, age of onset, pattern of inheritance, availability of treatment, genetic risk assessment
  > Features or limitations of the laboratory test
  > Details of the test, testing process, length of time to obtain test results
  > Interpretation of results
  > Implications of positive and negative results
  > Options available on the outcome of testing

Health and life insurance issues

- Private health insurance is community rated and so does not take into account genetic information but will take into account any existing condition. However, an asymptomatic individual with a positive predictive genetic test result does not have a pre-existing condition.
- Genetic information that includes a family history and the results of predictive genetic tests are taken into account in applications for life insurance products. This includes cover for death, disability/income protection, trauma/crisis care, business and insurance relating to bank loans.
- The Investment and Financial Services Association Ltd (IFSA), an organisation representing most insurance companies in Australia, has a policy on genetic testing and life insurance products. This policy does not extend to General Insurers who offer travel insurance.
  - The IFSA policy states that an individual will not be required to undergo a predictive genetic test in order to obtain life insurance or to increase the cover in a policy.
  - However, under the Insurance Contracts Act 1984, a person applying for insurance has a duty "to disclose to the insurer every matter that you know, or could reasonably be expected to know, that is relevant to the insurer’s decision."

- While some insurance companies will ask for more specific details than others, applicants must disclose all known genetic information about their relatives or themselves that would be relevant to the assessment of their risk, over and above the questions asked. This would include predictive test results of their relatives. Failure to do so may render a claim invalid.
- This information may have a range of consequences, depending on the condition involved and whether the genetic test was positive, uninformative or negative:
  > No effect on insurance premiums
  > Premiums previously that were non-standard (eg loaded) returning to standard (eg if a predictive genetic test is negative, it can remove the influence of a family history)
  > Lead to higher (non-standard) insurance premiums
  > Result in a reduced period of coverage
  > Result in an exclusion for one or more medical conditions
  > Lead to the offer of an alternate insurance product
  > Deferral or denial of an offer to insure an individual
- If an application is held or taken out before a genetic condition is diagnosed or before a risk is identified through a predictive genetic test, the applicant does not have to disclose this new information. Life insurance cover is guaranteed renewable and so as long as the premiums are paid, that cover will apply.
- As costs of insurance and ability to obtain cover may vary from one insurance company to the next, patients may wish to make multiple applications to a range of companies at the same time.
Ethical issues

- The ethical principles that guide all medical care apply in genetics. However, ethical dilemmas arise when there is tension or conflict between the rights of different family members.

- Key ethical principles include:
  - Justice (all should be treated equally, and there should be equity of access to services regardless of place of residence, ethnicity, gender, religion, age or disability)
  - Respect for autonomy (the right of an individual to self-determination, including privacy and confidentiality)
  - Beneficence (taking positive action to do good)
  - Non-maleficence (do no harm)

- There can be tensions when these principles are considered with respect to the right of an individual to:
  - Know, or not to know, information relevant to their own health (autonomy)
  - Disclose, or not, personal information (privacy)
  - Make an informed decision regarding genetic testing

- Genetic counselling emphasises that an autonomous choice be made, ie a choice that is informed, reflective of the individual's own values and made freely (without coercion). However, ethical dilemmas may arise, eg:
  - As a result of genetic testing, an individual’s result may disclose the genetic status of another family member who has not had testing (and may not wish to), eg identical twins
  - An individual refuses to disclose to other family members that they are at risk
  - Parents request that their child (under 18 years) be tested for an adult onset condition where there is no health benefit for the child, thus affecting the child’s future autonomy
  - In these situations, it is important to explore with the individual the potential harms and benefits and their reasons for their request. Referral to Genetics Services for counselling is strongly recommended
Privacy and confidentiality

• The results of a genetic test may be of interest to third parties.
• Test results, and the fact that the person has undergone testing, must be kept confidential, unless the person tested gives consent to release of the information.
• The Privacy Amendment (Private Sector) Act 2000 (Cth) and the National Privacy Principles (NPPs) set out in that Act are relevant to the handling of genetic information by GPs:
  > The issue of prohibition of the collection of health information without consent in NPP 10.1 of the Privacy Act (such as in the process of taking a family history) was addressed in December 2002 with the declaration a public interest determination (PID). The PID is in place for a period of up to five years and states that:

Health service providers may collect health information from health consumers about third parties without consent when both of the following circumstances are met:

– Collection of the third party’s information into a health consumer’s social, family or medical history is necessary to enable health service providers to provide a health service directly to the consumer; and
– The third party’s information is relevant to the family, social or medical history of that consumer.

> The Privacy Legislation Amendment Act 2006 (Cth) passed in September 2006
  – States that genetic information in a form that is, or could be, predictive of the health of the individual or a genetic relative of the individual is regarded as ‘health information’ and therefore how it is handled is now governed by the Privacy Act
  – Amended NPP 2.1 to allow use or disclosure of genetic information about an individual to a genetic relative in circumstances where the genetic information may reveal a serious threat to a genetic relative’s life, health or safety, but not necessarily an imminent threat. Any such use or disclosure will have to be done in accordance with guidelines relating to the use and disclosure of genetic information. The guidelines will be issued by the National Health and Medical Research Council and approved by the Privacy Commissioner
• For further discussion of these issues see later under ‘Informing other family members’.

Interpreting genetic test results

• Molecular genetic test results are expressed in several ways:
  > Description of the mutation type and the resulting amino acid sequence within the protein or polypeptide chain; or
  > Description of the site of the mutation in the DNA sequence. This may include whether the mutation was detected in one of the exons (the part of the gene that is transcribed and translated into the protein) or introns (the untranslated intervening sequences between the exons in the gene)
  > Analysis of the resulting protein from the gene being studied
Some terminology used in reporting molecular genetic test results

- Mutations in genes can have effects either because the mutation occurs within the coding part of a gene, thereby altering the nature and/or function of the protein product, or because the mutation occurs in other parts of the gene involved in gene regulation, e.g. the mutation changes how much of the protein product is made. The description of the mutation often reflects this.
  > Mutation analysis is based on the genetic code (A - adenine, C - cytosine, T - thymine and G - guanine) and how each triplet nucleotide sequence (codon) translates into amino acids
  > The code is degenerate, i.e. there can be more than one codon per amino acid
  > Other codons translate into ‘start’ (ATG) or ‘stop’ (TAA, TAG or TGA) signals, that indicate which parts of the gene should be translated into amino acids
  > The naming of the amino acids uses a short hand system as shown in Table 6

Table 6. Amino acid naming using the short code system

<table>
<thead>
<tr>
<th>Alanine- Ala (A)</th>
<th>Glycine – Gly (G)</th>
<th>Proline – Pro (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine – Arg (R)</td>
<td>Histidine – His (H)</td>
<td>Serine – Ser (S)</td>
</tr>
<tr>
<td>Asparagine – Asn (N)</td>
<td>Isoleucine - Ile (I)</td>
<td>Threonine – Thr (T)</td>
</tr>
<tr>
<td>Aspartic acid – Asp (D)</td>
<td>Leucine – Leu (L)</td>
<td>Tryptophan – Try (W)</td>
</tr>
<tr>
<td>Cysteine – Cys (C)</td>
<td>Lysine – Lys (K)</td>
<td>Tyrosine – Tyr (Y)</td>
</tr>
<tr>
<td>Glutamine – Gln (Q)</td>
<td>Methionine – Met (M)</td>
<td>Valine – Val (V)</td>
</tr>
<tr>
<td>Glutamic acid – Glu (E)</td>
<td>Phenylalanine – Phe (F)</td>
<td>STOP (X)</td>
</tr>
</tbody>
</table>

- Mutations can be classified as:
  > Point mutations or base substitutions
  > Frameshift mutations – deletions and insertions. Note that base substitutions and frameshift mutations could result in the formation of a novel ‘start’ or ‘stop’ signal within the gene sequence
  > Triplet repeat expansions

- See Table 7 for descriptions of these types of mutations and the effects on protein products with clinical examples. Note that sometimes the mutation is named using the amino acid change (as in the haemochromatosis example) or using the nucleotide change (as in the BRCA1 example).
### Table 7. Types of mutations

<table>
<thead>
<tr>
<th>Type of mutation</th>
<th>Description</th>
<th>Consequence to the protein product</th>
<th>Clinical examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Point or base substitution</strong></td>
<td>A single nucleotide (base) in the coding (exon) sequence of a gene is replaced by another nucleotide. This may change the codon sequence so that it is translated into a different amino acid (ie one amino acid is replaced by another, hence also called missense mutation).</td>
<td>A different amino acid sequence may result in a change in structure and/or function of the protein product.</td>
<td><strong>Haemochromatosis</strong>&lt;br&gt;In the C282Y mutation, cysteine (C) is replaced by tyrosine (Y) at amino acid position 282 along the HFE protein, resulting in excessive iron absorption. See <em>Hereditary haemochromatosis</em>.</td>
</tr>
<tr>
<td><strong>Frameshift mutation:</strong>&lt;br&gt;(i) Deletion</td>
<td>A single or multiple nucleotides (even up to many thousands) are deleted.</td>
<td>Generally the triplet grouping of nucleotides is disrupted by the deletion and so this changes the way in which the DNA is translated (ie the reading frame is changed). This could result in a shorter protein product or, more typically, a completely different protein sequence that is usually degraded.</td>
<td><strong>Cystic fibrosis</strong>&lt;br&gt;The ΔF508 (dF508 or F508del) mutation is a deletion of phenylalanine (F) at position 508 along the protein sequence. The resulting protein is missing this amino acid which has the effect of preventing the protein from reaching the cell surface membrane and so it is degraded. See <em>Cystic fibrosis</em>.</td>
</tr>
<tr>
<td><strong>Frameshift mutation:</strong>&lt;br&gt;(ii) Insertion</td>
<td>A single or multiple nucleotides are inserted.</td>
<td>The triplet grouping of nucleotides is disrupted by the insertion and generally this changes the way in which the DNA is translated (ie the reading frame is changed). This could result in a shorter protein product or, more typically, a completely different protein sequence that is usually degraded.</td>
<td><strong>Familial breast cancer due to a BRCA1 mutation.</strong>&lt;br&gt;Mutations in the BRCA1 gene can be due to a variety of mutations. A common mutation in Ashkenazi Jewish women is the 5382insC which is due to the insertion of a cytosine at nucleotide position 5382. This insertion changes the reading frame and results in a novel ‘stop’ signal, producing a shorter version of the protein that is then unable to carry out its normal function in DNA repair processes. See <em>Cancer in the family</em>.</td>
</tr>
</tbody>
</table>
Triplet repeat expansion

These are three nucleotides (triplet) that are consecutively repeated. They are naturally occurring and may be found in coding and non-coding regions of genes. Triplet repeat expansion is when the number of repeats increases to above the number in the normal range. The number of repeats can increase when passed onto children, and so are referred to as ‘dynamic mutations’.

If the triplet repeat is in the non-coding part of the gene, the effect may be to alter the amount of protein made.

Fragile X syndrome

The CGG repeat is in the regulatory non-coding region of the gene and when increased to a certain size can lead to the protein being ‘switched off’, ie no protein is made.

See Fragile X syndrome and other causes of developmental delay.

Huntington disease

The CAG repeat codes for glutamine, and when increased to a certain size leads to the protein having a ‘toxic’ function.

See Neurological conditions.

Genetic test result reports

- Two examples are provided of genetic test reports for haemochromatosis and carrier screening for conditions more commonly affecting members of the Ashkenazi Jewish community.
  - Reports vary in the detail of the description of the testing process and the level of interpretation of the test result
  - Some will recommend a referral to a clinical geneticist or genetic counseling
  - Different laboratories may use different methods of analysis for the same gene. For example, the BRCA 1 and BRCA2 genes involved in familial breast and ovarian cancer may be tested using full sequencing of the gene, analysis of the exons where mutations have been reported or analysis of the resulting protein to see if it has been shortened by a mutation (protein truncation testing - PTT)
  - Genetic testing may involve the examination of several different genes for the same or different conditions. This may be seen in targeted carrier screening in high risk groups such as the Jewish community where the testing may involve screening for a range of conditions
Figure 1. Example of a report for genetic testing for haemochromatosis

<table>
<thead>
<tr>
<th>Name of Laboratory</th>
<th>Address and Contact Details of Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Requesting Doctor’s Information:**

<table>
<thead>
<tr>
<th>Patient Details:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Collected (Date and time):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab No:</td>
</tr>
<tr>
<td>Your Reference number:</td>
</tr>
</tbody>
</table>

**Specimen type: Blood**

**Haemochromatosis (HFE) Molecular Studies**

<table>
<thead>
<tr>
<th>Mutation Tested</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cys282Tyr</td>
<td>Not detected</td>
</tr>
<tr>
<td>His63Asp</td>
<td>Heterozygous</td>
</tr>
</tbody>
</table>

**Interpretation of Molecular Studies**

1. Clinical haemochromatosis occurs more commonly in individuals who are Cys282Tyr (C282Y) homozygous and less commonly in Cys282Tyr/His63Asp compound heterozygous or His63Asp (H63D) homozygous individuals. The possibility, however, of compound heterozygosity of C282Y or H63D, with an additional rare mutation could occur.
2. At least 20 rare HFE mutations have been found to date.
3. Clinical penetrance has been variably reported between 10 and 75%, depending on genotype, population studied, gender, age and diet. The C282Y mutation is rare in non-Europeans.
4. C282Y/- genotype is most likely found in heterozygous carriers.
5. H63D/- genotype individuals do not appear to have an increased risk of developing iron overload.
6. Other genes have been associated with haemochromatosis ie SLC11A3, Tfr2, HAMP and HJV.
7. A literature review of haemochromatosis and the HFE gene is available at www.geneclinics.org

**Method of testing**

1. Real-time PCR and melt curve analysis with hybridization probes specific for Cys282Tyr and His63Asp.
2. Electrophoresis of allele-specific amplification (ARMS) products.

**Recommendations for molecular genetic testing**

Appropriate genetic counselling should accompany testing.
Figure 2. Example of a report for screening for carrier status based on Jewish ancestry

<table>
<thead>
<tr>
<th>Genetic condition</th>
<th>Mutation/s included in testing</th>
<th>*Mutation prevalence</th>
<th>*Diagnostic sensitivity</th>
<th># Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>D1152H, 1717-1G→A, G542X, W1282X, N1303K, df508, 3849+10kbC→T</td>
<td>1 in 30</td>
<td>95%</td>
<td>N/A</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>TATC+1278, IVS12+1(G→C), Gly269Ser</td>
<td>1 in 26</td>
<td>95%</td>
<td>1 in 520</td>
</tr>
<tr>
<td>Fanconi anaemia</td>
<td>IVS4+4A→T</td>
<td>1 in 80</td>
<td>90 %</td>
<td>1 in 800</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
<td>R696P, 2507+6T→C</td>
<td>1 in 32</td>
<td>99%</td>
<td>1 in 3200</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>E285A, Y231 X</td>
<td>1 in 41</td>
<td>98%</td>
<td>1 in 2050</td>
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<tr>
<td>Niemann-Pick disease</td>
<td>L302P, R496L, fsP330delC</td>
<td>1 in 80</td>
<td>95%</td>
<td>1 in 1600</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>2281 del6/ins7</td>
<td>1 in 107</td>
<td>90%</td>
<td>1 in 1070</td>
</tr>
</tbody>
</table>

* Mutation prevalence and diagnostic sensitivity refer to individuals of Ashkenazi Jewish ancestry

# Risk reduction refers to the likelihood of an individual of Ashkenazi Jewish ancestry carrying a given genetic condition after testing negative for the stated mutation/s.

NB Please note that mutation prevalence and diagnostic sensitivity will depend on the laboratory performing the test.

**Result of Testing:**
W1282X mutation detected.

**Interpretation:**
This result indicates this person IS A CARRIER of the W1282X mutation for cystic fibrosis and a non-carrier for the other mutations listed.

**Method of Testing:**
Allele-specific amplification (ARMS).

**Confirmatory Testing:**
CFTR gene mutation testing by electrophoresis of amplified and restriction digested DNA.
Giving results and post-test genetic counselling

- Careful consideration should be given to the way results are conveyed. This time is also an opportunity to explain again the implications of the result.
- Recognise the issues associated with genetic testing as outlined above on ‘Considerations in genetic testing’.
- Ensure that patients are fully informed about their residual risk due to the complexity of inheritance or environmental factors.
- Notification of a result (whether positive, negative or uninformative) may precipitate a crisis and the person may for some time be unable to absorb any information.
- Appropriate pre-test genetic counselling may help to reduce post-test anxiety.
- Post-test genetic counselling and follow-up support may require several consultations.
- The genetic counselling needs to be sensitive to the nature of decisions to be taken, should respect individual decisions, and should allow time to reach decisions.
- Appropriate follow-up when an abnormality is detected may require referral to other health professionals for treatment or management, professional genetic counselling services, other professional services, or support networks.

Implications for other family members

- Information provided to one individual about a genetic condition may also be relevant to other family members.
- Conversely, assessment of an individual’s risk may require information from other family members.

Informing other family members

- It is generally accepted that an individual has a responsibility to inform his/her family if they are at risk of a genetic condition as well as a right to the privacy and confidentiality of his/her genetic information.
- There is no established legal duty to warn in Australia.
- It is good practice to discuss with the individual the implications of the diagnosis or risk, including which family members should be informed and how they might be approached. In fact, individuals may often be concerned for other family members and want this information.
- Genetics Services can provide guidance about which family members should be informed. If the individual has been seen by Genetics Services, this is likely to have been discussed with them.
- Informing family members can be difficult and it is preferable that other family members contact Genetics Services or their own GP for a thorough explanation of their situation. Where possible, providing a letter or simple written information with contact details that can be given to other relatives can be useful.
- Helpful techniques include asking how the individual will tell other family members and preparing them for possible reactions to the news (e.g. denial, fear and anger). If other family members are also patients of your practice, consent could be obtained to discuss this issue with them at their next appointment.
Asking for information from other family members

- Information may be required from other family members to assess an individual’s risk. People may feel uncomfortable asking for this information.
- Discuss how they may approach the person (in person, phone call, letter).
- Explain the reasons for needing the information and give the individual some idea of how essential (or otherwise) the information is. They can then weigh the benefits of gaining this information against the difficulties of making contact.
- Consider providing a letter supporting the request for the individual to give to family members.
- Ask Genetics Services to seek written consent from other family members to access the relevant medical information.

Birth Defects Registers or Familial Cancer Registers

- Some States require mandatory notification of some abnormal genetic test results, identified in the first years of life by prenatal or postnatal testing.
- See ‘Australian Genetics Services’ at the front of this section.
- Registration with Familial Cancer Registries can assist patients and their families with appropriate testing information and management of surveillance as indicated by clinical or genetic testing.

Identification testing

- DNA identification testing may be conducted in a number of contexts including:
  > Testing to confirm or deny the biological parentage of a person (parentage/paternity testing). The testing may be conducted, within or outside family law and child support proceedings, for an adopted child or a child born as a result of an artificial reproductive technology procedure involving donated gametes, seeking information about his or her biological parents
  > The identification of human remains
  > To establish a member of a family for immigration purposes (kinship testing)
  > To determine ancestry.
Paternity (parentage) testing

- DNA parentage testing has developed since the mid-1980s and is generally considered to be a more reliable form of testing than blood group testing. As with serological testing, it cannot definitively prove that a man is the biological father of a child but instead produces a probability of paternity.
- It is assumed that the mother is the biological mother of the child, and that half of the child’s DNA has been inherited from her. The test is based on the identification of a series of DNA markers (STR – short tandem repeat sequences of DNA located in the non-coding regions of the DNA) that must have been inherited from the biological father. If the putative father does not carry all of the required DNA markers, he can be definitively excluded as the biological father of the child. If the putative father does carry all of these paternal markers, either he is the biological father of the child, or not the biological father but carries the genes by co-incidence.
- As it is not possible to prove paternity absolutely, the result is then an estimation of the probability that the putative father is the biological father of the child and a paternity index (PI) is generated. This is a probability figure that compares the chance that the man is the father in the mother-child-father combination to the chance that the man was randomly chosen from the population. The PI will either exclude a man as the father or demonstrate that there is a high probability that he is the father of the child.
- Using DNA profiles of all the people involved (mother, child and the two men who could be the father) a probability of being the father can be calculated for each of the possible fathers. A man can be excluded as the father if he does not match with the child on at least two STR loci. Inclusion as the father should preferably be associated with a 99.9% probability. Table 8 is an example of such a parentage test.
- Parenting and kinship testing is not carried out in the public health system. Private laboratories conduct testing in Australia and provide DNA testing kits. Contact Genetics Services for information.
- Where the testing is conducted for the purpose of family law proceedings, a regulatory framework governs the process. However, ‘private’ parentage testing is unregulated and offshore testing facilities via the Internet can also be accessed. So while parentage testing does not require the referral of a medical practitioner, if an opportunity arises to discuss issues relevant to using the commercial testing kits, important points include:
  > That it is essential that there is informed consent by both parents for a sample to be taken from a child
  > An exploration of whether the child is aware of the testing being undertaken, and discussing putting in place strategies for the child to gain an understanding of the reasons his or her parent is seeking the test and the possible impact of the test results on any existing relationships with that parent
  > An exploration of the consequences of the test for his or her relationship with the child or with the other parent
  > Understanding that the testing may take place when emotions are high and where parentage has been misattributed, perhaps for many years, there may be anger and grief

Kinship testing

- The testing involves the comparison of the DNA STR profiles from two living individuals or those of other putative relatives, as in parentage testing.
- If the profiles are sufficiently similar, a probability that the persons are biologically related will be provided.
Table 8. Example of DNA profiling used in paternity testing

Possible Father 1 would be excluded but there is a high probability that Father 2 is the child's father

<table>
<thead>
<tr>
<th>STR marker in Profiler Plus</th>
<th>D3</th>
<th>VWA</th>
<th>FGA</th>
<th>D8</th>
<th>D21</th>
<th>D18</th>
<th>D5</th>
<th>D13</th>
<th>D7</th>
<th>AMEL</th>
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<tr>
<td>Mother</td>
<td>14, 16</td>
<td>16, 18</td>
<td>19, 20</td>
<td>11, 13</td>
<td>30, 30</td>
<td>16, 19</td>
<td>11, 12</td>
<td>9, 12</td>
<td>10, 10</td>
<td>X, X</td>
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<tr>
<td>Child</td>
<td>14, 14</td>
<td>16, 18</td>
<td>19, 20</td>
<td>11, 13</td>
<td>30, 30</td>
<td>16, 19</td>
<td>11, 12</td>
<td>9, 12</td>
<td>10, 10</td>
<td>X, X</td>
</tr>
<tr>
<td>? Father 1</td>
<td>16, 18</td>
<td>17, 17</td>
<td>20, 22</td>
<td>13, 15</td>
<td>28, 30</td>
<td>14, 16</td>
<td>11, 11</td>
<td>9, 14</td>
<td>11, 13</td>
<td>X, Y</td>
</tr>
<tr>
<td>? Father 2</td>
<td>14, 15</td>
<td>16, 18</td>
<td>18, 20</td>
<td>11, 15</td>
<td>28, 29</td>
<td>14, 19</td>
<td>12, 12</td>
<td>12, 14</td>
<td>10, 13</td>
<td>X, Y</td>
</tr>
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</table>

**Ancestry and genetics**

- Findings from the Human Genome Project have confirmed that there is no genetic basis for race.
- There is considerable scepticism about the use of genetic tests that are marketed and promoted commercially to be able to determine ancestry; membership of a shared culture is much more than biological. Where testing is conducted, there are two main techniques used which involve mapping polymorphisms on the:
  - Y chromosome to trace paternal ancestry, ie to identify biological relationships between a father and son
  - Mitochondrial DNA to trace maternal ancestry, ie to identify biological relationships between a mother and her male and female children
- The tests rely on the availability of reference samples for comparison, as in kinship testing which may be very limited. Mitochondrial DNA and Y chromosome analyses are both extremely narrow in their focus when compared with the rich tapestry of a person’s genetic ancestry.
- Culture can also be reflected in a person’s genetic make-up. However, while a person may have a mutation that is more common in the Jewish community, the presence of that mutation alone does not mean that they identify with the Jewish culture.

**There is no genetic test for Aboriginality, for example.** Other forms of identification of membership of a group may be available including oral history, written documentation, cultural practices and personal beliefs. Even in their absence, the evidence for what constitutes family and kinship in the Aboriginal context is much broader than genetic markers can establish.
## List of fetal medicine services in public hospitals associated with the state genetics services in Australia

### Australian Capital Territory

<table>
<thead>
<tr>
<th>Location</th>
<th>Hospital</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The Canberra Hospital</td>
<td>Genetic Counsellor, PO Box 11, Woden ACT 2605&lt;br&gt;Ph: (02) 6244 2133&lt;br&gt;Fax: (02) 6244 4625</td>
</tr>
</tbody>
</table>

### New South Wales

<table>
<thead>
<tr>
<th>Location</th>
<th>Hospital</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camperdown</td>
<td>Royal Prince Alfred Hospital</td>
<td>Department of Molecular and Clinical Genetics, Building 65, Level 6 Missenden Road, Camperdown NSW 2050&lt;br&gt;Ph: (02) 9515 5080&lt;br&gt;Fax: (02) 9550 5389</td>
</tr>
<tr>
<td>Kogarah</td>
<td>St George Hospital</td>
<td>Women and Children's Health&lt;br&gt;Gray Street, Kogarah NSW 2217&lt;br&gt;Ph: (02) 9113 3635&lt;br&gt;Fax: (02) 9113 3694</td>
</tr>
<tr>
<td>Liverpool</td>
<td>Liverpool Hospital</td>
<td>Fetal Medicine Unit&lt;br&gt;Locked Bag 7103, Liverpool BC NSW 1871&lt;br&gt;Ph: (02) 9828 5631&lt;br&gt;Fax: (02) 9828 5570</td>
</tr>
<tr>
<td>Newcastle</td>
<td>John Hunter Hospital</td>
<td>Maternal and Fetal Medicine&lt;br&gt;Locked Bag 1, Hunter Region Mail Centre, Newcastle NSW 2310&lt;br&gt;Ph: (02) 4921 4694&lt;br&gt;Fax: (02) 4921 3133</td>
</tr>
<tr>
<td>Penrith</td>
<td>Nepean Hospital</td>
<td>Perinatal Ultrasound&lt;br&gt;Level 3 South Block, Derby Street, Penrith NSW 2751&lt;br&gt;Ph: (02) 4734 2578&lt;br&gt;Fax: (02) 4757 3206</td>
</tr>
<tr>
<td>Randwick</td>
<td>Royal Hospital for Women</td>
<td>Maternal/Fetal Medicine&lt;br&gt;Barker Street, Randwick NSW 2031&lt;br&gt;Ph: (02) 9382 6098&lt;br&gt;Fax: (02) 9382 6706</td>
</tr>
<tr>
<td>St Leonards</td>
<td>Royal North Shore Hospital</td>
<td>Fetal Medicine Unit&lt;br&gt;Pacific Highway, St Leonards NSW 2065&lt;br&gt;Ph: (02) 9926 6478&lt;br&gt;Fax: (02) 9926 7880</td>
</tr>
<tr>
<td>Westmead</td>
<td>The Children's Hospital</td>
<td>Department of Clinical Genetics&lt;br&gt;Locked Bag 4001, Westmead NSW 2145&lt;br&gt;Ph: (02) 9845 3273&lt;br&gt;Fax: (02) 9845 3204</td>
</tr>
<tr>
<td>State</td>
<td>Contacts, support and testing</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Northern Territory</strong></td>
<td>There is currently no clinical genetics service or outreach service available in the Northern Territory</td>
<td></td>
</tr>
<tr>
<td><strong>Queensland</strong></td>
<td>Royal Brisbane Women's Hospital&lt;br&gt;Antenatal Clinic&lt;br&gt;Cnr Bowen Bridge &amp; Butterfield Rds, Herston Qld 4029&lt;br&gt;Ph: (07) 3636 2269&lt;br&gt;Fax: (07) 3636 5379</td>
<td>Mater Mother's Hospital&lt;br&gt;Raymond Terrace, South Brisbane Qld 4101&lt;br&gt;Ph: (07) 3840 1593&lt;br&gt;Fax: (07) 3840 1621</td>
</tr>
<tr>
<td><strong>South Australia</strong></td>
<td>Women's and Children's Hospital&lt;br&gt;South Australian Clinical Genetics Service&lt;br&gt;Youth and Women's Health Service, North Adelaide SA 5006&lt;br&gt;Ph: (08) 8161 7375&lt;br&gt;Fax: (08) 8161 6088</td>
<td>Antenatal Diagnosis and Counselling Service&lt;br&gt;Department of Obstetrics and Gynaecology&lt;br&gt;Women's and Children's Hospital&lt;br&gt;South Australian Clinical Genetics Service&lt;br&gt;72 King William Road, North Adelaide SA 5006&lt;br&gt;Ph: (08) 8161 7633&lt;br&gt;Fax: (08) 8161 7654</td>
</tr>
<tr>
<td><strong>Tasmania</strong></td>
<td>Royal Hobart Hospital&lt;br&gt;Tasmanian Clinical Genetics Service&lt;br&gt;GPO Box 1061L, Hobart Tas 7001&lt;br&gt;Ph: (03) 6222 8296&lt;br&gt;Fax: (03) 6222 7961</td>
<td></td>
</tr>
<tr>
<td>Victoria</td>
<td></td>
<td></td>
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<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td><strong>Genetic Health Services</strong></td>
<td>10th Floor, Royal Children’s Hospital</td>
<td></td>
</tr>
<tr>
<td>Victoria (GHSV)</td>
<td>Flemington Road, Parkville</td>
<td></td>
</tr>
<tr>
<td>Clinics are conducted in 10 metropolitan and 11 rural and regional centres</td>
<td>Vic 3052</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ph: (03) 8341 6270</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fax: (03) 8341 6390</td>
<td></td>
</tr>
<tr>
<td><strong>Monash Medical Centre</strong></td>
<td>Monash Medical Centre</td>
<td></td>
</tr>
<tr>
<td></td>
<td>246 Clayton Road, Clayton</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vic 3168</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ph: (03) 9594 2026</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fax: (03) 9594 6022</td>
<td></td>
</tr>
<tr>
<td><strong>Royal Women’s Hospital</strong></td>
<td>Specialty Genetics Services</td>
<td></td>
</tr>
<tr>
<td></td>
<td>132 Grattan Street, Carlton</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vic 3053</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ph: (03) 9344 2121</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fax: (03) 9344 2066</td>
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<table>
<thead>
<tr>
<th>Western Australia</th>
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<tbody>
<tr>
<td><strong>King Edward Memorial</strong></td>
<td>Fetal Medicine Service</td>
</tr>
<tr>
<td>Hospital for Women</td>
<td>374 Bagot Road, Subiaco</td>
</tr>
<tr>
<td></td>
<td>WA 6008</td>
</tr>
<tr>
<td></td>
<td>Ph: (08) 9340 1525</td>
</tr>
<tr>
<td></td>
<td>Fax: (08) 9340 1678</td>
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</table>
## List of familial cancer services

### Australian Capital Territory

<table>
<thead>
<tr>
<th>Service</th>
<th>Address</th>
<th>Phone</th>
<th>Fax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Counsellor</td>
<td>Canberra Hospital</td>
<td>(02) 6244 2133</td>
<td>(02) 6244 4625</td>
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</table>

### New South Wales

<table>
<thead>
<tr>
<th>Service</th>
<th>Address</th>
<th>Phone</th>
<th>Fax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Prince Alfred Hospital</td>
<td>Missenden Rd, Camperdown, NSW 2050</td>
<td>(02) 9515 5080</td>
<td>(02) 9550 5389</td>
</tr>
<tr>
<td>St George Hospital</td>
<td>Gray St, Kogarah, NSW 2217</td>
<td>(02) 9350 3815</td>
<td>(02) 9350 3958</td>
</tr>
<tr>
<td>Hunter Family Cancer Service</td>
<td>PO Box 84, Warnath, NSW 2298</td>
<td>(02) 4985 3132</td>
<td>(02) 4985 3133</td>
</tr>
<tr>
<td>Prince of Wales Hospital</td>
<td>High St, Randwick, NSW 2031</td>
<td>(02) 9382 2551</td>
<td>(02) 9382 2588</td>
</tr>
<tr>
<td>Genetic Health Queensland</td>
<td>Herston Rd, Herston, QLD 4029</td>
<td>(07) 3636 1686</td>
<td>(07) 3636 1987</td>
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### Northern Territory

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<th>Service</th>
<th>Address</th>
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<tr>
<td>Genetic Counselling</td>
<td>Familial Cancer Unit c/- South Australian Clinical Genetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women's and Children's Hospital</td>
<td>North Adelaide, SA 5006</td>
<td>(08) 8161 7375</td>
<td>(08) 8161 6088</td>
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</tbody>
</table>

### Queensland

<table>
<thead>
<tr>
<th>Service</th>
<th>Address</th>
<th>Phone</th>
<th>Fax</th>
</tr>
</thead>
<tbody>
<tr>
<td>St Vincent's Hospital</td>
<td>Victoria Rd, Darlinghurst, NSW 2011</td>
<td>(02) 8382 3395</td>
<td>(02) 8382 3386</td>
</tr>
<tr>
<td>Westmead Hospital</td>
<td>Department of Medicine, Westmead, NSW 2145</td>
<td>(02) 9845 6947</td>
<td>(02) 9687 2331</td>
</tr>
<tr>
<td>Nepean Hospital</td>
<td>Clinical Genetics Department, Level 5 South Block, PO Box 63, Penrith, NSW 2750</td>
<td>(02) 4734 3362</td>
<td>(02) 4734 2567</td>
</tr>
<tr>
<td>Royal North Shore Hospital</td>
<td>Family Cancer Service, Level 2, Vindin House, St Leonards, NSW 2065</td>
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<td>South Australia</td>
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<td>Familial Cancer Unit</td>
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<td>Royal Hobart Hospital</td>
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<td></td>
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<tr>
<td>North Adelaide, SA 5006</td>
<td>Hobart, TAS 7001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph: (08) 8161 6995 Fax: (08) 8161 7984</td>
<td>Ph: (03) 6222 8296 Fax: (03) 6222 7961</td>
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<th>Western Australia</th>
</tr>
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<tbody>
<tr>
<td>The Royal Melbourne Hospital</td>
<td>Familial Cancer Program</td>
</tr>
<tr>
<td>Genetic and Family Cancer Clinic</td>
<td>King Edward Memorial Hospital</td>
</tr>
<tr>
<td>C/- Royal Melbourne Hospital</td>
<td>Level 3, Agnes Walsh House</td>
</tr>
<tr>
<td>Parkville, VIC 3050</td>
<td>374 Bagot Rd</td>
</tr>
<tr>
<td>Ph: (03) 9342 7151 Fax: (03) 9342 4267</td>
<td>Subiaco, WA 6008</td>
</tr>
<tr>
<td></td>
<td>Ph: (03) 9656 1199 Fax: (03) 9656 1539</td>
</tr>
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</tr>
<tr>
<td></td>
<td>Genetic Health Services Victoria</td>
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</table>
Bibliography


Accessible at http://www.genetics.com.au


Keating T and Reid G, 2005. Australasian Genetic Alliance and the Genetics support Council Western Australia, ‘Consumer input into genetics education for general practitioners’.

Genes hold hereditary information. All the instructions (about 25,000 genes) that make us who we are can be found in every cell of our body.

DNA (deoxyribonucleic acid) is a long strand of many genes and a chromosome is a single strand of DNA.

We have 23 pairs of chromosomes in every cell. This paired arrangement is because we inherit one of each pair of chromosomes from each parent. Babies inherit half their genes from their mother and half from their father.

Twenty-two of these pairs of chromosomes are the same in males and females. One of the pairs, the sex chromosomes, is different in males and females. Females have two X chromosomes while males have an X and a Y chromosome. The Y chromosome carries genes that determine male characteristics.

Some genes control simple characteristics like the colour of our hair and how tall we are, while others influence complex characteristics like intelligence. Some genes control how other genes work, telling them when to switch on and off and how much protein to make.

With 25,000 or so genes, there are bound to be some that are altered. We all carry genetic alterations (mutations). An alteration in an unimportant gene may have little effect on our lives. But an alteration in an important gene, so that it doesn’t work properly any more, or if the gene is missing altogether, could have serious consequences. A gene alteration can run in families, but may also occur as a random event, without any previous family history.

Scientists have now discovered what our DNA looks like and they know quite a lot about many genes.

But scientists are still a long way from knowing what all the genes do. There are still conditions which seem to have a genetic basis, but nobody yet knows what genetic alterations are involved. Also, there are still conditions that clearly have a genetic basis, for which no tests are available.

The knowledge available now is incomplete and may not be able to provide all the answers. But existing knowledge can help many people to a better understanding of a genetic disorder in their family.
Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- Australasian Genetic Alliance at http://www.australasiangeneticalliance.org.au
- MyDr at http://www.mydr.com.au
- The Centre for Genetics Education at http://www.genetics.edu.au
- HealthInsite at http://www.healthinsite.com
- MedicineNet at http://www.medicinenet.com
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
How do genetic conditions occur?

Genetic conditions occur in one of three main ways:

1. There is a problem with a chromosome.
2. There is an alteration in a gene. The alteration can be inherited from one or both parents, or can occur for no obvious reason for the first time in the family (this is known as a new mutation). There are three main patterns of inheritance – autosomal dominant, autosomal recessive and X-linked.
3. Alterations to one or more genes combine with factors in the environment – such as diet, lifestyle and chemical exposure – to cause a problem. This is known as multifactorial inheritance.

Chromosomal problems

Chromosomes are important parts of a cell. They are the parts which carry the genes.

We are meant to have 23 pairs of chromosomes, a total of 46 chromosomes, with one in each pair inherited from each parent.

Occasionally, things go wrong and a child is conceived with 45 chromosomes, or 47 chromosomes, or perhaps the right number but the wrong mix of chromosomes. Also, a child may be born with a change to the way the chromosomes are structured.

Chromosomal problems are not usually inherited, although occasionally they can be.

Autosomal dominant

In an autosomal dominant condition, an alteration in only one gene of a pair of genes is usually enough to cause the condition.

So if a person has an autosomal dominant condition, each of their children has a one in two chance of inheriting the altered gene. Each child also has a one in two chance of not inheriting the altered gene.

Autosomal dominant conditions can run in the family.

New problems with genes can come up at any time; someone with the condition may be the first affected person in the family, with no-one else in previous generations having the gene alteration. These new gene alterations, which occur at the time of conception, are called new mutations.
**Autosomal recessive**

In an autosomal recessive condition, alterations in both copies of a pair of genes are needed to cause the condition. Therefore, somebody with one altered gene will be a carrier (and is usually unaffected because the normal gene in that pair dominates) and somebody with two altered genes will have the condition.

A person who is a carrier for the condition has a one in two chance of any child being a carrier and a one in two chance of any child not being a carrier.

Carriers are unlikely to have a partner who is also a carrier, unless their partner is a blood relative. But if they do, then the chance of any child of two carriers having the condition is one in four.

Autosomal recessive conditions tend to occur only occasionally in the families in which they appear, but there will probably be quite a few carriers.

**X-linked recessive**

Most babies are born with 23 pairs of chromosomes – 22 standard pairs and then the pair that determines the sex of the baby. Girls have two X chromosomes and boys have an X and a Y chromosome.

Fathers pass their X chromosome to their daughters and their Y chromosome to their sons. Mothers pass one of their X chromosomes to both their sons and daughters.

In X-linked recessive conditions, the altered gene is found on the X chromosome. There is no equivalent gene on the Y chromosome.

So a woman with an altered gene on one of her two X chromosomes is a carrier and is usually not affected (because the normal gene dominates). But sometimes she may be mildly affected by the condition.

Any son of a woman who is a carrier has a one in two chance of having the altered gene, and a one in two chance of not having it. Any daughter of a woman who is a carrier has a one in two chance of being a carrier, and a one in two chance of not being a carrier.

A man with the condition will have daughters who are carriers and sons who are not affected.

X-linked recessive conditions can run in the family.

New problems with genes can come up at any time; a man with the condition may be the first affected person in the family, with no-one else in previous generations having the gene alteration. These new gene alterations, which occur at the time of conception, are called new mutations.
**Multifactorial inheritance**

Multifactorial inheritance is inheritance due to an interaction between an individual’s genetic make-up and environmental factors. Although these conditions tend to run in families, the patterns are less predictable than other forms of genetic condition.

Many common health problems have multifactorial inheritance. They include some forms of cancer, some forms of heart disease, diabetes and mental illness such as schizophrenia and manic depression.

**Note**

Things are not quite as straightforward as this. What we have described here is the general pattern, but there are two things to consider:

- The knowledge of genetics is growing, but is incomplete.
- Genes can behave in unpredictable ways, so all advice and testing is provided with the consideration that unexpected things can happen.

**Contacts and further information**

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email [gtis-australia@unimelb.edu.au](mailto:gtis-australia@unimelb.edu.au) or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
Talking with doctors

If you’re talking to your doctor about genes, it’s probably because of worries that you, or someone in your family, or someone that you care for, might have a genetic condition.

You might have a condition that seems to run in the family and you’re thinking about having children and want to know: What are the risks of my child having it?

Your mother might have developed breast cancer and you’re wondering: What does this mean for me? My sister? My daughter?

Or you may have just discovered your child has cystic fibrosis and you want to know everything.

These concerns are real. It can be very stressful wondering about what might or might not happen. You want to know where you can access accurate information, so that you avoid any misunderstandings or myths about genetics.

Whatever the situation, you will be able to deal with it better if you have more information. So consider the options available to you. You may want to:

- Work on a good relationship with a GP who can help you understand genetics
- Take someone with you when you see the doctor, especially another family member if possible
- Think about what you want to know before you go and write down a list of questions
- Talk to your doctor about what you understand about genetics – it helps your doctor enormously to find out what you know at the start
- Organise time for repeated visits – genetics can be quite complex and it may be difficult to sort everything out in one or two visits
- Read what you can – your doctor, local health department, genetics service, support group and genetics education counselling service, and local library can provide you with plenty of material to read
- Check out the internet, although it is best to stick to material that comes from reputable sources, such as hospitals, support groups, universities, genetics services and health services.

Contacts and further information

- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
Genes are passed from parent to child, so genetic conditions can run in families.

This is not always the case. It is possible to have a genetic condition that no-one else in the family has.

It is also possible for several members of a family to have a particular condition without the condition being genetic. For example, if everybody in a family smokes, that family can have lots of heart disease and cancer.

Having said that, genes and families go together quite strongly.

So if you’re thinking about genes, or about diseases running in the family, one important thing you can do is learn about your family’s health history.

When looking closely at genetic conditions that may run in your family, your doctor will want to draw a family tree. He or she will want to know about the person you’re talking about (whether that’s you or someone in your family), as well as all the parents, grandparents, uncles, aunts, cousins and children, especially those who are blood relatives.

Your doctor will ask a lot of questions in order to examine your family history. Your doctor will want to know:

• All the relationships in your family
• The ages of everyone involved
• Who is alive?
• How old were family members when they died and what did they die of?
• Do they or did they have any medical conditions?
• The names of doctors or hospitals that have cared for affected family members
• What’s the ancestry of your family? What country did grandparents and great-grandparents come from?
• Did anybody in the family have any miscarriages, stillborn children or children born with abnormalities?
• Has anybody in the family lived for long periods in a psychiatric institution?
• Has anybody in the family been adopted?
• Has anybody in the family had children with a relative?
• Has anybody in the family been told they have or are a carrier for a genetic condition?
• Has anybody in the family ever been tested for a genetic condition? What was the result?

If you can get answers to some or all of these questions, you and your doctor will be able to make a lot more sense of your family history. If you visit the webpage at http://www.genetics.edu.au/publications/fhtcons.htm you can see a sample family history.
Contacts and further information

• Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.

• Australasian Genetic Alliance at http://www.australiangeneticalliance.org.au

• The Centre for Genetics Education at http://www.genetics.edu.au

• For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
Testing and pregnancy
GP’s role

- Identify opportunities for pre-pregnancy counselling.
- Collect relevant family history.
- Assess whether information in the family history places the current pregnancy at increased risk.
- Consider carrier tests for those from specific ethnic groups.
- Provide information about screening and diagnostic tests during pregnancy.
- If necessary, refer on to appropriate Genetics Services and/or support groups.
- Discuss peri-conceptual folic acid supplementation, the implications of drug and medication use during pregnancy, and other lifestyle modifications, eg smoking, drugs, alcohol.
- Provide information about infectious diseases during pregnancy.

Counselling before and during pregnancy

- If possible, pre-pregnancy counselling is advised and should include:
  - Collection of relevant family history (see ‘Collecting the family history’ below, and Family history).
  - Recommending periconceptional folic acid supplementation (see ‘Folic acid before and during pregnancy’ below).
  - Provision of information about screening and diagnostic tests during pregnancy (see ‘Types of prenatal tests’ below).
  - Consideration of carrier tests for those from specific ethnic groups, eg thalassaemia, sickle cell screening and Tay-Sachs disease (see Haemoglobinopathies).
  - Assessment of drug and medication use and implications for pregnancy.
  - Discussion of lifestyle changes, eg alcohol and smoking cessation during pregnancy and changes to diet.
  - Provision of information about infectious diseases:
    - Rubella vaccination status
    - Varicella antibody status and immunization if non-immune
    - Discussion about listeria infection and toxoplasmosis
  - Provision of information about pre-implantation genetic diagnosis (PGD), for couples who are known carriers of a genetic condition and/or couples undergoing IVF (see ‘Pre-implantation genetic diagnosis’).
  - Where couples are known carriers of a genetic condition, refer to Genetics Services.
Collecting the family history

- See *Genetics in practice* for further information.
- The family history of the woman and her partner should be collected regarding:
  - Inherited conditions, eg cystic fibrosis, fragile X syndrome, Duchenne muscular dystrophy
  - Down syndrome and other chromosomal abnormalities
  - Birth defects, eg spina bifida, cleft lip/palate, cardiac defects
  - Intellectual disability
  - Recurrent miscarriage
  - Unexplained perinatal deaths
  - Consanguinity (see *Genetics in practice*)
  - Ethnic background

Folic acid and pregnancy

- About 1 in every 500 pregnancies is affected by a neural tube defect.
- Research has shown that 70% of cases of neural tube defects (spina bifida, anencephaly, cleft lip with or without cleft palate) can be prevented by increasing the intake of folic acid prior to, and during early pregnancy.
- Folate is a B group vitamin found in leafy green vegetables, wholegrain breads, cereals and legumes. It is also available in tablet forms as folic acid.

### Recommendations about folic acid in pregnancy

#### Women at population risk for neural tube defects

- Women planning a pregnancy should take supplementary folic acid, 0.5mg [500μg] folic acid tablet or multivitamin appropriate for use in pregnancy and containing at least 0.4 mg [400μg] of folic acid) every day for at least one month prior to possible conception and continued for the first three months of pregnancy.
- As many pregnancies are unplanned, all women of reproductive age should consider taking supplementary folic acid or a folate-rich diet.
- Folic acid tablets and multivitamins containing at least 0.4mg [400μg] folic acid are available from chemists, health food stores and some supermarkets.

#### Women at increased risk for neural tube defects

- Women are at higher risk of having a baby with a neural tube defect if:
  - They have had a baby with spina bifida, anencephaly or other neural tube defects
  - They themselves have had a neural tube defect
  - They are on certain medications for epilepsy
  - They have a close relative who has had a neural tube defect.
- These women should take supplementary folic acid every day for at least one month prior to possible conception and continued for the first three months of pregnancy. The dose recommended is usually 5mg [5000μg].

#### Important points about folic acid

- Women taking drugs to control epilepsy or seizures should ask their doctor whether they should increase the dose of folic acid to 5mg daily. However, specific evidence is limited in this area.
- Women planning to take multivitamins to provide folic acid supplementation should check with their pharmacist or doctor whether the multivitamin dose they are planning to use contains amounts of all the other vitamins/minerals that are safe for pregnancy, as well as providing the right amount of folic acid.
Assessing risk factors in pregnancy

**Down syndrome and other chromosomal abnormalities**

- All women are at risk of having a baby with a chromosomal abnormality, the most common being Down syndrome.
- The risk of Down syndrome increases with maternal age, as illustrated in Figure 1.

![Figure 1. Maternal age and risk of liveborn baby with Down syndrome](image)


**The effect of maternal age on screening tests for Down syndrome**

- Screening tests give a risk figure for Down syndrome that modifies the risk based on maternal age alone.
- The detection rate depends on the type of test.
- The detection rate and probability of an increased risk result increases with maternal age as the calculations of risk usually include the woman's age.
- It is important that the woman/couple understands that screening tests will not identify all pregnancies with Down syndrome and that an increased risk result will require further clarification. The result from a chorionic villus sampling or amniocentesis will most likely still be normal.
- Screening tests should be offered to all pregnant women.

**Factors that increase the risk of having a baby with Down syndrome and other chromosome abnormalities**

- Maternal age.
- A previous pregnancy with a chromosome trisomy.
- An increased risk result on a screening test.
- The presence of soft signs of Down syndrome or other fetal anomalies during ultrasound examination.
- A parent carrying a chromosome rearrangement, e.g., a translocation involving chromosome 21 may increase the risk for Down syndrome. See *Chromosomal conditions*. 
Neural tube defects

- The risk of a baby having a neural tube defect:
  > Is approximately 0.2%, but is higher if there is a past or family history of the condition
  > Does not increase with maternal age
  > Is increased for women taking certain anticonvulsants. Advice regarding risk is available from drug information services in obstetric hospitals or from Genetics Services

Genetic conditions and birth defects

- A family history of a birth defect (e.g., congenital heart defect), inborn error of metabolism (e.g., phenylketonuria) or other inherited conditions (e.g., thalassaemia) may indicate an increased risk of that condition.

- A family history should be collected from the woman and her partner. If the woman is concerned or there is a significant history they should be referred to Genetics Services for further risk assessment, preferably prior to conception.

Types of prenatal tests

- **Screening tests** determine if the baby has an increased risk of having a particular problem such as Down syndrome or a neural tube defect. They are not diagnostic and an increased risk result does not mean the baby will definitely be affected.

- Prenatal screening tests include:
  > Ultrasound
  > Early pregnancy (first trimester) screening: nuchal translucency ultrasound together with testing of the mother’s blood
  > Second trimester screening: testing the mother’s blood (maternal serum screening)

- Prenatal screening tests should not be considered routine, but rather offered as a choice to women.

- **Diagnostic tests** determine if the baby has, or will develop after birth, a genetic condition. Sampling procedures to obtain cells for chromosome analysis or specific genetic tests are invasive.

- Prenatal diagnostic tests include:
  > Ultrasound
  > Chorionic villus sampling (CVS)
  > Amniocentesis

- Prenatal diagnostic tests should not be considered routine, but rather offered as a choice to women.
Figure 2. Prenatal screening and diagnostic tests offered

The flow chart shows the possible pathways a woman may take with respect to prenatal testing. The numbers refer to the approximate percentages of women taking these options. Termination of pregnancy (TOP) is possible at any of these stages within the limitations imposed by State and Territory laws.

*a* Note that the timing for offering a CVS in South Australia is sometimes from 10 weeks gestation.
Table 1. Advantages and disadvantages of screening tests during pregnancy

<table>
<thead>
<tr>
<th>Screening test a</th>
<th>Gestation (weeks)</th>
<th>% Down syndrome pregnancies detected</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Combined first trimester screening | 10 - 12 (blood test) 11 1/2 - 13 1/2 (ultrasound with nuchal translucency) | 85 - 90% | • Early screen and therefore early diagnosis  
• Highest detection rate  
• No added risk of miscarriage  
• Detection of some fetal abnormalities  
• Benefits relating to early scan: > Accurate dating > Diagnosis of multiple pregnancy > Diagnosis of early pregnancy failure (miscarriage) | • Will detect some affected pregnancies that may spontaneously miscarry  
• Does not provide risk for neural tube defects but the ultrasound may detect anencephaly  
• Women may not access services so early in the pregnancy  
• Ultrasound requires accredited operator for accuracy b  
• Out-of-pocket expenses vary c |
| Second trimester maternal serum screening | 14 - 20 (15 - 17 ideal) | 70 - 75% d | • Available to women presenting in second trimester  
• No added risk of miscarriage  
• No out-of-pocket expenses for public patients if arranged through public hospital | • Later screening test  
• Inaccurate dates can result in inaccurate risk by calculations. A dating scan should be considered if dates are uncertain  
• Lower detection rate  
• No neural tube risk can be given if test done at 14 weeks  
• Out-of-pocket expenses vary |

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a False positive rate set at 5% at these detection rates  

b Nuchal translucency measurement should be performed by a Fetal Medicine Foundation (FMF) and RANZCOG (Royal Australian and New Zealand College of Obstetrics and Gynaecology) accredited operator  

c May be limited access in some states: in Victoria, it is currently not funded for public patients; in Queensland the blood test is not available publicly  

d Assumes the use of the quadruple test (four analytes) and ultrasound dating
<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Gestation (weeks)</th>
<th>% Down syndrome pregnancies detected</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorionic villus sampling (CVS)</td>
<td>From 11 weeks</td>
<td>&gt; 99%</td>
<td>• Early detection&lt;br&gt;• Definitive diagnosis&lt;br&gt;• Results potentially available in time for termination of pregnancy (TOP) by curette</td>
<td>• Miscarriage risk (~ 1% above background in expert hands)&lt;br&gt;• Detects chromosomally abnormal pregnancies that may otherwise spontaneously miscarry&lt;br&gt;• 1% risk of equivocal results (placental mosaicism or maternal cell contamination of sample)&lt;br&gt;• 0.1% failure to detect chromosome abnormality (abnormality is present in fetus but not in placenta, or maternal cell contamination of sample)</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>From 15 weeks</td>
<td>100%</td>
<td>• Test with lowest miscarriage rate&lt;br&gt;• Definitive diagnosis</td>
<td>• Miscarriage risk (~ 0.5% above background in expert hands)&lt;br&gt;• Diagnosis in second trimester, when pregnancy is more established&lt;br&gt;• Results available too late for TOP by curette – TOP may need to be performed by induction of labour or vaginal evacuation</td>
</tr>
<tr>
<td>Second trimester fetal anomaly ultrasound scan*</td>
<td>18 - 20</td>
<td>Very low pick up rate on soft markers alone</td>
<td>• Detects many physical fetal abnormalities, such as: neural tube, cardiac, limb, gastrointestinal, CNS&lt;br&gt;• No added risk of miscarriage&lt;br&gt;• Measures fetal growth and locates position of placenta</td>
<td>• Not all physical abnormalities can be detected&lt;br&gt;• 'Soft markers’ (risk factors for chromosomal abnormalities not definitive and difficult to interpret) – 50% of babies with Down syndrome will have soft markers/signs&lt;br&gt;• Not recommended as primary screening test for Down syndrome</td>
</tr>
</tbody>
</table>

*a Out-of pocket expenses vary for CVS, amniocentesis and scans according to state. Public patients attending a tertiary public hospital may not be charged if identified as ‘increased risk’

*b The timing of CVS is not uniform throughout Australia, eg in South Australia it is sometimes offered from 10 weeks gestation

*c Procedures after 20 weeks gestation may not provide results in timeframe permitting second trimester termination of pregnancy. Refer to your State abortion laws, and policies of local perinatal units
**Offering testing**

- All pregnant women or couples contemplating pregnancy should be offered information regarding screening tests. Women should be informed that they will be offered further testing if they have an increased risk result on a screening test.
- All women at increased risk should also be offered information about diagnostic tests.
- All women/couples undertaking screening and diagnostic tests should be made aware that there could be an unanticipated finding. For example, testing for Down syndrome may identify a fetus with Turner syndrome.
- If a woman decides to have prenatal testing, the best test will depend on the woman's gestation, risk and her concerns. Access to services may also influence the decision. The decision about which test is best is a personal one for each woman/couple.
- Not all tests are available in the public sector and some tests do not have a Medicare rebate.
- Risk can be difficult for individuals to understand (see ‘Ways of explaining prenatal risk figures’ below).

**Prenatal screening tests**

- Types of prenatal screening tests include:
  - Ultrasound scanning
  - Combined first trimester screening
  - Second trimester maternal serum screening

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**Important considerations about prenatal screening tests**

- Screening tests can determine who is at increased risk of having a baby with Down syndrome. Women choosing screening tests should be informed that they will be offered further testing if they have an increased risk and that they may choose to proceed to diagnostic testing. Reasons for not having diagnostic testing include concern about the risk of miscarriage, not wishing to know prior to the birth, and termination of pregnancy being unacceptable to the family.
- Screening tests are non-invasive so there is no increased risk of miscarriage from the procedure.
- Every screening test has a ‘false positive’ rate, where women receive an increased risk result even though their baby is unaffected. This rate is usually around 5%.
- In the majority of pregnancies with an increased risk result on a screening test, the baby is unaffected. A common misconception held by women is that screening tests ‘show’ that the fetus has Down syndrome. Anxiety at any increased risk result is normal (see, *Genetics in practice*).
- Low risk results do not exclude Down syndrome or other abnormalities.
- A second trimester ultrasound may detect some birth defects but is not recommended as a screening test for Down syndrome.
- Neural tube defects and some other conditions may also be detected with second trimester maternal serum screening.
Ultrasound scanning

- Ultrasound scans are screening tests for some birth defects, with varying degrees of accuracy depending on the condition.
- Ultrasound scans can be a diagnostic tool for some birth defects (e.g., neural tube defects).
- Ultrasound scans are non-invasive, and current evidence supports that they pose no threat to the baby.
- Ultrasound screening for fetal anomaly should not be considered a routine test, but should be offered as a choice for all pregnant women.

First trimester ultrasound

- Usually between 8 and 11 weeks gestation.
- Used to:
  > Confirm gestational age
  > Check the pregnancy when there has been a complication such as bleeding
  > View the position of the placenta
  > Confirm presence of multiple pregnancy
  > Check fetal growth, physical development and viability

Second trimester ultrasound

- Usually at 18 to 20 weeks gestation.
- This ultrasound for fetal anomaly should not be considered a routine test, but should be offered as a choice for all pregnant women.
- May be used to detect:
  > Neural tube defects (anencephaly, spina bifida)
  > Cardiac defects
  > Gastrointestinal malformations (gastroschisis, exomphalos)
  > Limb defects
  > Central nervous system defects
  > Urinary tract anomalies
  > Soft signs that may be associated with underlying chromosomal or other genetic conditions
Limitations of second trimester ultrasound

- Not all malformations can be detected by ultrasound at a second trimester fetal anomaly scan (18 to 20 weeks). The sensitivity depends on many factors including the:
  > Nature of the malformation
  > Experience of the operator
  > Position of the placenta
  > Maternal weight (obesity)
  > Resolution of the ultrasound equipment

- Visualisation of the fetus can be affected by factors such as the woman’s build and the position and size of the fetus.

- Second trimester ultrasound scan is not recommended as a primary screening test for Down syndrome.

- The significance of changes (soft signs of chromosome abnormality) detected by ultrasound may be difficult to interpret. Further investigations may be indicated. Advice can be sought from a specialist ultrasonographer, Genetics Services or an obstetrician in a high-risk pregnancy management unit.

Ultrasound and neural tube defects

- The best detection method for neural tube defects is an ultrasound scan during the second trimester (18 to 20 weeks).

- If a previous pregnancy has been affected by a neural tube defect or there is a 1° relative with a neural tube defect, a specialised ultrasound scan at both 12 to 13 weeks for anencephaly and 18 weeks for other neural tube defects, is recommended.

- The identification of a neural tube defect by ultrasound depends on the skill of the operator, the equipment, the position and gestation of the fetus, and maternal conditions.
Nuchal translucency screening

- Nuchal translucency (NT) describes the appearance of a fluid-filled space at the back of the fetal neck that can be seen using ultrasound early in pregnancy. The depth of the fluid in this space can be measured using ultrasound. The thicker the nuchal translucency the greater the risk of fetal anomalies such as Down syndrome, other chromosomal conditions, cardiac defects and some rare genetic conditions (see Chromosomal conditions).

- NT measurements should only be performed by trained and accredited operators, using a risk assessment program that incorporates NT, Crown-Rump Length (CRL) and maternal age. This test should be done when the fetus has a CRL of 45 to 84mm, which corresponds to the period 11 weeks 3 days to 13 weeks 6 days.

It should be noted that nuchal translucency screening alone is not recommended as a screening test for Down syndrome and that it should be combined with a biochemical test (see below ‘Combined first trimester screening’) if available.

Combined first trimester screening

- It is recommended that the NT screening test be done in conjunction with a maternal blood test. Two proteins present in the maternal blood are measured. These are PAPP-A (pregnancy associated plasma protein) and free ß-subunit of human chorionic gonadotrophin (free ß-hCG). Levels of these proteins vary, but tend to be different in women who are carrying fetuses with Down syndrome or trisomy 18. Increased free ß-hCG with decreased PAPP-A is suggestive of Down syndrome, while decreased levels of both analytes is suggestive of trisomy 18.

- By having the blood test in combination with the NT screening test, around 85-90% of babies who have Down syndrome and occasionally other problems will be picked up, compared to 70% or less using NT on its own.

- Approximately 5% of combined first trimester screening tests give an increased risk result. This figure varies depending on maternal age. Women with an increased risk result should be offered a diagnostic test. The majority of increased risk results are not due to Down syndrome, and most of these babies will be healthy.

- Results are usually available on the day of the NT ultrasound, if blood was collected prior to the ultrasound at 10 to 12 weeks gestation, although this will depend on the local provider.

- Results are provided as risks for Down syndrome and the other chromosomal trisomy 18, at the time of screening. ¹ Note then that this is not a risk of delivering an affected fetus. Approximately 30% of babies with Down syndrome do not survive to term.

- Depending on the State/Territory, combined first trimester screening is not always available in the public sector, and there may be out-of-pocket costs for the patient (refer to Table 1).

¹ However, in Western Australia the risk figure is adjusted to give the risk at the time of delivery.
Arranging combined first trimester screening

- Tests should be arranged a couple of weeks in advance to allow time to coordinate the blood test and ultrasound. The blood test should ideally be performed first.
- Arrange the ultrasound scan with a Fetal Medicine Foundation (FMF) accredited operator (see Table 1).
- Arrange the blood collection at an appropriate gestation (see Table 1). Blood can be collected at the local pathology service but the request should have clear instructions for the sample to go to the screening lab. This process varies between States, private and public sectors, and metropolitan and regional centres. For specific details regarding co-ordinating the results of the blood and nuchal translucency test contact your local FMF accredited operator of choice.

The factors that need to be entered into the risk calculation algorithm should be noted on the request form including:

- LMP & EDD
- Current weight
- Maternal age
- Previous child with a chromosomal abnormality
- Date and location of ultrasound scan
- Any other information requested on the form, eg ethnicity, IVF details

If the results of the scan are not received by the date on the form, the laboratory will contact the ultrasound practice or the requesting doctor.

Second trimester maternal serum screening

- The optimal time to have this test performed is between 15 and 17 weeks, but it can be performed until 20 weeks.
- Second trimester maternal serum screening uses a blood test in conjunction with the maternal age, gestational age and maternal weight to calculate a risk figure for Down syndrome. This screening test may also detect pregnancies with an increased risk for trisomy 18 (see Chromosomal conditions) and neural tube defects.
- Maternal blood contains hormones and proteins produced by the fetus and placenta, including alpha-fetoprotein (AFP), unconjugated estriol (μE3), free β-subunit of human chorionic gonadotrophin (free β-hCG), and inhibin A.
- Levels tend to be altered in pregnancies affected by Down syndrome, trisomy 18 or neural tube defects. In Down syndrome, the levels of AFP and μE3 tend to be reduced, and free β-hCG and inhibin A increased. In neural tube defects AFP may be increased and, in trisomy 18, levels of all these substances are decreased.
- The number and type of analytes used may vary between pathology services. The quadruple test measures four analytes (AFP, μE3, free β-hCG and inhibin A), whilst the triple test measures three analytes. Detection rates are improved when four analytes are used.
- Using the quadruple test with ultrasound dating:
  > 75% of fetuses with Down syndrome are detected by second trimester maternal serum screening, and approximately 5% of tests give an increased risk result. Women aged 40 and over have higher detection rates, with 95% of affected pregnancies receiving an increased risk result. At least 50% of all women in this age group will receive an increased risk result.
  > 85% of babies with a neural tube defect will be detected using maternal serum screening alone. When combined with a detailed ultrasound, the detection rate for spina bifida can be as high as 95%, and 100% for anencephaly.
- Results are usually available within 24 to 48 hours of collection, but may take longer in parts of regional Australia. Women at increased risk are offered diagnostic testing. The majority of increased risk results are not due to Down syndrome and most of these babies are unaffected. The possibility of false positive results and the management options should be discussed with women prior to screening, as should the fact that this blood test cannot definitively identify babies with Down syndrome, trisomy 18, or neural tube defects.
Arranging second trimester maternal serum screening

The factors that need to be entered into the risk calculation algorithm should be noted on the request form:

- Ultrasound-based gestation or LMP
- Current weight
- Maternal age
- Previous child with a chromosomal abnormality as well as previous child or close relative with a neural tube defect
- Date of collection
- If the woman has insulin-dependent diabetes
- And any other information requested on the form, eg ethnicity, IVF details

- Some States’ and Territories’ Antenatal Screening Programs receive government funding to perform this testing on public patients, and so there is no out-of-pocket cost.
- For private patients, the cost depends on the pathology provider.
- This test does not need to be repeated unless blood was collected at less than 14 weeks gestation.

Counselling for an increased risk result

- Cut-off risks are chosen to decide who is at an increased risk as a result of screening. Women at increased risk can then be offered diagnostic testing. Cut-off risks for trisomy 18 and Down syndrome are listed below. For neural tube defects an AFP level is measured in MoM (multiple of the population median, corrected for gestation). Note that there is some State variation.

Table 3. Cut-off risks used to determine increased risk in prenatal screening

<table>
<thead>
<tr>
<th>Screen</th>
<th>Down Syndrome</th>
<th>Trisomy 18</th>
<th>Neural tube defect</th>
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<tbody>
<tr>
<td>Combined first trimester screening</td>
<td>1 in 300</td>
<td>1 in 300</td>
<td></td>
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<tr>
<td>Second trimester maternal serum screening</td>
<td>1 in 300 a</td>
<td>1 in 300 b</td>
<td>≥ 2MoM c</td>
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</tbody>
</table>

a Cut-off in Victoria is 1 in 250
b Cut-off in Victoria is 1 in 200, cut-off in NSW is 1 in 250
c Cut-off in Victoria is ≥ 2.5MoM

- First confirm the gestational age as incorrect gestational age estimation can affect accuracy of results.
- It may be helpful to discuss the results with the service provider prior to informing the woman/couple.
- Listen and give the woman/couple time to absorb the news, consider available options and to make decisions about further testing. Informed decision-making is assisted by the provision of up-to-date, unbiased information.
- Ensure the woman understands that while the pregnancy is at increased risk for the condition, the result is not definitive.
- A common misconception held by women is that screening tests ‘show’ the fetus has Down syndrome. It can take some listening, clarification and explanation to counteract this belief. Anxiety at any increased risk result is normal (see Genetics in practice).
- Reassure the woman that the majority of babies with an increased risk result will be normal and healthy.
- Discuss the option of diagnostic testing. Not all women decide to proceed to diagnostic testing. Reasons for not having diagnostic testing include concern about the risk of miscarriage, not wishing to know prior to the birth, and termination of pregnancy being unacceptable.
  - Post-test counselling is available from specialist obstetricians and Genetics Services. Referral should be considered for discussion of diagnostic tests and counselling for women with increased anxiety.
Ways of explaining prenatal screening risk figures

Giving an increased risk result:
A 29 year old woman receives an increased risk result for Down syndrome after a serum screen test. The risk is 1 in 100. Prior to the test her risk was based on maternal age alone and was 1 in 1002.

• Comparison to other women getting the same test result:
  “Of 100 women with this test result, on average, one will have a baby with Down syndrome and 99 will have babies who do not have Down syndrome.”

• Risk relative to maternal age:
  “Your risk is now similar to that of a 39 to 40 year old who has not had any screening. Women who have this level of risk are offered further testing to determine if the baby has Down syndrome.”

Prenatal diagnostic tests

• Types of prenatal diagnostic tests include:
  > Chorionic villus sampling (CVS)
  > Amniocentesis
  > Ultrasound

Important considerations about prenatal diagnostic tests

• CVS and amniocentesis testing require invasive sampling procedures to obtain cells for chromosome analysis or specific genetic tests.

• It is not possible to detect or diagnose every possible condition a child might have using prenatal diagnosis.

• Both CVS and amniocentesis have a risk of miscarriage. The risk is operator dependent, so tests should be performed by an experienced operator.

• Indications for offering diagnostic testing include:
  > Advanced maternal age (≥37 yr in Victoria, ≥35 yr elsewhere)
  > A previous pregnancy with a chromosome abnormality
  > The presence of soft signs of chromosome abnormality during ultrasound examination
  > A parent carrying a chromosome translocation (5% of Down syndrome is caused by an unbalanced translocation involving chromosome 21 that was inherited from a parent with a balanced form of the translocation, see Chromosomal conditions)
  > An increased risk result on a screening test
  > An increased risk of having a baby with a genetic condition – usually when there is a family history of an inherited genetic condition

• Prior to testing, there should be a full discussion of the advantages and disadvantages of the procedures, the implications of the possible test results and subsequent management options, including methods of termination of pregnancy and the available supports.
**Chorionic villus sampling (CVS)**

- This procedure is usually performed from 11 weeks, routinely between 11 and 13 weeks gestation. It should not be performed prior to 10 weeks gestation due to the risk of limb defects.
- A sample of chorionic villus (pre-placental tissue) is removed by a fine needle, either transabdominally, or less frequently transvaginally, under ultrasound guidance (see Figure 6).
- The tissue is used for chromosome analysis, and in some specific situations, may be used for diagnosis (DNA or biochemical analysis) of a genetic condition where there is a family history.
- It is a procedure that can be performed earlier in pregnancy than amniocentesis, and has the benefits of an early scan that may detect anencephaly.
- Some women experience cramping and, occasionally, vaginal bleeding after CVS.
- The miscarriage rate, in experienced hands, is estimated at ~1% above the background risk.

2 In South Australia CVS is sometimes performed between 10 and 11 weeks

**Important points about CVS**

- CVS has a 1% risk of equivocal results. This includes the risk of placental mosaicism – the presence of a mixture of cells with normal and abnormal karyotype, or maternal cell contamination of the sample. In this case, amniocentesis may be necessary to clarify the karyotype of the fetus.
- CVS has a 0.1% rate of failure to detect a pregnancy with a chromosomal anomaly, due to the occasions when there is an abnormal karyotype in the baby, but not in the placenta.
- CVS may not detect fetal chromosomal mosaicism.
- Test results take about one week.
### Amniocentesis

- The procedure is performed from 15 weeks routinely, to approximately 19 to 20 week gestation.
- A sample of amniotic fluid is removed from around the fetus by a fine needle, under ultrasound guidance (see Figure 7).
- Testing is performed on amniotic fluid cells, most of which originate from the fetus, compared with CVS, where placental cells are tested.
- Test results take between one and three weeks.
- Discomfort is usually minimal, though a very small number of women experience pain as the needle passes through the peritoneum.
- The miscarriage rate is lower than that for CVS and estimated to be around 0.5% above the background risk in experienced hands.
- Amniocentesis may not detect mosaicism, because of the limited number of cells counted in a routine test.
- As amniocentesis is a second trimester test, the pregnancy is more advanced when results become available, compared with CVS.
- NB: amniocentesis is not the preferred screening test for neural tube defects. An ultrasound at 18 to 20 weeks gestation is more accurate.

![Figure 7. Amniocentesis](image.png)

### Arranging CVS and amniocentesis

- Refer to a private ultrasound practice or public hospital ultrasound department.
- The woman’s blood group should be given on the request form, as rhesus negative women will require an anti-D injection.
- There are no out-of-pocket costs in the public system if there is an indication for testing.
- For private patients, there are costs for both the sampling procedure and chromosome analysis. Contact service providers for details listed at the end of this section.
Ultrasound diagnostic testing

- May be used to detect:
  > Neural tube defects (anencephaly, spina bifida)
  > Cardiac defects
  > Gastrointestinal malformations (gastroschisis, exomphalos)
  > Limb defects
  > Central nervous system defects
  > Urinary tract anomalies
  > Soft signs that may be associated with underlying chromosomal or other genetic conditions

Genetic testing

Chromosome analysis

- Prenatal diagnostic testing involves fetal or placental cells being examined to look at the number and structure of each chromosome. A full chromosome analysis, called a karyotype, allows the diagnosis of chromosomal abnormalities. A karyotype takes 7 to 14 days and the result will be sent to the referring clinician.

- Where there are strong indications of a fetal anomaly (e.g., a markedly increased risk screening result), or where a preliminary result is required quickly, FISH (fluorescent in situ hybridisation) analysis may also be performed on samples obtained using CVS or amniocentesis. FISH results may be available in 1 to 2 days.

Indications for FISH:

- Fetal anomaly detected on routine second trimester ultrasound scan.
- Markedly increased risk result on a screening test.
- Late gestation.
- Parental anxiety.

Benefits of FISH:

- Provides a quick preliminary result for the presence of Down syndrome and certain other chromosome trisomies within 24 to 72 hours.
- FISH will detect chromosome abnormalities. The number of probes used will determine the type of chromosome abnormalities detected.
  > ‘Three-probe FISH’ will detect Down syndrome and sex chromosome abnormalities
  > ‘Five-probe FISH’ will detect Down syndrome, trisomy 18, trisomy 13 and sex chromosome abnormalities

The limitations of FISH

- FISH can give false positive results, and thus an abnormal result needs to be interpreted cautiously if other indications of trisomy are not present.
- FISH can give false negative results. A normal FISH result only excludes full trisomies of the chromosomes tested (usually 13, 18, 21, X, Y). FISH usually cannot rule out structural abnormalities of these chromosomes, nor trisomies of other chromosomes.
- FISH does not replace a complete chromosome analysis (karyotype) and this should still be completed.
- FISH results may be inconclusive if both normal and abnormal cells are present (mosaicism).
Arranging a FISH test

- FISH is requested by the obstetrician or the ultrasonographer.
- There is no Medicare rebate for FISH.
- The charge for FISH depends on the laboratory doing the testing and the number of probes used.
- Costs for three-probe FISH may be less than for five-probe FISH.
- Contact the pathology or ultrasound service for details of costs.
- Results are usually available in 24 to 72 hours.

Genetic conditions requiring DNA testing

- A woman/couple with a family history of a genetic condition must be referred to Genetics Services as soon as possible, preferably prior to pregnancy.
- Testing for inherited conditions (eg cystic fibrosis or thalassaemia) requires knowledge of the causative genetic mutation in the family. This may require extensive, time-consuming tests before a prenatal test can be offered. Referral once the woman is pregnant may be too late to offer prenatal diagnosis.
- In cases of rarer conditions the laboratory may need to be notified in advance. Some tests are only available interstate or even overseas, and much co-ordination is needed for shipping and testing to ensure a timely result.
- CVS is the preferred diagnostic procedure when a pregnancy is known to be at increased risk of a genetic condition. Prenatal diagnosis of genetic conditions requires the coordination of the sampling procedure, cytogenetic laboratory and DNA laboratory. The woman/couple should therefore be referred to Genetics Services as soon as the pregnancy is confirmed. The time until results are available will depend upon the type of test performed.

Pre-implantation genetic diagnosis (PGD)

- PGD is the genetic testing of embryos prior to implantation in the womb and relies on usual IVF techniques to generate embryos in vitro. Embryos are usually tested at day 3 (6 - 10 cells) after fertilisation.
- If fertilisation using conventional IVF is unsuccessful, ICSI (Intra Cytoplasmic Sperm Injection) technology may be used.
  > As shown below, pre-implantation genetic diagnosis uses assisted reproduction technology (ART). Hormones are used to stimulate a woman's ovaries and enable the collection of a number of eggs or oocytes. After the eggs are removed, the eggs are fertilised in the laboratory with sperm. Those eggs that are successfully fertilised are allowed to divide and multiply for 3-6 days, by which stage they contain about 8 cells or have developed into a blastocyst. Not all fertilised eggs make it to this stage.
  > One or two cells are removed in order to test for the specific genetic condition in question. The removal of these cells does not appear to harm the developing embryo. Only those embryos that do not appear to be affected will be transplanted into the mother’s uterus usually on the same day. Generally, no more than one or two embryos will be transferred to the uterus at any one time to avoid the possibility of multiple births. In some IVF centres, unaffected embryos that are not used can be frozen for transfer in another cycle.

The PGD process

Tests that can be performed

- Identification of sex for diagnostic reasons but not for family balancing.
- FISH analysis to identify chromosome trisomies and translocations.
- DNA testing for selected single gene conditions.
- Testing can only be performed if the gene mutation(s) causing the condition are known and testing for the mutation(s) is accurate on a single cell.
**Advantages of PGD**

- If a woman and her partner are trying to avoid a pregnancy affected with a certain genetic condition, the risk of this can be minimised without termination of the pregnancy.
- Referral for specialised counselling is required. This provides a forum to discuss issues in detail with an experienced counsellor who has been trained in this area.

**Figure 8. Pre-implantation genetic diagnosis**

- Egg + Sperm → Fertilised using IVF techniques
  - Post fertilisation (day 3-6 depending on laboratory)
  - Remove one or two cells for testing
  - Test DNA or chromosomes
    - Genetic condition excluded → Embryo transferred
    - Genetic condition detected → Embryo not transferred

**Limitations of PGD**

- There is no guarantee of achieving a pregnancy. Most couples undergo several cycles of treatment before achieving an ongoing pregnancy.
- Accuracy is high, but not 100%.
- The woman must undergo IVF procedures.
- The procedures and testing are expensive.
- It is time consuming and requires meticulous lab work.
- There is a risk of multiple pregnancy if more than one embryo is implanted.

**Counselling issues**

- Risks and success rates of PGD must be made clear in relation to other methods of avoiding genetic risk.
- There can be personal moral dilemmas regarding the use of embryos not implanted.
- Grief and loss.
- Attitude to prenatal diagnosis
Managing a pregnancy with an abnormal karyotype

(See also Genetics in practice.)

• It may be helpful to discuss the results with the service provider or clinical geneticist prior to informing the woman/couple.

• Pre-test counselling should prepare the woman/couple for the possibility of a chromosome abnormality which may not have been anticipated.

• Listen and give the woman/couple time to absorb the news and consider their options.

• Referral to specialist Genetics Services is recommended for sex chromosome abnormalities and mosaic results and should be considered for all other abnormal karyotypes.

• Not all chromosome abnormalities have a major effect on the baby. Medical texts are often out of date. It is important that the woman/couple receives up-to-date, unbiased information about the potential effects of a chromosome abnormality. Discussion with support groups can be helpful for parents (see Contacts, support and testing).

• Decisions regarding the pregnancy should only be made once there has been a full discussion of the implications of the test results and the management options. This might include referral to Genetics Services, discussion with obstetricians and paediatricians, and referral to the relevant support group (see Contacts, support and testing).

Managing a pregnancy with a fetal anomaly

• Referral of public patients to a high-risk clinic, perinatal management unit or fetal diagnostic unit is strongly recommended for a management plan and coordination of ongoing care. Further prenatal testing may be needed to clarify the diagnosis, e.g. abdominal wall defect may be due to a chromosomal trisomy.

• Pre-test counselling should prepare the woman/couple for the possibility of a structural abnormality which may be detected incidentally.

• Women and families can benefit from detailed discussion with support groups. The Fetal Medicine or Genetics Services will usually arrange for the family to meet clinicians who have experience in the management of babies with disability and birth defects. These services are located in the public and private sector.

• A management plan may include providing the couple with:
  > The opportunity for consultation with appropriate specialists
  > Further diagnostic procedures
  > Further ultrasound scans in the presence of the appropriate clinical specialist (e.g. cardiologist present if cardiac defect is suspected)
  > Genetic counselling
  > Ongoing support if the pregnancy continues to term
  > Specific plans for delivery, postnatal care and support
  > Contact details of the relevant support groups
Counselling regarding termination of pregnancy

- It is common for women/couples to be deeply shocked after receiving difficult/bad news. They often immediately request a termination. It is important to allow some time for the woman/couple to come to terms with the news and consider their decision. This may include discussions with relevant health professionals and support groups.
- If termination of pregnancy is an option, the woman/couple should be encouraged to make their decision based on their personal values and accurate, up-to-date and unbiased information.
- When women/couples have a choice of the method of termination, all options and the associated risks and advantages should be discussed, preferably with an obstetrician or prenatal Genetics Services.
- Whether or not they wish to see the baby after termination should be discussed in advance.
- If a post-mortem examination is required for accurate diagnosis, this should also be discussed in advance.
- Grief after a termination is a normal reaction to the loss of a wanted pregnancy and can be complicated by feelings of guilt and anxiety for future pregnancies.
- Ongoing support for the woman/couple is important, regardless of their decision. Women/couples may turn to their GP for support, or benefit from consultation with a genetic counsellor with experience in prenatal diagnosis. Contact your local AGA Peak Body (see Contacts, support and testing) for a local support group.

Management of a pregnancy identified as increased risk by screening, but found to have a normal fetal karyotype

- The woman/couple will experience a raised level of anxiety, even with the best counselling support.
- After a diagnostic test (such as CVS or amniocentesis followed by karyotyping) excludes a chromosomal condition (Down syndrome, trisomy 18 or 13), the pregnancy remains at increased risk of other fetal anomalies or obstetric complications.
- All women with increased risk following screening tests, but normal fetal karyotypes, should be referred for an 18 to 20 week detailed morphology ultrasound, and be monitored closely throughout the remainder of the pregnancy.
Frequently asked questions

‘What if the woman presents late?’
A woman who is not at increased or high risk of having a baby with Down syndrome and first presents after 20 weeks gestation is limited to an ultrasound scan for fetal anomalies, which should be immediately arranged.

For a woman aged 35 years and over (or 37 in Victoria) at EDD, an amniocentesis with FISH could be considered up to the end of the 20th week, although terminations of pregnancy are usually required to be done at less than 20–22 weeks. This may vary in different States and Territories according to their laws. FISH analysis could be performed to give a preliminary result within 48 hours of the amniocentesis, with the final karyotype result taking up to two weeks. The pregnancy is then fairly advanced and termination of pregnancy may not be available as an option.

‘What do I say to a woman who is anxious while waiting for her results?’
From the time the test is arranged, it is important that the woman be given accurate information and realistic expectations, including the maximum period to wait for test results. She should be informed that the time taken to receive results does not indicate if they will be normal or not. Talking about the most likely outcomes can be helpful, but avoid false reassurance. Often listening to the woman’s anxieties and using counselling skills such as active listening, normalising and acknowledging the distress and uncertainty are useful. Make information available upon request.

‘What do I do if a woman says there is ‘something abnormal’ on a test result but I haven’t received them yet?’
Contact the laboratory that conducts the test to clarify the situation.

‘What do I say to a woman whose Down syndrome risk has increased, but is still below the cut-off for a diagnostic procedure?’
Explore the meaning of this result for the woman. While her risk is greater than other women her age, her risk of having a baby with Down syndrome is still low. Some women may not be prepared to accept a certain level of risk and may still choose to have a diagnostic test.

‘Can a woman have both first and second trimester screening tests?’
Intuitively, more screening will identify abnormalities better – however this does not occur in practice. For a marginal increased detection rate for Down syndrome, the false positive rate will rise substantially. If a woman has both screening tests, she is more likely to be identified at increased risk, and offered an invasive diagnostic procedure. The more invasive procedures performed, the greater the risk of causing spontaneous loss of an unaffected fetus. Therefore, it is strongly recommended not to have both first and second trimester screening tests.
Correcting misunderstandings

'I'm young, so I don’t need to have any tests for Down syndrome’
Although younger women are at lower risk than older women, many babies with Down syndrome are still conceived by women who would not be defined as at increased risk due to their age (ie 35 or 37 years and above). Screening tests should be offered to women of all ages.
Diagnostic testing can follow if requested.

'The tests were all OK, so my baby is normal’
Tests during pregnancy can detect increased risk or presence of certain conditions only. No test, or combination of tests, will detect all birth defects or medical conditions.

'My blood test was normal, so my baby doesn’t have Down syndrome’
Blood/screening tests cannot detect all pregnancies with Down syndrome. A woman with a ‘normal’ (low risk) screening test result does have a chance of having a baby with Down syndrome but this risk is not high enough for diagnostic testing to be indicated.

'The blood test says there’s something wrong with my baby’
Blood/screening tests during pregnancy do not detect birth defects; they indicate which pregnancies have an increased risk of certain genetic conditions and birth defects. Most fetuses with ‘abnormal’ (increased risk) test results do not have Down syndrome. This is an indication for referral for diagnostic procedures.

'The blood test says there is something wrong so I need a diagnostic test’
If the blood/screening test was second trimester maternal serum screening, increased risk results are due to inaccurate dates (if LMP only given) in 30% of cases. Check dates by ultrasound. An increased risk result on a screening test is an indication for diagnostic testing; however, a small number of women choose not to have diagnostic testing.

'If I have another screening test, I might get a better result’
Screening tests are most accurate when done at the correct time in the pregnancy. Retesting is only performed if dates are inaccurate. It is strongly recommended not to have both first and second trimester screening tests (see above, ‘Frequently asked questions’).

'I am over 35 years so I need to have a CVS or amniocentesis’
Women aged 35 years and over (or 37 years in Victoria) at EDD may choose to have a diagnostic test, may prefer the option of screening tests, or may choose to have no tests at all. Women in this age group should be aware that they are more likely to have an increased risk result from a screening test as age is part of the risk calculation, in which case they will then need to consider diagnostic testing.

'It’s not worth having any tests because I wouldn’t terminate the pregnancy’
Some people feel it is beneficial to know if the fetus has an anomaly to prepare for the birth and future. Others prefer to wait until delivery. All women should have the opportunity to consider testing.
### List of fetal medicine services in public hospitals associated with the state genetics services in Australia

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<th>Australian Capital Territory</th>
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<tbody>
<tr>
<td><strong>The Canberra Hospital</strong></td>
<td><strong>Genetic Counsellor, PO Box 11, Woden</strong></td>
<td><strong>ACT 2605</strong></td>
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<tr>
<td></td>
<td><strong>Ph:</strong> (02) 6244 2133</td>
<td><strong>Fax:</strong> (02) 6244 4625</td>
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<td><strong>Royal Prince Alfred Hospital</strong></td>
<td><strong>Department of Molecular and Clinical Genetics,</strong></td>
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<td><strong>Building 65, Level 6 Missenden Road, Camperdown</strong></td>
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<td><strong>Locked Bag 4001, Westmead</strong></td>
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<td><strong>NSW 2145</strong></td>
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<td></td>
<td></td>
<td><strong>Ph:</strong> (02) 9845 3273</td>
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<td><strong>Fax:</strong> (02) 9845 3204</td>
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**Northern Territory**

<table>
<thead>
<tr>
<th>Service</th>
<th>Contact Information</th>
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<tbody>
<tr>
<td>There is currently no clinical genetics service or outreach service available in the Northern Territory</td>
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**Queensland**

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Contact Information</th>
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<tbody>
<tr>
<td>Royal Brisbane Women's Hospital</td>
<td>Antenatal Clinic, Cnr Bowen Bridge &amp; Butterfield Rds, Herston Qld 4029 Ph: (07) 3636 2269 Fax: (07) 3636 5379</td>
</tr>
<tr>
<td>Mater Mother's Hospital</td>
<td>Raymond Terrace, South Brisbane Qld 4101 Ph: (07) 3840 1593 Fax: (07) 3840 1621</td>
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**South Australia**

<table>
<thead>
<tr>
<th>Hospital</th>
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<tbody>
<tr>
<td>Women's and Children's Hospital</td>
<td>South Australian Clinical Genetics Service Youth and Women's Health Service, North Adelaide SA 5006 Ph: (08) 8161 7375 Fax: (08) 8161 6088</td>
</tr>
<tr>
<td>Antenatal Diagnosis and Counselling Service</td>
<td>Department of Obstetrics and Gynaecology Women's and Children's Hospital South Australian Clinical Genetics Service 72 King William Road, North Adelaide SA 5006 Ph: (08) 8161 7633 Fax: (08) 8161 7654</td>
</tr>
<tr>
<td>Perinatal Dysmorphology Group</td>
<td>Department of Obstetrics and Gynaecology Flinders Medical Centre, Bedford Park SA 5042 Ph: (08) 8204 4577 Fax: (08) 8204 3143</td>
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**Tasmania**

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<tr>
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<tr>
<td>Royal Hobart Hospital</td>
<td>Tasmanian Clinical Genetics Service GPO Box 1061L, Hobart Tas 7001 Ph: (03) 6222 8296 Fax: (03) 6222 7961</td>
</tr>
</tbody>
</table>
Testing and pregnancy

Victoria

<table>
<thead>
<tr>
<th>Genetic Health Services Victoria (GHSV)</th>
<th>10th Floor, Royal Children’s Hospital Flemington Road, Parkville Vic 3052 Ph: (03) 8341 6270 Fax: (03) 8341 6390</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinics are conducted in 10 metropolitan and 11 rural and regional centres</td>
<td></td>
</tr>
<tr>
<td>Monash Medical Centre</td>
<td>Monash Medical Centre 246 Clayton Road, Clayton Vic 3168 Ph: (03) 9594 2026 Fax: (03) 9594 6022</td>
</tr>
<tr>
<td>Royal Women’s Hospital</td>
<td>Specialty Genetics Services 132 Grattan Street, Carlton Vic 3053 Ph: (03) 9344 2121 Fax: (03) 9344 2066</td>
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</tbody>
</table>

Western Australia

<table>
<thead>
<tr>
<th>King Edward Memorial Hospital for Women</th>
<th>Fetal Medicine Service 374 Bagot Road, Subiaco WA 6008 Ph: (08) 9340 1525 Fax: (08) 9340 1678</th>
</tr>
</thead>
</table>

Bibliography


Further information


Scroll down the list to find “Prenatal Testing Special tests for your baby during pregnancy”.

28 Testing and pregnancy
Most children born in Australia are born healthy. But about 2 to 3 babies in 100 are born with a condition that means they will need medical care. Some of the conditions can be detected early in pregnancy, while others cannot.

If you are thinking about becoming pregnant, you should talk to your doctor about your particular situation. You may have conditions in the family that you would like to talk about, or you may have health problems, dietary preferences or other issues you wish to discuss.

You should also talk to your doctor about:

- Taking enough of a vitamin called folate, or folic acid. Folate is present in green leafy vegetables, but many women find it hard to eat enough folate naturally. So all women should take extra folate for at least one month before becoming pregnant, as well as for the first three months of pregnancy. This will lower the risk of having a baby with a neural tube defect, which is a problem in the development of the spinal cord (spina bifida) and/or brain (anencephaly).
- Your family history (see fact sheet on 'Your family history').
- Your ancestry. For example, certain genetic disorders of the blood cells, known as haemoglobinopathies (see fact sheet 15 on 'Haemoglobinopathies'), are relatively common in people with a family background from southern Europe, the Middle East, South-East Asia, Africa, the Indian subcontinent, South America, the Caribbean and the Pacific Islands. There are also a number of disorders that are more common in those with Jewish ancestry. People with one of these family backgrounds could be carriers of an altered gene and may wish to consider genetic testing.
- The increased chance for older women of having a baby with Down syndrome or some other chromosome alteration.
- Whether any prescription or other drugs you take could be harmful to a developing baby.
- The potential effects of alcohol and smoking on a developing baby.
- Making sure you are immune to rubella (German measles).

As a result of these conversations, you may benefit from some genetic testing or genetic counselling. Your GP should be able to arrange that, if required.
Contacts and further information

- All states and the ACT have familial cancer services. Contact them through your local state or territory health department.
- Pregnancy and alcohol at http://www.alcoholguidelines.gov.au
- MyDr at http://www.mydr.com.au
- The Centre for Genetics Education at http://www.genetics.edu.au
- HealthInsite at http://www.healthinsite.com
- MedicineNet at http://www.medicinenet.com
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
Most children born in Australia are born healthy. But about 2 or 3 in 100 are born with a condition that means they will need medical care.

Some of the more common conditions are:
- Congenital heart disease
- Disorders of the kidney and bladder
- Hip dislocation at birth
- Club foot
- Down syndrome and other chromosome alterations
- Spina bifida and related conditions, which are known as neural tube defects and which are problems in the development of the spinal cord and/or brain
- Cleft lip and/or palate
- Developmental delay.

Some of these can be detected in pregnancy, while others cannot.

Screening tests and/or diagnostic tests are available for some of these disorders. They are not compulsory – it is your choice whether or not to have these tests.

Before having any tests, you need to consider what you would do if a test came back positive or indicates some degree of risk. What would you do if a test showed your unborn child had an abnormality? Would you consider a termination of pregnancy? Would you not consider one? Would you just like to know, even if you don’t plan to do anything about it? Or would you rather not know?

**Screening tests**

These tests do not give a firm diagnosis, but aim to give parents an idea of whether or not they have a higher than normal risk of having a child with the disorder being screened for.

None are perfect – sometimes screening tests miss the conditions they are meant to detect.

If a screening test picks up an increased risk, then there are diagnostic tests – chorionic villus sampling, amniocentesis or ultrasound – that can sort out whether or not the baby has the disorder.
First trimester screening test

This test is designed to identify women at increased risk of having a baby with Down syndrome, but it can sometimes also identify other problems.

The test has three parts. The first is a blood test at 10 to 12 weeks of pregnancy. The second is an ultrasound, called a nuchal translucency or NT test, at 11 to 13 weeks. The third part is the woman’s age, which is also taken into account.

These three pieces of information are combined to calculate the risk that the baby has Down syndrome. Couples with an increased risk will be offered genetic counselling to consider their choices; the choice of whether or not to have a diagnostic test – either chorionic villus sampling or amniocentesis – to check the baby’s chromosomes.

Nuchal translucency test

Nuchal translucency is used to estimate if a baby is at an increased risk of having a chromosomal abnormality. It uses ultrasound to see and measure a fluid filled sac at the back of the unborn baby’s neck during early pregnancy.

The nuchal translucency test, which is part of the first trimester screening test, can sometimes be done on its own, without the blood test. This ultrasound is carried out between 11 and 13 weeks of pregnancy and is reasonably accurate, but not as accurate as the combined first trimester screening test.

Second trimester maternal serum screening test

This blood test is best done between 15 and 17 weeks of pregnancy, but it can be carried out between 14 and 20 weeks. The second trimester screening test is suitable for women who did not have either the first trimester screening test or the nuchal translucency test. It can tell parents whether the baby is at increased risk of Down syndrome (and/or some other chromosomal alterations) or a neural tube defect, which is a problem in the development of the spinal cord and/or brain.

The second trimester test is not as accurate as the first trimester screening test.

Ultrasound

Most pregnant women will have an ultrasound at 18 to 20 weeks. This ultrasound checks the baby’s growth, the stage of pregnancy, and the amount of amniotic fluid, the position of the baby and placenta. This ultrasound also looks for physical problems such as neural tube defects, heart and kidney malformations, cleft lip and limb abnormalities.

Diagnostic tests

These tests aim to give a firm diagnosis of a potential problem. They are more accurate than screening tests. Like all tests, they are only looking for specific gene alterations or chromosome alterations (see fact sheet on ‘What is a gene?’). They are not perfect and they may occasionally miss something.
Chorionic villus sampling
This test can detect chromosomal alterations as well as genetic conditions, which your doctor knows to look for because they have happened before in the family, or because a genetic screening test has shown that you could have an affected baby.

Chorionic villus sampling is usually done at around 11 weeks of pregnancy and preferably by 13 weeks. Usually, a needle is guided through the abdomen to the tissue that will form the placenta, and a small fragment of tissue is removed. Occasionally a plastic tube is guided through the vagina and cervix instead. In both cases, the procedure is monitored by ultrasound so that the needle or plastic tube is kept away from the baby. Most women find it uncomfortable rather than painful.

Women who have chorionic villus sampling have a slightly increased risk of miscarrying afterwards. The risk is between 1 in 100 and 1 in 200.

The results are usually available in two to three weeks.

Amniocentesis
This test can detect chromosomal alterations. The test can also detect gene alterations, which your doctor knows to look for because they have happened before in the family, or because a genetic screening test has shown that you could have an affected baby.

Amniocentesis is usually done at 15 to 16 weeks of pregnancy and preferably before 20 weeks. A needle is guided into the fluid around the baby and a small amount of fluid is removed. The procedure is monitored by ultrasound so that the needle is kept away from the baby. Most women find it uncomfortable rather than painful.

Women who have amniocentesis have a slightly increased risk of miscarrying afterwards. The risk is about 1 in 200.

The results are usually available in two to three weeks.

Ultrasound
A detailed ultrasound may be used to look for certain disorders that have happened before in the family. Ultrasound can also be carried out at any time if problems arise in the pregnancy.
Contacts and further information

- All states and the ACT have familial cancer services. Contact them through your local state or territory health department.
- Your local hospital antenatal clinic.
- MyDr at http://www.mydr.com.au
- HealthInsite at http://www.healthinsite.com
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
Newborn Screening

**GP’s role**

- Provide information about newborn screening to parents prior to delivery.
- Liaise with testing services if further testing is required or a condition is suspected.

- Newborn screening is a blood test that aims to detect certain rare, genetic and/or metabolic conditions that may be life threatening and/or cause intellectual disability prior to onset of symptoms, with the goal of reducing the effect of the condition on the child through earlier treatment.
- About 1 per 1000 (0.1%) babies tested will be diagnosed with a condition as a result of newborn screening.
- Newborn screening is a test provided for all babies free of charge.
- Blood for testing is collected by heel-prick 48 to 72 hours after birth. The blood is dried onto a newborn screening card.

**The newborn screening process**

- Verbal agreement is required from the parents of the child before the heel-prick test is performed, and must be recorded in the medical notes.
- Newborn screening services produce an information pamphlet for parents to consider before their agreement to perform the test is sought. The pamphlet may also be available in languages other than English.
- When parents raise concerns, the opportunity is provided to discuss the test and address any concerns.
- If parents refuse to give their consent after this discussion, the test is not performed.

**Storage of newborn screening cards**

- Newborn screening services store the cards after testing. Name-identified cards may be used for quality assurance, re-testing or research (with parental consent). After a fixed period (dependent on the State/Territory), cards are destroyed or de-identified for research purposes.
Figure 1. The newborn screening (NBS) process

1. **Baby born**
   - Informed consent sought from parents for NBS
   - Agreement

2. **Agreement still not given**
   - Concerns discussed with parents
   - Agreement

3. **Agreement not given**
   - Test not performed

4. **Sample taken by heel-prick, blood dried on to newborn screening card**
   - Sample sent to newborn screening laboratory

5. **Tests performed**
   - Condition indicated
   - No condition indicated

6. **Condition indicated**
   - Confirmatory tests performed
     - Condition not confirmed
     - Condition confirmed
     - Condition confirmed
     - Management plan initiated
     - Some cards used for quality assurance, retesting or research with parental consent
     - Card destroyed after a defined time or de-identified and returned for possible research

   - Card securely stored by newborn screening laboratory
     - Card destroyed after a defined time or de-identified and returned for possible research

   - Card sent to newborn screening laboratory

Newborn screening results

Where no further testing is required
• For the majority of babies, no condition will be suggested by newborn screening.
• Parents and doctors are not notified of ‘normal’ results.
• Screening does not detect all affected babies, and therefore symptoms in a child warrant further investigation.

Where further testing is required
• Parents will be notified if follow-up testing is required.
• Follow-up testing will be required either because there was a problem with the initial blood sample or because one result was abnormal or borderline.
• About 1 to 2% of babies tested require repeat or subsequent diagnostic testing.
• The majority will receive ‘normal’ results in which case their doctor will be sent the result.
• For metabolic conditions and congenital hypothyroidism, a rapid response to the screening result is necessary as delay in diagnosis increases morbidity.
• Treatment, counselling and support are provided free of charge by the services associated with the Newborn Screening Services in each State or Territory.

Policies governing conditions included in newborn screening
• The Newborn Screening policy developed jointly by the Human Genetics Society of Australasia and the Division of Paediatrics of the Royal Australasian College of Physicians recommends that a condition should be included in newborn screening, provided that:
  > There is benefit for the individual from early diagnosis (ie early treatment/intervention is beneficial)
  > This benefit is reasonably balanced against financial and other costs
  > There is a reliable screening test available
  > There is a suitable system in place to deal with diagnostic testing, counselling, treatment and follow-up of patients identified by the test
Newborn screening

Whilst there is some variation between States and Territories in Australia as to which conditions are screened for, the following conditions are currently screened for Australia-wide:

- Cystic fibrosis
- Phenylketonuria
- Galactosaemia
- Primary congenital hypothyroidism
- Rare metabolic conditions

Cystic fibrosis

- See *Cystic fibrosis* for more detailed information.
- Cystic fibrosis (CF) is primarily a respiratory and gastrointestinal condition affecting approximately 1 in 2500 babies.
- In CF there is reduced function of a protein (CFTR) involved in the transport of chloride ions, resulting in mucus plugging, infection and neutrophil-dominated inflammation in the lungs, and exocrine pancreatic insufficiency in at least 80% of cases.
- CF follows an autosomal recessive pattern of inheritance.
- Carriers for CF are asymptomatic.

**Common clinical features**

- Frequent respiratory tract infections and later, chronic sinopulmonary disease
- Malabsorption, with loose stools and failure to gain weight
- Meconium ileus
- Males have azospermia

**Test**

- Newborn screening for CF is a three-step process as outlined in Figure 2 below. The first step is a screening test for immunoreactive trypsinogen (IRT), (an indirect measure of pancreatic injury that is present at birth in most newborns who have CF) on the dried blood spot specimen. In those with elevated IRT levels, the second step is to test for common mutations in the gene responsible for CF (ΔF508 is the most common – see *Contacts, support and testing* for an explanation of the terminology regarding mutations). The third step is a sweat test for those with heterozygous DNA results.
**Figure 2: Newborn screening for CF**

*This diagram has been adapted from Massie J, 2001. 'How to treat cystic fibrosis', Australian Doctor, 18 May.

Note: In most States, only the common ΔF508 mutation is tested for, and around 5% of babies will be missed by this approach. Some States include other mutations as part of newborn screening. Expanded mutation testing is not used universally however, principally because of cost.

**Treatment**
- Treatment includes monitoring of health, growth and development by a CF clinic in conjunction with the child’s paediatrician or GP, early treatment and prophylaxis for bacterial respiratory infections, physiotherapy, a high calorie diet and pancreatic enzyme replacement.
- Early treatment can slow the progress of CF.

**Implications for other family members**
- Each future sibling of a child with CF has a 1 in 4 chance of also inheriting the condition. Pre-implantation genetic diagnosis (PGD) and prenatal diagnostic testing using direct mutation analysis or linkage studies are available options (see Contacts, support and testing and Testing and pregnancy).
- Relatives of a person with CF may be carriers for the condition and referral to Genetics Services for genetic counselling is recommended. For example, a healthy sibling of a person with CF has up to 2 in 3 chances of being a carrier for CF.
- Similarly, relatives of CF mutation carriers may themselves be carriers for CF and referral is again appropriate.
Phenylketonuria

- Phenylketonuria (PKU), while rare, is one of the most common metabolic conditions affecting newborns, with approximately 1 in 10,000 to 14,000 Australians affected.
- PKU is caused by the absence of a fully active form of the liver enzyme phenylalanine hydroxylase, which is responsible for the conversion of the amino acid phenylalanine to tyrosine.
- Accumulation of phenylalanine and its metabolites in the blood and tissues damages the brain.
- PKU follows an autosomal recessive pattern of inheritance.
- Carriers for PKU are asymptomatic.

### Common clinical features
- Babies with PKU are asymptomatic at birth.
- If untreated, PKU causes severe, progressive intellectual disability.

### Test
- Levels of phenylalanine in the blood are determined using mass spectometry.
- Diagnosis requires confirmation of blood levels and a full metabolic screen on a new blood sample, and possibly an overnight admission to hospital for tests to exclude the rare cofactor disorders of pterin metabolism.

### Treatment
- Patients are treated or monitored by a multi-disciplinary metabolic team including metabolic specialists and dieticians in collaboration with a paediatrician.
- A strictly monitored low-protein diet with special supplements to provide tyrosine and essential amino acids is necessary to avoid the complications of PKU.
- Compliance with the diet (which is highly restrictive) is critical if a child with PKU is to reach their maximum potential.
- It is usually recommended that this diet be continued for life. While there is some dissention about this, it is certain that diet should be continued through the teenage years, and women need to be on this diet if there is any possibility of pregnancy. There are risks for adolescents and adults who stop this diet.
- Monitoring of blood phenylalanine levels is important. It is an essential amino acid and levels must be sufficient for the body's requirements, but low enough to avoid damage to the central nervous system.

### Implications for other family members
- A woman with PKU who is planning a pregnancy must, before conception, start a comprehensive diet aimed at keeping phenylalanine levels within a defined range. Phenylnalanine level must be monitored frequently to prevent it reaching a level that would be teratogenic to the fetus.
- Each future sibling of a child with PKU has a 1 in 4 chance of also inheriting the condition. Pre-implantation genetic diagnosis (PGD) and prenatal diagnostic testing using direct mutation analysis or linkage studies are available options (see Contacts, support and testing and Testing and pregnancy).
- Relatives of a person with PKU may be carriers for the condition and referral to Genetics Services for genetic counselling is recommended.
- Similarly, relatives of PKU mutation carriers may themselves be carriers for PKU, and referral is again appropriate.
**Galactosaemia***

*Note that Victoria does not currently screen for galactosaemia*

- Classical galactosaemia has an incidence of about 1 in 50,000.
- It is caused by a deficiency in the enzyme galactose-1-phosphate uridylytransferase that results in the accumulation of galactose and galactose-1-phosphate.
- Galactosaemia follows an autosomal recessive pattern of inheritance.
- Carriers for galactosaemia are asymptomatic.

### Common clinical features

- Babies with galactosaemia are asymptomatic at birth, but develop symptoms in the first week of life.
- If untreated, galactosaemia causes the following and may be fatal:
  - Failure to thrive
  - Lethargy
  - Vomiting
  - Liver disease
  - Jaundice
  - Cataracts
  - Intellectual disability
  - Septicaemia

### Test

- Levels of galactose and galactose-1-phosphate in the blood are determined by enzyme assay.
- The enzyme galactose-1-phosphate uridyly transferase is measured on the same dried blood spot if the metabolite levels are elevated.
- Rarely, other forms of galactosaemia, mainly galactokinase deficiency, are diagnosed by this test.

### Treatment

- A diet completely free of galactose is necessary to avoid the complications of all forms of galactosaemia.
- For newborn babies, this requires a special formula.

### Implications for other family members

- Each future sibling of a child with galactosaemia has a 1 in 4 chance of also inheriting the condition.
  - Pre-implantation genetic diagnosis (PGD) and prenatal diagnostic testing using direct mutation analysis or linkage studies are available options (see *Contacts, support and testing* and *Testing and pregnancy*).
- Relatives of a person with galactosaemia may be carriers for the condition and referral to Genetics Services for genetic counselling is recommended.
- Similarly, relatives of galactosaemia mutation carriers may themselves be carriers for galactosaemia, and referral is again appropriate.
Primary congenital hypothyroidism

- Affects approximately 1 in 4000 babies.
- Primary hypothyroidism is due to an absent, ectopic or malfunctioning thyroid gland.
- About 80% of cases result from an absent or ectopic thyroid. About 20% of cases are due to dyshormonogenesis, a collection of metabolic disorders affecting the production of thyroid hormone.
- Congenital hypothyroidism is not usually inherited, but rather occurs sporadically. Therefore, other family members are not usually at increased risk.

**Common clinical features**
- Newborns may be asymptomatic at birth. Early neonatal signs are prolonged jaundice (>7 days), umbilical hernia, constipation, macroglossia, feeding problems and hypotonia.
- Without treatment, developmental delay and growth retardation occur. One form of dyshormonogenesis (Pendred syndrome) is associated with deafness.

**Test**
- Thyroid stimulating hormone (TSH) is assayed by an immunoassay.
- Elevated levels of TSH are an indication of primary hypothyroidism.
- Further serum thyroid function tests are required for diagnosis. In addition, a thyroid scan and audiology test may be performed in some tertiary centres.
- If the thyroid gland is normally sized and placed, transient hypothyroidism might be present, and follow-up testing may be recommended.

**Treatment**
- Thyroxine is taken orally for life.
- Regular blood tests are required to monitor thyroxine and TSH levels.
- Supervision by a paediatrician is recommended.

**Implications for other family members**
- 95% of these cases occur sporadically and subsequent pregnancies are not at increased risk.
- 5% of cases are due to a single mutation. These are inherited as autosomal recessive conditions with a 1 in 4 risk of recurrence in subsequent pregnancies.
Other amino acidopathies:

- These conditions result from other defects in the metabolism of amino acids in which organic acids are not produced. This may be a defect in a transporter or an enzyme of amino acid metabolism.
- These conditions are rare but can be life threatening.
- Treatment consists of a low-protein diet, supplements and medications.
- Early treatment is associated with reduced mortality and morbidity.

Test

- Mass spectrometry is used to detect abnormal metabolites in the blood.
- Results are usually available within 24 to 48 hours of sample receipt at the laboratory.
- Additional testing may be necessary for confirmation of diagnosis.

Rare metabolic conditions

- Newborn screening also includes a screen for over 20 additional rare metabolic conditions using mass spectrometry.
- See list of ‘Rare metabolic conditions that are recommended in Australian newborn screening programmes’ that may be included.
- Most of these metabolic conditions follow a pattern of autosomal recessive inheritance.
- In some cases the baby may present in crisis prior to diagnosis by newborn screening.
- Three groups of conditions can be detected: disorders of fatty acid oxidation, organic acidaemias, and other acidopathies.

Disorders of fatty acid oxidation:

- Defects in the ‘burning’ of fatty acids.
- The most common condition is medium chain acyl-coA dehydrogenase (MCAD) deficiency:
  > Can be life threatening
  > Children with this condition are usually well but may suffer metabolic decompensation if fasting
  > May present with lethargy and coma, or hypoglycaemic seizure, during intercurrent illness
  > Management consists of avoiding fasting and taking special measures when the child has an intercurrent infection
  > Newborn siblings of known cases are at high risk in the first 3 to 4 days of life, and should be monitored and offered 3-hourly feeds

Organic acidaemias/acidurias:

- These conditions result from defects in metabolism of, most commonly, amino acids.
- These conditions are rare but can be life threatening.
- Some of these conditions require treatment with a low-protein diet, supplements and medications.
- Early treatment is associated with reduced mortality and morbidity.
Rare metabolic conditions that are recommended in Australian newborn screening programmes:
These conditions are detected by measuring levels of specific metabolites in the blood:

**Amino acidopathies**
- Argininosuccinic acidemia (ASA lyase deficiency)
- Citrullinaemia (argininosuccinate synthase deficiency, citrin deficiency)
- Tyrosinemia (fumaryl acetoacetase deficiency, tyrosine aminotransferase deficiency)
- Homocystinuria (cystathionine beta-synthase deficiency)
- Maple syrup urine disease (MSUD, classical and intermediate)
- Phenylketonuria (including pterin deficiencies)

**Fatty acid oxidation disorders**
- MCAD (medium chain acyl-CoA dehydrogenase deficiency)
- LCHAD (3-hydroxy long chain acyl-CoA dehydrogenase deficiency)
- VLCAD (very long chain acyl-CoA dehydrogenase deficiency)
- Carnitine transporter defect
- CPT-I deficiency (carnitine-palmitoyl-CoA acyltransferase I deficiency)
- CPT-II deficiency (carnitine-palmitoyl-CoA acyltransferase II deficiency)
- CACT deficiency (carnitine-acylcarnitine translocase deficiency)
- TFP (trifunctional protein deficiency)
- MADD glutaric acidemia type II (multiple acyl-CoA dehydrogenase deficiency)

**Organic acid disorders**
- Beta-ketothiolase deficiency (mitochondrial acetoacetyl-CoA thiolase deficiency)
- Glutaric acidemia type I (glutaryl-CoA dehydrogenase deficiency)
- Multiple carboxylase deficiency (holocarboxylase synthetase deficiency)
- 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCoA lyase) deficiency
- Isovaleric acidemia
- Methylmalonic acidurias (mutase deficiency, CblA, CblB, CblC, CblD defects)
- Propionic acidemia
- 3-methylcrotonyl-CoA carboxylase deficiency
Bibliography


All babies in Australia have a screening test done within a few days of birth if their parents agree. The test is done by pricking the baby’s heel, getting some blood and sending it to a laboratory.

At the laboratory, the blood is tested for about 25 different conditions. The most common ones are:

- Congenital hypothyroidism, in which not enough thyroid hormone is produced and which causes intellectual disability if untreated
- Phenylketonuria, which causes intellectual disability if untreated
- Cystic fibrosis, which affects the lungs and gastrointestinal system
- Galactosaemia, which causes serious problems such as poor growth, liver disease and intellectual disability if untreated.

These conditions are serious and sometimes life-threatening. Diagnosing them early can make an enormous difference to a child’s life.

More than 99 babies out of 100 will have normal results. Parents are not contacted if the results are normal.

Occasionally, the testing is unclear. Parents will be contacted so that the blood test can be re-done and there may be other tests. It can take a couple of weeks to sort things out.

Only about one baby in 1000 is found to have any of the problems being looked for. Parents are contacted and an appointment will be made to see a specialist. More tests will be done to confirm that the problem is present and treatment will be started.

Please note: like every test, this one is not perfect. It is possible for a child to have one of these conditions, but for the testing to miss it. So even if your baby has had these tests and you have been told all is well, the tests do not provide a guarantee. If you are worried about your child, see a doctor.

**Contacts and further information**

- All states and the ACT have familial cancer services. Contact them through your local state or territory health department.
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)

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Cancer in the family

GP’s role

- Take, and keep updated, a family history (see Genetics in practice), including:
  - Three generations, maternal and paternal 1st and 2nd relatives (where possible).
  - Cultural and ethnic background, e.g., gene mutations associated with breast and ovarian cancer are more common in Ashkenazi Jews.
  - The primary site and age at diagnosis of any cancer (where possible). For those people who have imprecise knowledge of cancer in their relatives, death certificates are a good source of information.
- Using the family history, assess risk according to national guidelines: average or slightly above average, moderate and potentially high risk.
- If you are unsure about the significance of the family history, contact a familial cancer service for advice (see list of familial cancer services).
- Manage average/moderately increased risk patients using the management guidelines.
- Refer patients identified at potentially high risk to a familial cancer service or Genetics Services.

- Familial cancer describes clustering of certain cancers in families. Only 5 to 10% of cancers involve a strongly inherited predisposition.
- Familial cancers are usually characterised by:
  - Multiple close relatives on the same side of the family with cancers of the same or related type
  - Cancers occurring at an early age
  - An individual with two or more primary cancers of the same or different type

Familial cancer services

- These services provide risk assessment, genetic counselling and, if appropriate, genetic testing for a causative mutation where there is a strong family history of cancer and/or where tumour testing suggests a genetic susceptibility to cancer.
- Predictive genetic testing to determine risk in unaffected members of high risk families requires the identification of the family-specific mutation in the gene involved. Mutation searching for familial cancer mutations is an expensive and often lengthy process that can potentially produce ‘informative’ results (see Contacts, support and testing).
- Those found to have inherited a gene mutation that confers a high risk of developing cancer can be offered individualised cancer screening and strategies for prevention.
- Blood relatives proven not to have inherited the family-specific mutation still have an average risk of developing the cancer based on their age and should follow recommendations for population screening. However, they can be spared the intensive screening needed by someone who has/may have the mutation.
- Sometimes a causative mutation cannot be found in a person with a strong family history or clinical expression of a cancer known to involve genetic susceptibility. In this case, it cannot be presumed that a mutation is not present. Therefore 1st relatives should be considered to be at 50% (or 1 in 2) risk of having inherited a mutation and participate in a screening and prevention program according to appropriate guidelines.
The following information has been taken from the Australian Cancer Network (2006), *Familial aspects of bowel cancer: a guide for health professionals.*


- The lifetime risk of colorectal cancer to age 75 years in the general population is 1 in 17 for men and 1 in 26 for women.
- Although colorectal cancer mainly affects people over the age of 50 years, it can occur at any age. There are about 12,600 new cases and 4,700 deaths each year.

### Genetics

- The causes of colorectal cancer are complex and involve interactions between environmental and genetic factors. Cancer develops as the result of a multi-step process involving genetic mutations in cells lining the colorectal wall. Most colorectal cancers arise from adenomatous polyps.
- Between 2 to 5% of patients with colorectal cancer have inherited a mutated gene that predisposes them to colorectal cancer.
- The types of colorectal cancer known to involve genetic susceptibility are familial adenomatous polyposis (FAP) including MUTYH–associated polyposis (MAP), and hereditary non-polyposis colorectal cancer (HNPCC). Table 1 summarises the genes known to be involved in genetic susceptibility to colorectal cancer.
- Mutation searching for familial colorectal cancer gene mutation is an expensive and often lengthy process that can potentially produce ‘uninformative’ results (see *Contacts, support and testing*).

> Sometimes a causative mutation **cannot** be found in a person with FAP or HNPCC. In this case, it cannot be presumed that a mutation is not present. Therefore, 1° relatives should be considered to be at 50% (or 1 in 2) risk of having inherited a mutation and participate in a screening and prevention program according to national guidelines (see ‘Category 3 (potentially high risk)’ detailed below).

> Asymptomatic family members shown not to have the mutation causing cancer in the family on predictive testing, still have an average risk of developing colorectal cancer based on their age and should follow recommendations for population screening. However, they can be spared the intensive screening needed by someone who has/may have the mutation.

### Table 1. Genes in which mutations are known to be associated with an inherited predisposition to colorectal cancer and other sites

<table>
<thead>
<tr>
<th>Inherited cancer syndrome</th>
<th>Mutated gene</th>
<th>Mode of inheritance</th>
<th>Population frequency</th>
<th>Risk of colorectal cancer to age 75 years in those identified with a family specific mutation</th>
<th>Other sites with an increased risk of cancer (% lifetime risk)</th>
</tr>
</thead>
</table>
| HNPCC                     | Mismatch repair (MMR) | Autosomal dominant | ~ 1 in 1,000         | 70 - 90%                                                                                           | Endometrium (40%)  
Ovary and stomach (10%)  
Urinary tract, small intestine, pancreas, bilary tree and brain |
| FAP                       | APC         | Autosomal dominant | ~ 1 in 10,000        | 90 - 100%                                                                                            | Duodenum (5%)                                             |
| MAP                       | MUTYH       | Autosomal recessive | ~ 1 in 50 - 100      | Under investigation, thought to be 90 - 100%                                                         | Duodenum (4 - 25%)                                        |
Familial adenomatous polyposis (FAP)

- A rare condition, usually due to a mutation in one of the two copies of a tumour suppressor gene called the *adenomatous polyposis coli* (APC) gene (see Table 1).
- Without treatment, those with proven FAP have a lifetime risk of colorectal cancer of almost 100%.
- Individuals with a mutated APC gene usually develop hundreds of adenomas throughout the colon and rectum that may appear in the teenage years or in early adult life. If left untreated, one or more of these adenomas will progress to cancer, often at an early age, so prophylactic surgery must be considered.
- Pathological lesions may occur outside the large colon, such as upper GI cancer (especially of the duodenum), desmoid tumours and osteomas.
- Inheritance of a mutated APC gene follows an autosomal dominant pattern. Sometimes there is no family history because a new mutation has occurred around the time of conception. This happens in 20 to 30% of cases.
MUTYL-associated polyposis (MAP)

- A rare condition similar to FAP.
- Follows a pattern of autosomal recessive inheritance.
- Due to mutations in both copies of the base excision repair MUTYH gene (see Table 1).

**Management**

- Flexible sigmoidoscopy yearly or second yearly starting from age 12 to 15 years until polyposis develops, then prophylactic colectomy.
- If family genetic testing is inconclusive and no polyposis develops, sigmoidoscopy reduced to every 3 years after the age of 35 years, then change to population screening if examinations normal to age 55 years.
- Prophylactic surgery, eg restorative proctocolectomy, is appropriate for those with proven FAP.
Hereditary non-polyposis colorectal cancer (HNPCC)

- Also sometimes known as ‘Lynch syndrome’.
- Without treatment, the lifetime risk is less than for FAP but may be up to 80% in some families.
- A rare condition due to an inherited mutation in a copy of one of a group of DNA mismatch repair (MMR) genes (see Table 1).
- Inheritance of a mutated MMR gene follows an autosomal dominant pattern. Sometimes there is no family history because some individuals with a mutated MMR gene will not develop cancer (or have not done so at the time the history is taken).
- Individuals most likely to have a mutated MMR gene copy are those from families with a strong history of colorectal cancer, characterised by: early age of onset (<50 years) and a tendency for proximal colonic malignancy or multiple colorectal cancers.
- Cancers occurring outside the large colon may also be a feature. The most common of these is endometrial cancer, but the syndrome also includes cancers of the ovary, stomach, small colorectal, renal pelvis or ureter, biliary tract, and brain.
- Cancers associated with HNPCC tend to show high levels of microsatellite instability and may lack immunohistochemical expression of MMR proteins in tumour tissue.
- Consideration of tumour testing should be given for all patients diagnosed with colorectal cancer aged 50 years or under, or where there is a suggestive family history.

Management

- Colonoscopy every one to two years from age 25 years, or five years earlier than the youngest diagnosis in the family (whichever comes first). Faecal occult blood testing (FOBT) may be offered in alternate years or to subjects unwilling to accept colonoscopy.
- There are options for surveillance at other sites, usually starting from age 25 to 35 years.
- Prophylactic surgery may be appropriate for some.

Figure 1. Example of a potentially high risk HNPCC cancer family
Prevention

- The following healthy lifestyle recommendations may be protective against colorectal cancer and should be recommended to people of all ages:
  > Exercise regularly
  > Maintain a healthy weight including:
    - Limit energy intake
    - Reduce dietary fat (<25% of calories as fat)
    - Consume poorly-soluble cereal fibre
    - Eat vegetables and fruit
    - Avoid or limit alcohol consumption
    - Do not smoke (or quit smoking)

Assessing colorectal cancer risk based on family history

Asymptomatic patients can be classified into one of three categories of relative risk based on their family history.

Category 1 (average or slightly above average risk)
Covers about 98% of the population.

Average risk
- No personal history of colorectal cancer, colorectal adenomas or chronic inflammatory colorectal disease and no confirmed family history of colorectal cancer.

Slightly above average risk
- One 1\textsuperscript{st} or 2\textsuperscript{nd} relative with colorectal cancer diagnosed at age 55 years or older.
- Two 1\textsuperscript{st} or 2\textsuperscript{nd} relatives diagnosed with colorectal cancer at age 55 years or older, but on different sides of the family.

Management
- For those aged 50 years or over:
  > Offer FOBT at least every two years from the age of 50 years. Inform that a positive test result will require further investigation
  > A national colorectal cancer screening program, using FOBT, is being implemented in Australia for people between the ages of 55 and 74 years. The screening program began in mid 2006 with an offer of FOBT, initially for those aged 55 and 65 years. Advice on access to FOBT for those outside the national screening program is available from the Cancer Helpline (Phone 131120)
  > In addition, it is acceptable to offer sigmoidoscopy (preferably flexible) every 5 years
  > Update family history regularly
Category 2 (moderately increased risk)

- Covers about 1 to 2% of the population.
- One 1° relative with colorectal cancer diagnosed before the age of 55 years (without the potentially high risk features detailed below).
- Two 1° or one 2° relative(s) on the same side of the family with colorectal cancer diagnosed at any age (without the potentially high risk features detailed below).

Management

- Offer colonoscopy at 5 year intervals or 10 years younger than the earliest diagnosis of colorectal cancer in the family (whichever comes first).
- Advise that 70 to 90% of people in this group will not develop cancer.
- Update family history regularly. Reassess risk if there is a new diagnosis of cancer in the family.
- If you are unsure about the significance of the family history, contact a familial cancer clinic for advice (see list of familial cancer services).

Category 3 (potentially high risk)

- Covers much less than 1% of the population.
- Three or more 1° relatives or a combination of 1° and 2° relatives on the same side of the family diagnosed with colorectal cancer.
- Two or more 1° or 2° relatives on the same side of the family diagnosed with colorectal cancer, plus any of the following high risk features:
  - Multiple colorectal cancers in a family member
  - Colorectal cancer before the age of 50 years
  - A family member who has/had an HNPCC-related cancer (endometrial, ovarian, stomach, small colorectal, renal pelvis or ureter, biliary tract, brain cancer)
- At least one 1° or 2° relative with a large number of adenomas throughout the large colon (suspected FAP).
- Member of a family in which a gene mutation that confers a high risk of colorectal cancer has been identified (for FAP, HNPCC or MAP).

Management

- Offer referral to a familial cancer service either directly or through Genetics Services (see list of familial cancer services).
- Not all patients with the above family history will have a genetic susceptibility to colorectal cancer.
- Genetic testing is available for some to clarify risk.
- Advise that their risk of colorectal cancer is potentially high but surveillance and prophylactic measures are available.
  - Refer to a colorectal cancer specialist to plan appropriate surveillance and management
  - Specific recommendations for those identified with FAP or HNPCC are detailed above
Familial breast and ovarian cancer

- Breast cancer
  - Affects about 1 in 11 women before the age of 75 years
  - The most common cause of cancer deaths in women
  - Also occurs in men, but it is rare
- Epithelial ovarian cancer
  - Affects about 1 in 100 women before the age of 75 years
  - The leading cause of death from gynaecological cancer
- There are many risk factors that can influence a woman’s chance of developing breast or ovarian cancer.
- The main risk factors are:
  - Being a woman
  - Increasing age: most women who develop breast or ovarian cancer are over the age of 50
  - Family history of breast and/or ovarian cancer
- Family history does not necessarily imply an inherited genetic cause. However, at least 1 to 5% of breast cancers, and 5 to 10% of ovarian cancers, involve the inheritance of a mutated gene.

Genetics
- Mutations in the BRCA1 and BRCA2 genes are associated with both breast and ovarian cancer (see Table 2).
- Environment also plays a role in causing breast and ovarian cancer, but the specific environmental factors are still unknown. They may include exposure to various hormones, and radiation, lifestyle and diet.
- Mutations in some other genes have also been associated with an increased risk of developing breast or ovarian cancer, as well as some other cancers (see Table 2).
- The vast majority of affected women do not carry an inherited mutation in a known breast or ovarian cancer predisposing gene.
- Inheriting a gene mutation in the BRCA1 or BRCA2 gene means an individual inherits a predisposition or susceptibility to breast and ovarian cancer.
- In women who develop breast cancer before the age of 40 years or bilateral breast cancer, the prevalence of BRCA1 and BRCA2 gene mutations is higher.
- Inheriting a mutation in a BRCA1 or BRCA2 gene also slightly increases the chance that a person will develop other cancers.
- Inherited mutations in the BRCA1 and BRCA2 genes:
  - Follow an autosomal dominant pattern of inheritance, meaning that if a person has a mutated copy of one of these genes, each of their children has a 50% chance of inheriting the mutation.
  - Can be inherited from either the mother or the father.
  - Are thought to be involved in 1 to 5% of all breast cancers and up to 10% of all ovarian cancers.
- Mutation searching for a familial breast and ovarian cancer gene mutation is an expensive and often lengthy process that can potentially produce ‘uninformative’ results (see Contacts, support and testing).
  - Sometimes a causative mutation cannot be found in a person with breast or ovarian cancer. In this case, it cannot be presumed that a mutation is not present. Therefore 1° relatives should be considered to be at 50% (or 1 in 2) risk of having inherited a mutation and participate in a screening and prevention program according to national guidelines (see ‘Category 3’ for breast cancer and ‘Category 2 (potentially high risk)’ for ovarian cancer, detailed below).
  - Asymptomatic family members, shown on predictive testing not to have inherited the mutation conferring a predisposition to breast and ovarian cancer, still have an average risk of developing these cancers based on their age. These individuals should follow recommendations for population screening. However, they can be spared the intensive screening needed by someone who has/may have a mutation.
Breast cancer

Assessing breast cancer risk based on family history

- Asymptomatic patients can be classified into one of three categories of relative risk based on their family history of breast cancer.

Category 1 (average or slightly above average risk)

- Covers more than 95% of the female population.
- No confirmed family history of breast cancer.
- One 1° relative diagnosed with breast cancer at any age.
- Two 2° relatives on the same side of the family diagnosed with breast cancer at the age of 50 years or older.
- Two 1° or 2° relatives diagnosed with breast cancer, at age 50 years or older, but on different sides of the family (i.e., one on each side of the family).

Management

- It is recommended that women 50 to 69 years attend the BreastScreen Australia program for free screening mammograms every two years. Women aged 40 to 49 years are also eligible for this program, but mammographic screening is not recommended for women younger than 40 years.
- A firm recommendation regarding clinical breast examination (CBE) is not possible as there is no evidence to either encourage or discourage the use of CBE as a screening method in women of any age.

Category 2 (moderately increased risk)

- Covers less than 4% of the female population.
- One 1° relative diagnosed with breast cancer before the age of 50 years (without the additional high risk features in ‘Category 3’ below).
- Two 1° relatives, on the same side of the family, diagnosed with breast cancer (without the additional high risk features in ‘Category 3’ below).
- Two 2° relatives, on the same side of the family, diagnosed with breast cancer, with at least one before the age of 50 years (without any of the additional high risk features in ‘Category 3’ below).

Management

- A more precise risk assessment and management plan may be available from a specialist cancer service or familial cancer service (see list of familial cancer services).
- While evidence about optimal management strategies for this group does not exist, the following recommendations are based on expert consensus opinion: advise the woman to, at the very least, attend for screening mammograms as recommended for Category 1 additional surveillance, such as mammography from a younger age, or more frequently; this should be considered on an individual basis.
- A firm recommendation regarding clinical breast examination (CBE) is not possible as there is no evidence to either encourage or discourage the use of CBE as a screening method in women of any age.
- Discuss possible participation in a relevant approved clinical trial for the prevention of breast cancer.
Category 3 (potentially high risk)

- Covers much less than 1% of the female population.
- Includes women who are at potentially high risk of ovarian cancer (see ‘Category 2’ for familial ovarian cancer below)
- Two 1\textsuperscript{st} or 2\textsuperscript{nd} relatives on one side of the family diagnosed with breast or ovarian cancer plus one or more of the following features on the same side of the family:
  > Additional relative(s) with breast or ovarian cancer
  > Breast and ovarian cancer in the same women
  > Breast cancer diagnosed before the age of 40 years
  > Ashkenazi Jewish ancestry (Jews from Central and Eastern Europe)
  > Bilateral breast cancer
  > Breast cancer in a male relative
- One 1\textsuperscript{st} or 2\textsuperscript{nd} relative diagnosed with breast cancer at age 45 years or younger plus another 1\textsuperscript{st} or 2\textsuperscript{nd} relative on the same side of the family with sarcoma at age 45 years or younger.
- Member of a family in which the presence of a high risk breast cancer gene mutation has been established.

Management

- Offer referral to a familial cancer service directly or through Genetics Services (see list of familial cancer services) for risk assessment and management planning.
- Genetic testing may be available if the woman wishes to clarify her genetic risk or that of her family, or wishes to consider risk-reducing surgery.
- Develop an individual surveillance program in consultation with a cancer specialist (including familial cancer services where possible). Discussion should include information about the advantages and disadvantages of a program that may include:
  > Attending regular clinical breast examinations
  > Annual mammography with or without imaging techniques
  > Surveillance for ovarian cancer
- The age at which screening commences may be influenced by aspects of family history.
- Although this should be determined on an individual basis, it is generally accepted practice to begin screening at least five years prior to the age of diagnosis of the closest relative.
- Discuss possible participation in a relevant approved clinical trial for the prevention of breast cancer.
Ovarian cancer

Assessing ovarian cancer risk based on family history

- Asymptomatic patients can be classified into one of two categories of relative risk based on their family history of ovarian cancer.

**Category 1 (average OR moderately increased risk)**

- Covers more than 99% of the female population.
- No confirmed family history of epithelial ovarian cancer.
- One 1° or 2° relative diagnosed with ovarian cancer at any age (provided the family is not of Ashkenazi Jewish ancestry and does not have any additional cases of breast cancer).
- Two 1° or 2° relatives diagnosed with ovarian cancer, but on different sides of the family (i.e., one on each side of the family).

**Management**

- Screening for the general population for epithelial ovarian cancer cannot be justified on the basis of the low prevalence of ovarian cancer and the inadequate sensitivity of the currently available tests.
- Advise about the current best practice for the early detection of cancers in the population.
- Advise to report promptly any health changes.

**Category 2 (potentially high risk)**

- Covers much less than 1% of the female population.
- Includes women who are at potentially high risk of breast cancer (see ‘Category 3’ for familial breast cancer above).
- One 1° relative diagnosed with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry.
- One woman with ovarian cancer at any age, and another with breast cancer diagnosed before the age of 50 years, where the women are 1° or 2° relatives of each other.
- Three or more 1° or 2° relatives on the same side of the family diagnosed with any cancers associated with HNPCC (see ‘Familial colorectal cancer’).
- A woman suspected of having HNPCC (see ‘Familial colorectal cancer’).
- Member of a family in which the presence of a high-risk ovarian cancer gene mutation has been established.
- Two 1° or 2° relatives on the same side of the family diagnosed with epithelial ovarian cancer, especially if one or more of the following high risk features occurs on the same side of the family:
  - Additional relative(s) with breast or ovarian cancer
  - Breast and ovarian cancer in the same women
  - Bilateral breast cancer
  - Breast cancer in a male relative
  - Breast cancer diagnosed before the age of 40 years
Management

- Offer referral to a familial cancer service directly or through Genetics Services (see list of familial cancer services) for risk assessment and management planning.
- Genetic testing may be available if the woman wishes to clarify her genetic risk or that of her family, or wishes to consider risk-reducing surgery.
- As bilateral salpingo-oophorectomy has been shown to reduce the risk of ovarian and breast cancer in women with a mutation in BRCA1 or BRCA2, advise the woman to see a gynaecological oncologist to discuss her options.
- Should a woman choose not to undergo risk-reducing surgery, an appropriate individual surveillance program should be developed in consultation with a cancer specialist (including familial cancer clinics where possible). This program may include:
  > Promptly reporting any health changes
  > Transvaginal ultrasound (the age at which this commences may depend on the family cancer history and if the high-risk ovarian cancer gene mutation has been established in the woman or her family)
  > CA125 measurements (after menopause). There is no evidence that these tests reduce mortality from ovarian cancer but they may be considered for women who have not undergone risk-reducing salpingo-oophorectomy
  > Surveillance relevant to other cancers, eg attending for clinical breast examination, mammography for breast cancer; or other surveillance if the family cancer history is consistent with HNPCC
- Discuss possible participation in a relevant approved clinical trial.

Figure 2. Example of a potentially high risk breast/ovarian cancer family

- Breast cancer
- Ovarian cancer
- Lung cancer
- ‘d’ - deceased
- ‘dx’ - diagnosed
Table 2. Genes in which mutations are known to be associated with an inherited predisposition to breast or ovarian cancer and possible cancer at other sites

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation frequency</th>
<th>Major sites at risk</th>
<th>Risk of cancer at age 75 years where a family specific mutation has been identified</th>
<th>Other sites with up to a 10% lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>1/1,000 &lt;sup&gt;b&lt;/sup&gt;</td>
<td>Breast, Ovary</td>
<td>40 - 80%</td>
<td>Prostate</td>
</tr>
<tr>
<td>BRCA2</td>
<td>1/1,000 &lt;sup&gt;b&lt;/sup&gt;</td>
<td>Breast, Ovary</td>
<td>40 - 80%</td>
<td>Male breast, prostate, pancreas</td>
</tr>
<tr>
<td>p53 (Li Fraumeni syndrome)</td>
<td>1/10,000</td>
<td>Breast, Bone, Soft Tissue</td>
<td>50% &lt;10 - 50%</td>
<td>Brain, lung, adrenal gland</td>
</tr>
<tr>
<td>Mismatch repair genes (HNPCC) &lt;sup&gt;c&lt;/sup&gt;</td>
<td>1/1,000</td>
<td>Large Colon, Uterus</td>
<td>50 - 80%</td>
<td>Ovary, other gastrointestinal, renal tract, brain</td>
</tr>
</tbody>
</table>

<sup>a</sup> There is a wide range of risk associated with mutations in these genes

<sup>b</sup> 1 in 100 for individuals of Ashkenazi Jewish ancestry

<sup>c</sup> HNPCC refers to hereditary non-polyposis colorectal cancer
Melanoma


- In Australia, melanoma affects about 1 in 26 men and 1 in 34 women in their lifetime.
- The chance of developing melanoma increases with age, but affects people of all age groups.
- Melanoma is one of the most common forms of cancer in young adults.
- Risk factors for melanoma include:
  > A personal history of:
    - Melanoma occurring at an early age (median age of onset for familial melanoma is 33 years)
    - Multiple primary melanomas
    - Large number of naevis (more than 10 on the arms and 200 on the body)
    - The presence of multiple atypical (dysplastic) naevi
  > A family history of:
    - Multiple cases of melanoma on the same side of the family
    - Melanoma occurring at an early age
    - Ocular melanoma
    - Pancreatic carcinoma in more than one family member

**Genetics**

- An inherited mutation in certain genes is thought to be involved in up to 5% of cases of melanoma.
- Two genes have so far been identified where it is believed that inherited mutations are associated with a predisposition to melanoma:
  > CDKN2A codes for proteins that have a central role in controlling the process of cell growth and division. Gene mutations in the CDKN2A gene have been found in approximately 20 to 50% of families in different populations with three or more affected 1o relatives
  > CDK4, mutations in which have been found in fewer families with multiple cases of melanoma
- Gene mutations in the CDKN2A and CDK4 genes follow an autosomal dominant pattern of inheritance, meaning that, if a person has a mutated copy of one of these genes, each of their children has a 50% chance of inheriting this gene mutation.
- Inheriting a gene mutation in one of these genes means an individual inherits a predisposition or susceptibility to melanoma, and the risk of developing melanoma is higher than the population risk.
- The indicators that melanoma in a family could be due to an inherited mutation include:
  > Three or more 1o or 2o relatives with melanoma
  > Several primary melanomas in one person
  > Young age of onset of the first melanoma (less than 40 years)
  > The presence of atypical or unusual moles early in life
- These families would be candidates for participating in research programs where genetic testing for mutations in candidate genes may be performed.
Management

- All individuals at potentially high risk of melanoma should be offered referral directly to a familial cancer service or through Genetics Services (see list of familial cancer services).
- Surveillance should be arranged in association with the familial cancer service, and discussions will include:
  - Education about sun protection and early detection
  - Intensive surveillance, commencing from age 10 years, including:
    - Three-monthly self-examinations
    - Whole-body photography, which may be used as a baseline
    - Skin surface microscopy as a baseline
    - Skin and scalp examination by a dermatologist, 6- or 12-monthly
    - A low threshold for the excision biopsy of any suspicious lesions
Prostate cancer

http://www.ncci.org.au/services/prostate_GPresources.htm

- Family history is a risk factor for prostate cancer.
- Male 1° relatives of men with prostate cancer <60 years have at least a two-fold increased risk of prostate cancer.
- The incidence is further increased in families where two or more members on the same side of the family are affected.
- This could be as a result of family members sharing susceptibility genes, and/or being exposed to similar lifestyle and environment.
- Male carriers of a gene mutation associated with breast cancer (BRCA1 or BRCA2) have up to a 10% lifetime increased risk of prostate cancer.

Genetics

- The inheritance of prostate cancer predisposition is not well understood and no highly penetrant gene contributing to a significant proportion of familial prostate cancer has yet been identified.
- Currently, genetic testing for prostate cancer is still in the research phase, but it is anticipated that genetic testing may eventually be used to accurately identify high-risk men who may benefit from targeted screening.

Management

- Offer digital rectal examination and prostate specific antigen (PSA) screening if the man has a 1° relative with prostate cancer < 60 years.
- There is however currently considerable debate over population screening for prostate cancer using digital rectal examination, and testing for prostate specific antigen (PSA) levels in the male population over age 50 years.
- The natural history of the indolent form of the condition may warrant no other management than observation. However, attempts to detect an early operable condition could be warranted in people who have two or more family members affected by prostate cancer at a young age, since it is in these families that prostate cancer tends to occur in younger men.
Other rare cancer syndromes for which genetic testing is available in Australia

Von Hippel-Lindau syndrome (VHL syndrome)

- Population frequency is approximately 1 in 36,000 births.
- VHL is characterised by:
  > Haemangioblastomas of the brain, spinal cord, and retina
  > Renal cysts and clear cell renal cell carcinoma
  > Phaeochromocytoma
  > Endolymphatic sac tumours
- Caused by a mutation in the VHL tumour suppressor gene.
- Inheritance follows an autosomal dominant pattern.
- 20% of VHL is a result of a sporadic gene mutation.

Multiple endocrine neoplasia (MEN) 1 and 2

- Both MEN 1 and MEN 2 have a population frequency of approximately 1 in 30,000 births.
- MEN 1 is characterised by the development of a combination of endocrine tumours including:
  > Parathyroid tumours
  > Pituitary tumours
  > Endocrine tumours of the gastro-entero-pancreatic (GEP) tract
  > Carcinoid tumours
- MEN 2 is characterised by the development of
  > Medullary carcinoma of the thyroid
  > Phaeochromocytoma.
- MEN 1 and 2 follow an autosomal dominant pattern of inheritance, however
  > 10% of MEN 1 cases are sporadic
  > 5% of MEN 2 cases are sporadic
Bibliography


## List of familial cancer services

<table>
<thead>
<tr>
<th>Australian Capital Territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Counsellor</td>
</tr>
<tr>
<td>Canberra Hospital</td>
</tr>
<tr>
<td>PO Box 11</td>
</tr>
<tr>
<td>Woden, ACT 2605</td>
</tr>
<tr>
<td>Ph: (02) 6244 2133 Fax: (02) 6244 4625</td>
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<table>
<thead>
<tr>
<th>New South Wales</th>
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<tbody>
<tr>
<td>Royal Prince Alfred Hospital</td>
</tr>
<tr>
<td>Department of Molecular and Clinical Genetics</td>
</tr>
<tr>
<td>Missenden Rd</td>
</tr>
<tr>
<td>Camperdown, NSW 2050</td>
</tr>
<tr>
<td>Ph: (02) 9515 5080 Fax: (02) 9550 5389</td>
</tr>
<tr>
<td>St George Hospital</td>
</tr>
<tr>
<td>Hereditary Cancer Clinic</td>
</tr>
<tr>
<td>Cancer Care Centre</td>
</tr>
<tr>
<td>Gray St</td>
</tr>
<tr>
<td>Kogarah, NSW 2217</td>
</tr>
<tr>
<td>Ph: (02) 9350 3815 Fax: (02) 9350 3958</td>
</tr>
<tr>
<td>St Vincent’s Hospital</td>
</tr>
<tr>
<td>Family Cancer Clinic</td>
</tr>
<tr>
<td>Victoria Rd</td>
</tr>
<tr>
<td>Darlinghurst, NSW 2011</td>
</tr>
<tr>
<td>Ph: (02) 8382 3395 Fax: (02) 8382 3386</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Northern Territory</th>
</tr>
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<tbody>
<tr>
<td>Genetic Counselling</td>
</tr>
<tr>
<td>Familial Cancer Unit c/- South Australian Clinical Genetics</td>
</tr>
<tr>
<td>Women’s and Children’s Hospital</td>
</tr>
<tr>
<td>North Adelaide, SA 5006</td>
</tr>
<tr>
<td>Ph: (08) 8161 7375 Fax: (08) 8161 6088</td>
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<table>
<thead>
<tr>
<th>Queensland</th>
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<tbody>
<tr>
<td>Genetic Health Queensland</td>
</tr>
<tr>
<td>Herston Rd</td>
</tr>
<tr>
<td>Herston, QLD 4029</td>
</tr>
<tr>
<td>Ph: (07) 3636 1686 Fax: (07) 3636 1987</td>
</tr>
</tbody>
</table>
### South Australia

Familial Cancer Unit  
South Australian Clinical Genetics Service  
Women’s and Children’s Hospital  
North Adelaide, SA 5006  
Ph: (08) 8161 6995 Fax: (08) 8161 7984

### Tasmania

Tasmanian Clinical Genetics Service  
Royal Hobart Hospital  
PO Box 1061L  
Hobart, TAS 7001  
Ph: (03) 6222 8296 Fax: (03) 6222 7961

### Victoria

- The Royal Melbourne Hospital  
  Genetic and Family Cancer Clinic  
  C/- Royal Melbourne Hospital  
  Parkville, VIC 3050  
  Ph: (03) 9342 7151 Fax: (03) 9342 4267

- The Jack Brockhoff Foundation Familial Cancer Centre  
  Peter MacCallum Cancer Institute  
  Locked Bag 1, A’Beckett St  
  Melbourne, VIC 3052  
  Ph: (03) 9656 1199 Fax: (03) 9656 1539

- Familial Cancer Genetics Unit  
  Genetic Health Services Victoria  
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  Flemington Rd  
  Parkville, VIC 3052  
  Ph: (03) 8341 6201 Fax: (03) 8341 6390

- Familial Cancer Centre  
  Monash Medical Centre  
  Clayton, VIC 3168  
  Ph: (03) 9594 2026 Fax: (03) 9594 6022

### Western Australia

Familial Cancer Program  
King Edward Memorial Hospital  
Level 3, Agnes Walsh House  
374 Bagot Rd  
Subiaco, WA 6008  
Ph: (08) 9340 1603 Fax: (08) 9340 1725
Cancer sometimes runs in families, but not to the extent that many people think.

Nobody really understands why cancers occur in some people and not others. But it is clear that the risk of getting cancer is influenced by a combination of factors such as what we eat, how we live our lives, the environment around us and our genetic background. Only about 5 to 10 people out of 100 who get cancer have a strong genetic indicator, which would suggest a high likelihood of getting the condition.

That may not seem true. Everybody knows families where quite a few people have had cancer. But families tend to eat similar foods, live similar lifestyles and live in similar environments – it is not only the genes that are causing problems.

Cancers that do run in families and might have a genetic alteration underlying them tend to be:

- Cancers that usually affect several relatives from the same side of the family.
- Cancers that are found fairly early in life.
- Where some people in the family may have had two or more separate cancers, of either the same or a different type.

The most common types of cancer that run in families are:

- Breast and ovarian cancer, which often go together in families.
- Bowel cancer, which can go together with certain cancers elsewhere in the body.

**Breast and ovarian cancer**

More than 90 women out of 100 with breast or ovarian cancer did not get the condition through inheriting the genes associated with breast and ovarian cancer.

You might think there is a strong genetic indicator that there is a high likelihood of the condition occurring in your family if:

- Two or more close relatives (grandmother, mother, aunt, sister, niece) on the same side of the family developed breast cancer before the age of 50, or ovarian cancer before the age of 40, and
  - There is an additional relative or relatives who had breast or ovarian cancer.
  - A family member had cancers in both breasts.
  - A female relative had both breast and ovarian cancer.
  - A male in the family had breast cancer.
  - You have Jewish ancestry.

Obviously, you would also take note if someone in the family has been told they have an altered breast or ovarian cancer gene.
The main genes involved with breast cancer and ovarian cancer are well known – they are BRCA1 and BRCA2. Note that everybody has these genes, which normally protect against cancer. Problems only arise if one of these genes is altered so that it doesn't work properly anymore and no longer stops the cancer developing. One way of thinking about this is that the cancer protection gene has become faulty.

Women with an altered BRCA1 gene have an increased risk of developing both breast cancer and ovarian cancer. This risk is thought to be between 40 and 80 in every 100 cases for breast cancer and between 10 and 60 in every 100 cases for ovarian cancer.

Women with an altered BRCA2 gene have similar increased risks. They also have an increased risk of pancreatic cancer.

Men with an altered BRCA1 gene have an increased risk of breast and prostate cancer. Men with an altered BRCA2 gene have an increased risk of breast, prostate and pancreatic cancer.

Note that inheriting a faulty gene only means inheriting a high likelihood of getting cancer – it does not mean inheriting cancer. A large proportion of those who inherit the faulty gene will not develop the cancer.

Testing can look for alterations in BRCA1 and BRCA2. But genetic counselling should come first, as there are many things to discuss beforehand; testing is expensive and interpreting the test result is sometimes difficult.

People who have breast or ovarian cancer in the family and whose doctor thinks they are at high risk of having one of these conditions, should discuss a referral to a familial cancer clinic. There, the family history will be examined carefully and options such as genetic testing will be discussed.

People who have breast or ovarian cancer in the family and whose doctor thinks they are at moderate risk of having one of these conditions, should ask for a referral to a familial cancer clinic to talk about the best way to reduce their risk of cancer.

**Bowel cancer**

More than 95 people in 100 with bowel cancer have not inherited it.

You may think you have a high likelihood of getting bowel cancer if:

- Two or more close relatives (grandparents, parents, brothers, sisters, aunts and uncles) on the same side of the family developed bowel cancer;

  and

  - Bowel cancer was diagnosed before the age of 50.
  - A family member had two or more bowel cancers.
  - There are certain other cancers in the family (see HNPCC).
  - A close family member (grandparent, parent, brother, sister, aunt and uncle) with bowel cancer also had a large number of benign growths or polyps, in the bowel.

Obviously, you would also take note if someone in the family has been told they have an altered bowel cancer gene.
Among those who do have a genetic indicator that points to a high likelihood of getting the condition, there are three main conditions to consider – hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP). HNPCC and FAP show an autosomal dominant pattern of inheritance. MAP shows an autosomal recessive pattern of inheritance (see fact sheet 2 on "How do genetic conditions occur?").

People with HNPCC also have an increased risk of developing cancer of the uterus, ovary, stomach and other sites.

People with FAP or MAP also have an increased risk of developing cancers in the duodenum (which connects the stomach and the bowel) and other sites.

Testing can look for alterations in the HNPCC, FAP and MAP genes. But genetic counselling should usually come first, as there are many things to discuss beforehand; testing may be expensive and interpreting the test result is sometimes difficult.

People who have bowel cancer in the family and whose doctor thinks they are at high risk of having one of these conditions, should discuss a referral to a familial cancer clinic.

People who have bowel cancer in the family and whose doctor thinks they are at moderate risk of having one of these conditions, should have a regular examination of the bowel with a colonoscope.

**Contacts and further information**

- All states and the ACT have familial cancer services. Contact them through your local state or territory health department.
- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email [gtis-australia@unimelb.edu.au](mailto:gtis-australia@unimelb.edu.au) or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
Cardiovascular conditions
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<th>Section</th>
<th>Page</th>
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<td>Cardiomyopathies</td>
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<td>Investigations</td>
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<tr>
<td>Management</td>
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Cardiovascular conditions

GP’s role

- Refer to cardiac/lipid/Genetics Services for:
  - Diagnosis of the underlying cardiac condition in the family (commonly this will be a clinical rather than a genetic diagnosis)
  - Estimation of the genetic risk for family members and appropriate genetic testing if available
- Family screening of at-risk individuals in association with specialist services including genetic counselling.
- Initiation of appropriate preventive strategies as indicated.
- Refer to relevant support group (see Contacts, support and testing).

Familial hypercholesterolaemia (FH)

Clinical features

- Diagnostic criteria for familial hypercholesterolaemia are based on the modified UK criteria:
  a: DNA mutation
  b: Tendon xanthomas in patient or 1^o/2^o relative
  c: Family history MI <50 years in 2^o or <60 years in 1^o relative
  d: Family history of cholesterol >7.5 in 1^o or 2^o relative
  e: Cholesterol >7.5 (adult) or >6.7 (age <16 years)
  f: LDL-C >4.9 (adult) or >4.0 (age <16 years)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Combinations of criteria as described above</th>
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<tr>
<td>Definite FH</td>
<td>(e or f) + a</td>
</tr>
<tr>
<td>Probable FH</td>
<td>(e or f) + b</td>
</tr>
<tr>
<td>Possible FH</td>
<td>(e or f) + (c or d)</td>
</tr>
</tbody>
</table>

- Affected individuals suffer metabolic and clinical features including:
  > Lifelong marked hypercholesterolaemia (low density lipoprotein cholesterol (LDL-C) > 5 mmol/L)
  > Cholesterol deposition that occurs in tissues: tendinous xanthomata (particularly involving the Achilles), corneal arcus, palpebral xanthomas and xanthelasma
  > Atherosclerosis beginning in early childhood. Children with FH are known to have endothelial dysfunction and increased carotid intima media thickness (CIMT), both surrogate markers of cardiovascular disease
  > Rapidly progressive carotid atherosclerosis in FH during childhood, at a rate proportional to plasma LDL cholesterol levels
Genetics

• FH is due to an inherited susceptibility to high levels of LDL-C. Other environmental factors such as a lifestyle and diet associated with coronary heart disease (CHD) must be present for the condition to develop.
• Elevated LDL generally follows a pattern of autosomal dominant inheritance with approximately 50% risk for offspring and siblings of affected family members.
• FH involves mutations in the genes for the LDL receptor (LDLR), the LDL ligand and a protease known as NARC-1.
• To date, about 1000 mutations have been identified in the LDLR gene but most are family-specific which makes the search for an unknown mutation challenging and expensive.
• Homozygotes typically have higher levels of LDL and a more severe phenotype than heterozygotes.
• A mutation in the apolipoprotein B gene (APOB) may result in a clinical and biochemical picture that is indistinguishable from classic FH, although cholesterol levels are generally not as elevated and tendon xanthomas are less common.
• An autosomal recessive form of FH has also been described. The clinical picture of this condition is similar to that of individuals who are homozygous for the mutations in genes associated with the autosomal dominant form of the condition, although it is generally less severe and more variable, with greater responsiveness to therapy.

Prevalence

• Familial hypercholesterolaemia is thought to account for about 5 to 10% of CHD that occurs before the age of 55 years. It is estimated that, of the roughly 40,000 cases of FH in Australia, about 20% are diagnosed and less than 10% are being adequately treated. However, less than 5% have been formally identified.
• In the general population, frequency of FH heterozygosity for a mutation in the genes involved in the autosomal dominant form of FH is about 1 in 500, while the homozygous state is exceedingly rare (about 1 in 1,000,000 people).
• There is greater frequency of the heterozygous state in people whose ancestry is:
  - Christian Lebanese, 1 in 170
  - Afrikaaner (Dutch descent), 1 in 70 to 1 in 100
  - French Canadian, 1 in 200 to 1 in 270

Investigations

• Genetic testing to determine if a high cholesterol level is associated with FH should be aimed at those with ancestry from the population groups above.

Management

• If detected early, FH can be treated by lifestyle modification and statins.
• Without treatment:
  - 50% of heterozygous males will develop CHD before the age of 50 years and 100% by the age of 70 years
  - Approximately 12% of the heterozygous females will have CHD by age 50 years. However this increases to 74% by age 70 years
• In homozygotes with mutations in the genes involved in the autosomal dominant form of FH, drugs are less effective and it is typically lethal at an early age without special intervention, such as LDL aphaeresis and liver transplantation.
• Refer to a specialist lipid clinic or Genetics Services.
Implications for family members

- Children of an affected parent should be screened when a cholesterol-lowering diet can be safely implemented and advice given about avoidance of smoking.
- Statin therapy is only used in children from severely affected families.
- Genetic testing at an appropriate age can assist with identification of risk status as:
  > A normal lipid profile does not necessarily rule out carrier status for an FH-causing gene mutation
  > A false negative and false positive rate based on LDL levels alone in affected families is approximately 15%

Coronary artery disease (CAD)

Genetics

- The vast majority of cases of CAD are not due to a single genetic factor as is the case for conditions like familial hypercholesterolaemia or other rare disorders of lipoprotein metabolism.
- It is likely that there are a number of different genes influencing individual plasma lipid levels that interact with environmental factors to increase CAD susceptibility. Polymorphisms of one set of genes called the apolipoprotein-E (APO) genes have also been implicated in this process.
- Risk for death from ischaemic heart disease (ICHD) is increased over population risk for 1° relatives. The risk is different for relatives of male and female family members affected with ICHD (see Table 2).
- Research is continuing to define the genetic contribution of APO genes to ICHD and genetic testing remains on a research basis.

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Male index case</th>
<th>Female index case</th>
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</thead>
<tbody>
<tr>
<td>Male 1° relative</td>
<td>1 in 12 (5-fold increase)</td>
<td>1 in 10 (6.5-fold increase)</td>
</tr>
<tr>
<td>Female 1° relative</td>
<td>1 in 36 (2.5-fold increase)</td>
<td>1 in 12 (7-fold increase)</td>
</tr>
</tbody>
</table>

Hypertension

Genetics

- There are a number of different genes involved in predisposing to hypertension that interact with environmental factors such as diet, obesity and stress.
- For individuals with two or more affected relatives, risk is increased 3-fold over the general population risk.
- Primary pulmonary hypertension is very rare but is dominantly inherited in some families.
  > The gene BMPR2 (bone morphogenetic protein receptor, type II) has been identified as causative
  > Contact Genetics Services (see Contacts, support and testing) if patients seem to have this form of hypertension with a suggestive family history
Cardiomyopathies

(a) Familial hypertrophic cardiomyopathy (FHCM)

**Clinical features**
- Hypertrophic cardiomyopathy (HCM) is a primary cardiac disorder characterised by hypertrophy, usually of the left ventricle.
- The clinical presentation of HCM can vary from minimal or no symptoms with an asymptomatic course, to the development of serious complications including heart failure and sudden death.
- Symptoms may include:
  - Chest pain
  - Symptoms related to pulmonary congestion
  - Impaired consciousness

**Genetics**
- Most cases of HCM are hereditary with the most common form of inheritance being autosomal dominant.
- There is considerable genetic heterogeneity in FHCM.
- There are at least ten genes associated with FHCM.
- The most common set of genes are those that code for various components of the cardiac sarcomere.
- There is also considerable variability in the clinical impact of different gene mutations within the same gene and also between individuals with the same mutation.

**Prevalence**
- FHCM is estimated to affect 1 in 500 in the Australian population.
- In 5% of individuals who are found to have causative gene mutations, multiple mutations (e.g., two different mutations in the same gene compound heterozygotes, or mutations in two different genes – double heterozygotes) are found.
- Current data suggests that these individuals have a more severe phenotype compared to individuals who are heterozygous or in whom no gene mutation has been identified.

**Investigations**
- 1° relatives of affected individuals should have regular cardiac screening including investigations such as echocardiography and ECG.
- The suggested time intervals for clinical screening of unaffected at-risk family members should follow the intervals outlined in Table 2.
- Affected individuals will require regular cardiac investigations and monitoring of symptoms.
- Genetic testing is currently available in commercial laboratories overseas, although it is likely that genetic testing will become available in Australia in the future.
Management

- The clinical management of HCM is complex in part due to the heterogeneous symptoms exhibited by affected individuals as well as the marked variability in the natural history of the disease. Many treatment options are available to HCM patients including:
  - Lifestyle modifications, eg avoiding competitive sports (in all patients with HCM)
  - Use of pharmacological agents, eg calcium channel blockers, beta blockers, and diuretics
  - For those with significant left ventricular outflow tract obstruction with symptoms unresponsive to drug therapy, surgical intervention may be indicated
  - The use of ischaemic cardiomyopathy (ICM) therapy in the prevention of sudden death

(b) Dilated (congestive) cardiomyopathy (DCM)

Clinical features

- DCM is a myocardial disorder characterised by dilation and contractile dysfunction of the left, plus or minus, right ventricles.
- Up to 50% of ‘idiopathic’ cases of DCM have a positive family history of the disease (familial DCM). There are no specific clinical features that reliably distinguish familial from non-familial DCM.
- Some families have a clinical presentation that is characterised by DCM alone, while in other families DCM may be associated with:
  - Other cardiac manifestations such as conduction-system disorders, valve defects, atrial/ventricular septal defects or left ventricular non-compaction
  - Non-cardiac manifestations, such as skeletal myopathy, partial lipodystrophy and/or sensorineural deafness

Genetics

- DCM is a genetically and clinically heterogeneous condition that can affect newborns, children, adolescents, adults, and the elderly.
- The condition may be the end result of damage from a variety of agents, such as alcohol, viruses and some other conditions.
- However, at least 30% of cases of DCM are inherited (familial DCM).
- Familial DCM may follow a pattern of autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance.

### Table 2. Recommended frequency of clinical screening for unaffected family members

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Frequency of clinical screening (yearly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>2 - 3</td>
</tr>
<tr>
<td>11 - 20</td>
<td>1</td>
</tr>
<tr>
<td>21 - 30</td>
<td>2 - 3</td>
</tr>
<tr>
<td>31+</td>
<td>3 - 5</td>
</tr>
</tbody>
</table>
Prevalence
- The prevalence is around 1 in 2000 births.

Investigations
- 1° relatives of affected individuals should have cardiac screening including investigations such as echocardiography and ECG.
- Affected individuals will require regular cardiac investigations and monitoring of symptoms.
- Several genes have been identified but genetic testing is on a research basis only.

Management
- Affected family members with DCM should receive standard pharmacological management as indicated by the severity of symptoms and signs of heart failure.
- For asymptomatic at-risk family members, periodic cardiac screening (ECG and trans-thoracic echocardiography) is recommended.
- The frequency of follow-up assessment should be determined by the average age of onset of the disease in symptomatic family members and ‘suspicious’ echocardiographic changes, and may range from 6-12 months to 5 years.

Congenital heart conditions

Genetics
- Most cases of congenital heart conditions are the result of mutations in multiple genes and/or an interaction between single or multiple mutated genes and the fetal environment.
- Familial conditions due to a mutation in single genes or chromosomal abnormalities are rare.
- Severity and presentation are very variable perhaps because of the effects of modifier genes and/or environmental influences.
- Genetic counselling is important to identify the possible genetic basis (see Contacts, support and testing).

Prevalence
- Nearly 1 in 100 newborns have a congenital heart condition. It is the leading non-infectious cause of death in this age group.

Investigations
- Where there is a family history of a congenital heart condition, a more detailed fetal ultrasound scan of the heart should be performed during pregnancy.

Management
- About 1/3rd of those affected will need surgical or catheter-based intervention in the first year of life.
- With developments in surgical techniques, the mortality rate for surgical repair of some common conditions, such as tetralogy of Fallot, is currently less than 3%.

Implications for other family members
- The population risk of having a child with a congenital heart condition is 0.5 to 1%.
- Relatives of a family member affected with a congenital heart condition are at increased risk for having a child with a congenital heart condition (see Table 3).
Table 3. Risks for relatives of a family member affected with a congenital heart condition

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Risk to relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected family member is an isolated case</td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>2-3%</td>
</tr>
<tr>
<td>Half-siblings or other 2° relatives</td>
<td>1-2%</td>
</tr>
<tr>
<td>Offspring of:</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>2-3%</td>
</tr>
<tr>
<td>Mother</td>
<td>5-6%</td>
</tr>
<tr>
<td>More than one affected family member</td>
<td></td>
</tr>
<tr>
<td>Two affected siblings</td>
<td>10%</td>
</tr>
<tr>
<td>Sibling and parent</td>
<td>10%</td>
</tr>
<tr>
<td>More than 2 affected 1° relatives</td>
<td>About 50%</td>
</tr>
</tbody>
</table>

**Long QT syndrome (LQTS)**

**Clinical features**
- LQTS is a group of familial conditions that is an important cause of unexpected sudden death, especially in children and young adults.
- LQTS most commonly presents with syncope and sudden death during or following exercise in otherwise fit and healthy young people.
- Cardiovascular manifestations include:
  - Prolonged QT interval on ECG
  - Syncope
  - Ventricular fibrillation
  - Rapid ventricular tachycardia
  - Sudden cardiac death
- Symptoms usually develop during childhood, but may occur at any age.

**Genetics**
- LQTS is a group of ion channel conditions. Abnormal function of cardiac ion channels lead to cardiac arrhythmias.
- At least eight genes are known to be involved.
- Two major clinical syndromes with LQTS have been characterised on the basis of the pattern of inheritance:
  - The more common autosomal dominant form with a pure cardiac phenotype (Romano-Ward syndrome)
  - A rarer autosomal recessive form characterised by the co-existence of cardiac abnormalities and congenital deafness and especially long QT intervals (Jervell and Lange-Nielsen variant)

**Prevalence**
- Prevalence is around 1 in 5000.
Management
• Refer to cardiologist for clinical cardiac assessment, involving ECG and exercise tests.
• Genetic testing results can help guide management, particularly in asymptomatic at risk relatives. Refer to Genetics Services to discuss the availability and value of genetic testing (see Contacts, support and testing).
• Treatment of choice for most individuals with LQTS is drug therapy with beta-adrenergic blockers. Beta blockers may be used prophylactically for gene-positive asymptomatic children and adults.
• Treatment with an implantable automatic cardioverter-defibrillator (ICD) may be indicated for some individuals. ICDs can be used in conjunction with anti-arrhythmic drug therapy.

Inherited conditions of connective tissue with cardiovascular effects

A number of connective tissue conditions that follow a pattern of autosomal dominant inheritance are characterised by cardiovascular manifestations. These include Marfan syndrome and Ehlers Danlos syndrome Type IV.

(a) Marfan syndrome

Clinical features
• Marfan syndrome affects three major systems: ocular, skeletal and cardiovascular.
  > Ocular effects include myopia, present in most people with Marfan syndrome, and displaced lens, seen in ~50% of cases
  > Skeletal effects include unusually long, slender limbs and fingers (arachnodactyly), hollow and pigeon chest, scoliosis and joint hypermobility
  > Cardiovascular effects are the most life-threatening. These are characterised by a dilatation of the ascending aorta, leading to cardiomyopathy and congestive heart failure, and aortic dissection or rupture, associated with a degeneration of the elastic fibres in the tunica media of the aorta. This is seen in about 90% of cases of Marfan syndrome
• Exercise and pregnancy, resulting in higher cardiac output, increases susceptibility to aortic rupture.
• Mitral valve prolapse is also common.

Genetics
• Approximately 15% of cases of Marfan syndrome are due to a spontaneous mutation occurring for unknown reasons at or following conception (de novo cases).
• Follows a pattern of autosomal dominant inheritance.
• Is caused by mutations in the FBN1 gene which encodes fibrillin-1, a major protein component of the extracellular matrix structures (microfibrils) found in the aorta, suspensory ligaments of the lens, and in connective tissue of bone.
• Several hundred different mutations have been found in the fibrillin gene.

Prevalence
• Prevalence is around 1 in 10,000.
Management
- Refer to cardiologist for clinical cardiac assessment.
- Refer to Genetics Services for counselling regarding implications for other family members and discussion of genetic testing, if available.
- Treatment involves:
  > Drug therapy (beta-adrenergic blockers)
  > Advice to avoid heavy exercise and contact sports
  > Regular ophthalmological examination

(b) Ehlers Danlos syndrome type IV

Clinical features
- Spontaneous rupture or dissections of the aorta or large- to medium-sized arteries in the second to third decade of life due to an abnormality in the structural integrity of the arterial walls.
- Hypermobility of skin and joints, skin fragility and bruising.

Genetics
- Ehlers Danlos syndrome is a group of conditions caused by mutations in various genes encoding the collagen polypeptides and their synthesis.
- Type IV syndrome (vascular type) is rare.
- Follows a pattern of autosomal dominant inheritance.
- Is caused by mutations in the gene encoding type III collagen.

Management
- Refer to cardiologist for clinical cardiac assessment.
- Refer to Genetics Services for counselling regarding implications for family members and discussion of genetic testing, if available.

Further information
National Heart Foundation of Australia Heartline, Ph: 1300 362787.
Bibliography


myDr. http://www.mydr.com.au

National Organisation for Rare Disorders (NORD). http://www.rarediseases.org

NetDoctor. http://www.netdoctor.co.uk


Most heart conditions have a genetic contribution.

For some of them, the main problem is an alteration in one gene. Conditions like this include:
- Familial hypercholesterolaemia
- Some types of cardiomyopathy, such as hypertrophic cardiomyopathy
- Some types of arrhythmias.

For most heart conditions, however, the disorder is associated with having several genes that indicate a high likelihood of getting the condition, together with lifestyle and environment. Conditions like this include:
- High blood pressure
- Heart attacks
- Most congenital heart defects.

If you or someone in your family has a heart condition, including problems with high blood pressure or high cholesterol, then it is worth looking at your family history (see fact sheet on ‘Your family history’) and discussing it with your doctor.

In some cases, you and other members of your family might be asked to see doctors, be examined and have blood or other tests to look for potential signs of heart disease.

Only a small proportion of people with heart disease will need to see a genetic counsellor or have any form of genetic testing.

**Familial hypercholesterolaemia**

People with familial hypercholesterolaemia have very high levels of cholesterol in their blood throughout their life. The walls of the arteries are affected in childhood and heart disease strikes at an earlier age than usual if the condition is not treated.

Without treatment, about half of men with familial hypercholesterolaemia will have heart disease by the time they are 50 and all will have heart disease by the time they are 70. In a very small number of affected men, heart disease comes on in their 20s. Women are affected too, although usually not as severely.

A number of different genetic alterations can be involved – they all follow a pattern of autosomal dominant inheritance in families (see fact sheet on ‘How do genetic conditions occur?’).

While familial hypercholesterolaemia can occur in any family, it is more common in people whose ancestry is Lebanese, Dutch Afrikaaner or French Canadian.
High blood pressure
In most people, high blood pressure is caused by a number of factors such as diet, weight and stress. Genetics also plays a part.

There are likely to be a number of different genes involved in high blood pressure. However, there is no specific test for a genetic alteration that would determine if a person had a high likelihood of having high blood pressure.

Congenital heart defect
Heart defects that exist from birth are known as congenital heart defects. Congenital heart defects affect nearly 1 in 100 babies. Some of these heart defects are very serious – about a third of affected babies need an operation in the first year of life – while others are not so serious. Some get better with time.

Usually, congenital heart defects are caused by a combination of factors, including genetic alterations. But, usually, there is no single genetic cause and no genetic test that can be done.

People with congenital heart defects in the family should tell their doctors and consider genetic counselling to find out their risk of having a baby with the condition. Pregnant women with congenital heart disease in the family can have a very detailed ultrasound in mid-pregnancy to see whether or not their child is affected.

Cardiomyopathy
The term cardiomyopathy covers a range of conditions in which the heart muscle does not work as well as it should.

There are two main types of cardiomyopathy – hypertrophic and dilated.

Hypertrophic cardiomyopathy means the muscles of the heart become thicker and do not work as well as they should. Many people with hypertrophic cardiomyopathy have an underlying genetic alteration and, in most cases, there is an autosomal dominant pattern of inheritance (see fact sheet on 'How do genetic conditions occur?

Dilated cardiomyopathy means the muscles of the heart have stretched and loosened, something like a balloon that has been over-inflated. Most people with dilated cardiomyopathy do not have an underlying genetic alteration – it is usually caused by other factors such as viral infection.

No genetic testing is available yet in Australia for cardiomyopathy, except in research studies. The immediate family of people with hypertrophic cardiomyopathy or unexplained dilated cardiomyopathy should see their doctors about having their heart tested.
Arrhythmias

An arrhythmia is a disturbance of the normal heart rhythm. Most people with arrhythmias do not have a known genetic alteration. But there are two types of arrhythmias that have an underlying genetic component – the long QT syndrome and a condition known as Brugada disease.

These conditions can cause arrhythmias, fainting spells or sudden death in children or young adults. Close relatives may need to see a cardiologist to check whether they also have the condition. If a gene alteration is identified in an affected person, close family members may wish to have testing to predict whether they are at risk of the same condition.

Contacts and further information

• Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
• National Heart Foundation at http://www.heartfoundation.org.au
• Better Health Channel at http://www.betterhealth.vic.gov.au
• Australasian Genetic Alliance at http://www.australasiangeneticalliance.org.au
• MyDr at http://www.mydr.com.au
• The Centre for Genetics Education at http://www.genetics.edu.au
• HealthInsite at http://www.healthinsite.com
• MedicineNet at http://www.medicinenet.com
• For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
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  Chromosomal conditions
Chromosomal conditions

GP’s role

• In the case of either personal/family history of recurrent miscarriage, infertility, or developmental delay, consider a karyotype for the couple as part of their diagnostic process (during the pre-conception or prenatal period if applicable).

• Where a parental karyotype is abnormal, refer to Genetics Services (see Contacts, support and testing).

• Refer to a paediatrician if a baby is suspected of having Down syndrome or other chromosomal abnormality.

• Refer parents to a relevant support group (see Contacts, support and testing).

Chromosomal terminology

• The arms of chromosomes are denoted as ‘p’ for the short arm and ‘q’ for the long arm (see Figure 1).

• The representation of a person’s chromosome complement is referred to as a karyotype. An individual may have a normal or abnormal karyotype.

• A karyotype is written as the total number of chromosomes present followed by the sex chromosome composition. For example, a normal male is denoted as 46,XY and a normal female as 46,XX.

• Changes in whole chromosome number (aneuploidy) are denoted using a ‘+’ or ‘-’ sign against the particular chromosome. For example:
  > Trisomy 21 (Down syndrome) male 47,XY,+21
  > Mosaicism for trisomy 18 female 47,XX,+18/46,XX
  > Turner syndrome 45,X

• Changes in structure are caused by rearrangements. For example, gain or loss of part of a chromosome, eg 5p-syndrome: 46,XY,del(5)(p15), is a deletion of part of the short arm of chromosome 5 with a breakpoint at band 15.

• Translocations are denoted by the letter ‘t’ followed by details of the chromosomes involved, eg 46,XY, t(5;17) indicates a male with a reciprocal translocation between chromosomes 5 and 17.

• Some chromosomal changes have no impact on growth, development or health because there is no net change to the genetic information.
Changes in chromosomal number (aneuploidy)

- Around 60% of recognised spontaneous miscarriages are chromosomally abnormal, the majority being due to autosomal trisomies, 45,X and triploidy.
- Autosomal chromosome aneuploidies seen in live births include trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) (see Table 1).
- First and second trimester prenatal screening tests estimate the risk for trisomy 21 but may also suggest risk for other trisomies (see Testing and pregnancy).
- Sex chromosome aneuploidy includes 45,X syndrome (Turner syndrome), 47,XXY (Klinefelter syndrome), XYY and triple X (see Table 2).
- The chance of having a baby with a chromosomal aneuploidy increases with maternal age (see Testing and pregnancy).
- Prenatal diagnostic testing for chromosomal disorders is available by chorionic villus sampling (CVS) or amniocentesis.

Recurrence risk

- The recurrence risk in a family with a child with standard non-translocation trisomy 21 is estimated to be a 1% increase above the age-related risk.
- There is no detectable increase in risk for 2° relatives.
- Recurrence risk for sex chromosome aneuploidy is very low.
### Table 1. Clinical features and management issues associated with the most common autosomal aneuploidy syndromes

<table>
<thead>
<tr>
<th></th>
<th>Trisomy 21 (Down syndrome)</th>
<th>Trisomy 13 (Patau syndrome)</th>
<th>Trisomy 18 (Edwards syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>1 in 660 births</td>
<td>1 in 5,000 births</td>
<td>1 in 3,000 births</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Features may be less severe in the case of mosaicism.</td>
<td>Not usually compatible with prolonged survival.</td>
<td>Features may be less severe in the case of mosaicism.</td>
</tr>
<tr>
<td></td>
<td>The number of physical characteristics present does not have any relationship to intellectual ability or vice versa.</td>
<td>Features likely to present in neonates include:</td>
<td>Features likely to present in neonates include:</td>
</tr>
<tr>
<td></td>
<td>Features likely to present in neonates include:</td>
<td>• Craniofacial malformations such as cleft lip and/or palate</td>
<td>• Severe developmental delay and disability</td>
</tr>
<tr>
<td></td>
<td>• Hypotonia</td>
<td>• Ocular malformations (microphthalmia)</td>
<td>• Multiple malformations such as:</td>
</tr>
<tr>
<td></td>
<td>• Facial characteristics such as short, sometimes webbed neck, low nasal bridge, epicanthal folds, upward slanting of eyes</td>
<td>• Neurological malformations (for example, holoprosencephaly, neural tube defects)</td>
<td>&gt; Cardiac defects</td>
</tr>
<tr>
<td></td>
<td>• Cardiac and/or gastrointestinal manifestations</td>
<td>• Limb anomalies (postaxial polydactyly)</td>
<td>&gt; Urinary tract and renal malformations</td>
</tr>
<tr>
<td></td>
<td>• Brachycephaly</td>
<td>• Cardiovascular anomalies</td>
<td>&gt; Joint contractures</td>
</tr>
<tr>
<td><strong>In infancy:</strong></td>
<td>• Developmental delay</td>
<td>• Ventral wall defects (omphalocele)</td>
<td>&gt; Low birth weight</td>
</tr>
<tr>
<td></td>
<td>Conditions that occur more commonly:</td>
<td>• Diaphragmatic defects</td>
<td>&gt; Hearing loss</td>
</tr>
<tr>
<td></td>
<td>• Intellectual disability</td>
<td>• Urinary tract and renal anomalies (hydronephrosis, cystic kidneys)</td>
<td>&gt; Rocker-bottom feet</td>
</tr>
<tr>
<td></td>
<td>• Cardiac malformations</td>
<td>In infancy:</td>
<td><strong>Life expectancy</strong></td>
</tr>
<tr>
<td></td>
<td>• Gastrointestinal</td>
<td>• Severe intellectual disability</td>
<td>Average age is 55+</td>
</tr>
<tr>
<td></td>
<td>malformations</td>
<td>Not all individuals will have all the associated characteristics.</td>
<td>The average length of survival of an infant with trisomy 13 is approximately four days, usually due to the presence of cardiac defects, associated with poor brain stem control.</td>
</tr>
<tr>
<td></td>
<td>• Auditory and/or visual defects</td>
<td>The prognosis for babies with partial or mosaic trisomy 18 can be less severe.</td>
<td>Of those babies who are liveborn, 30% die in the first month of life and 90% die by 12 months.</td>
</tr>
<tr>
<td></td>
<td>• Hypothyroidism</td>
<td></td>
<td>The prognosis for babies with partial or mosaic trisomy 13 can be less severe.</td>
</tr>
<tr>
<td></td>
<td>• Epilepsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Atlantoaxial instability</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Respiratory problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dementia of the Alzheimer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Immunodeficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Leukaemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not all individuals will have all the associated characteristics.
<table>
<thead>
<tr>
<th>Chromosomal conditions</th>
<th>Trisomy 21 (Down syndrome)</th>
<th>Trisomy 13 (Patau syndrome)</th>
<th>Trisomy 18 (Edwards syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical management issues</strong></td>
<td>Most interactions will be for everyday medical problems unrelated to the syndrome. Down syndrome related medical issues that are present will require additional checks and referral to appropriate specialists.</td>
<td>Referral to paediatric services.</td>
<td>Referral to paediatric services.</td>
</tr>
<tr>
<td><strong>Intervention strategies</strong></td>
<td>Early intervention can assist parents to provide developmentally appropriate activities. Intervention services (including physiotherapy, occupational and speech therapies) integrate multiple health professionals, the parents and carers. Most people with Down syndrome can learn to read, write, handle money, do simple maths, use a calculator and become competent and independent.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence and extended family risk</strong></td>
<td>In a family with standard non-translocation trisomy 21, recurrence risk is estimated to be: Maternal age &lt; 35 years, ~1 in 100 Maternal age &gt; 35 years, approximately twice the population age-specific risk The theoretical risk of recurrence for mosaicism is probably similar to the above. In the case of familial Robertsonian translocations involving chromosome 21, the recurrence risk of Down syndrome for the children of male translocation carriers is ~1% and for female translocation carriers is ~12%. Where the translocation is not inherited, parents have less than a 1% risk of having another affected child. For all of the above, there is no detectable increase in risk for 2o relatives. An individual with Down syndrome has, in theory, a 50% chance of having a child with trisomy 21; however, the rates of fertility are very low.</td>
<td>In a family with standard non-translocation trisomy 13, recurrence risk is very low and almost unknown. This risk will differ in the case of translocations involving trisomy 13.</td>
<td>In a family with standard non-translocation trisomy 18, recurrence risk is very low and almost unknown. This risk will differ in the case of translocations involving trisomy 18.</td>
</tr>
</tbody>
</table>
Table 2. Clinical features and management issues associated with the most common sex chromosome aneuploidy syndromes

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Clinical features</th>
<th>Features likely to be present include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>47,XXY (Klinefelter syndrome)</td>
<td>1 in 500 - 1,000 births</td>
<td>• Primary hypogonadism</td>
</tr>
<tr>
<td>47,XXY</td>
<td>~1 in 1,000 births</td>
<td>• Pubertal gynaecomastia</td>
</tr>
<tr>
<td>45,XY (Turner syndrome)</td>
<td>1 in 2,000 births</td>
<td>• Small testes (generally &lt;6mL; may not be diagnosed until puberty when the development of secondary sexual characteristics may be delayed and incomplete)</td>
</tr>
<tr>
<td>47,XXX</td>
<td>1 in 1,000 births</td>
<td>• Relatively tall stature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infertility</td>
</tr>
</tbody>
</table>

Boys are often shy, apprehensive and passive. This, coupled with delayed language development, may lead to the learning difficulties experienced at school.

Features may be less severe in the case of mosaicism.

**Clinical features**

- Features likely to be present include:
  - Tall or very tall stature (usually becoming apparent after the age of five or six)
  - Severe cystic acne during adolescence
  - Usually normal intelligence
  - May exhibit mild delays in reaching developmental milestones
  - Learning and reading disabilities, speech delays and language problems can occur
  - Hyperactivity, aggression or antisocial behaviour may occur

Other physical features may include:
- Webbed neck
- Heart defects, especially coarctation and bicuspid aortic valve
- Renal abnormalities
- High-arched palate and/or various other malformations

Majority will be mosaic in some tissues or organs.

Features may be less severe in the case of mosaicism.

The majority will have no or very few associated symptoms, while others may have various symptoms including:
- Learning difficulties, particularly language-based disabilities (e.g., dyslexia)
- Usually normal intelligence with IQs that tend to be lower than that of their siblings
- Infants and children with a triple X karyotype may tend to have delayed acquisition of certain motor skills and delayed language and speech development
- Tall stature

Features may be less severe in the case of mosaicism.
<table>
<thead>
<tr>
<th>Medical management issues</th>
<th>47,XXY (Klinefelter syndrome)</th>
<th>47,XY</th>
<th>45,X (Turner syndrome)</th>
<th>47,XXX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral to paediatric endocrinologist for treatment with testosterone to promote virilisation including the growth of the testes. However, the function of the testes is not restored with the therapy and infertility will persist. Recently, a small number of men have had children following testicular sperm aspiration and intracytoplasmic sperm injection (ICSI) of the egg at IVF. Hormone therapy usually starts at around 11 or 12 years. Gynaecomastia may require surgery.</td>
<td>Treatment of acne may help self-image.</td>
<td>Elevated circulating FSH levels in girls in infancy or adolescence indicate gonadal failure. Referral to paediatric endocrinologist. Available therapies include oestrogen and growth hormone treatments. Hypertension requires treatment. Frequent otitis media can cause deafness and predispose to cholesteatoma. Close monitoring and treatment required. Referral for IVF (GIFT) may be considered. Increased risk of chronic inflammatory bowel disease, hypothyroidism, diabetes mellitus.</td>
<td>Developmental assessment by age six months to evaluate muscle tone and strength.</td>
<td></td>
</tr>
<tr>
<td>Intervention strategies</td>
<td>The use of testosterone therapy has been demonstrated to have an impact on the development of self-esteem, to increase sexual libido and consequently to reduce behavioural problems experienced by some boys. Intervention services (including physiotherapy, occupational and speech and reading therapies) integrate the support of multiple health professionals, the parents and carers.</td>
<td>Early intervention can help parents provide developmentally appropriate activities. Intervention services (including physiotherapy, occupational and speech and reading therapies) integrate the support of multiple health professionals, the parents and carers.</td>
<td>Assistance in addressing the associated sleeping condition related to high activity levels, as well as apparent immaturity in various areas. Feeding difficulties sometimes require specific intervention due to physical problems such as the high arched palate, requiring special teats or Rosti (cleft palate) feeding bottles and advice from an infant feeding consultant or speech therapist.</td>
<td>Language and speech assessment by age two years to evaluate expressive and receptive language development. Reading assessment by school age to either rule out or confirm dyslexia.</td>
</tr>
<tr>
<td>Recurrence risk</td>
<td>Recurrence risk for sex chromosome aneuploidy is very low.</td>
<td>Recurrence risk for sex chromosome aneuploidy is very low.</td>
<td>Recurrence risk for sex chromosome aneuploidy is very low.</td>
<td>Recurrence risk for sex chromosome aneuploidy is very low.</td>
</tr>
</tbody>
</table>
Changes in chromosomal structure

- Changes in chromosomal structure are a result of chromosome breakage and rearrangement of some of the chromosomal material.
- Structural rearrangements include translocations, inversions, deletions and other uncommon changes.
- The two types of translocations are reciprocal and Robertsonian translocation.

**Reciprocal translocations**

- Reciprocal translocations arise when an exchange of chromosomal material takes place between two different chromosomes.
- This is the most common type of translocation, with an incidence of around 1 in 500 in the general population.
- Reciprocal translocations may be either inherited (familial) or sporadic (de novo) where neither parent has the rearrangement. The recurrence risks (see below) vary in each type and depend on the nature of the translocation itself.
- When there is no net gain or loss of genetic material, the rearrangement is said to be ‘balanced’.
- Balanced translocations in an individual do not usually impact on growth or development, but can have reproductive effects due to inheritance of unbalanced forms of the translocation in the conceptus.

**Recurrence risk**

- If a couple has a pregnancy with a sporadic (de novo) reciprocal translocation, the recurrence risk in another pregnancy for a sporadic reciprocal translation is extremely low.
- The major risk for couples where one partner has a ‘balanced’ reciprocal translocation is either miscarriage or an affected liveborn, both due to inheriting the translocation in an unbalanced form. The recurrence risk for this couple may be up to 20%.
- Some couples with a balanced translocation may be at very low risk of having a liveborn affected child because the unbalanced forms are invariably lethal and end in miscarriage or fetal death.

**Robertsonian translocations**

- Robertsonian translocations occur in around 1 in 1,000 live births.
- This type of translocation involves acrocentric chromosomes (13, 14, 15, 21 and 22).
- The long arm of one chromosome fuses to the long arm of another chromosome, with loss of both short arms producing a longer chromosome, e.g. fusion between chromosomes 14 and 21.
- In Robertsonian translocations both long arms of the chromosomes are still present, only fused together. The loss of the short arms has no impact as they contain non-essential DNA (i.e. no functional genetic material).
- When there is no change in the total amount of functional genetic material, the Robertsonian translocation is described as ‘balanced’, even though there are only 45 chromosomes.
- Balanced Robertsonian translocations in an individual do not usually impact on growth or development, but can have reproductive effects, as with reciprocal translocations, when the fetus receives the translocation in an unbalanced form.
- Approximately 5% of cases of Down syndrome are due to an unbalanced Robertsonian translocation involving chromosome 21, with 46 chromosomes present.
- Approximately 1 to 2% of cases of Down syndrome are due to inheriting an unbalanced Robertsonian translocation from a parent who is carrier of a balanced translocation.
**Recurrence risk**

- If a couple has a pregnancy with a sporadic *(de novo)* unbalanced Robertsonian translocation, the recurrence risk in another pregnancy for a sporadic Robertsonian translocation is extremely low.
- The major risk for couples where one partner has a balanced Robertsonian translocation is either miscarriage or an affected liveborn due to having inherited the translocation in an unbalanced form. The recurrence risk varies with the chromosomes involved. This couple will also be capable of conceiving normal and carrier offspring.

**Mosaicism**

- Mosaicism can occur following failure of a chromosome pair to separate during cell division after conception, resulting in two or more karyotypically different cell lines.
- Where a chromosomal change causing an abnormality is mosaic and there are normal cells present, the clinical effect is likely to be less severe if it is in only a small proportion of the cells.
- It is not usually necessary to check the chromosomes of the parents of a child with a mosaic chromosome abnormality. Theoretical risk of recurrence in most cases is only slightly different from the general population.
- The presence and degree of mosaicism can vary according to the tissue being sampled. A cytogenetic test on blood may not always reveal the presence of a chromosomal abnormality where mosaicism exists, and other tissues may need to be tested if there is clinical suspicion of a chromosomal condition.

**Bibliography**


Chromosomal conditions

Chromosomes are important parts of a cell. They are the parts which carry the genes.

We are meant to have 23 pairs of chromosomes in each cell, a total of 46 chromosomes, with one chromosome in each pair inherited from each parent.

Occasionally, things go wrong, and a child is conceived with 45 chromosomes, or 47 chromosomes, or perhaps the right number but the wrong mix of chromosomes. Also, a child may be born with a change to the way the chromosomes are structured.

More often than not, babies conceived with chromosomal alterations have such serious problems that their mothers miscarry. Sometimes, they survive.

The most common chromosomal alterations in surviving babies are:

- Trisomy 21 or Down syndrome
- Trisomy 18 or Edwards syndrome
- Trisomy 13 or Patau syndrome
- XXY or Klinefelter syndrome
- 45X or Turner syndrome
- XXX or triple X syndrome
- XYY syndrome.

Individually, these conditions are all uncommon, although in total, about 6 babies in 1000 are born with a chromosomal alteration.

While babies with the same chromosome condition will tend to have similar features, it is impossible to predict what any individual child will look like, what their abilities may be, or what medical problems they may face. General information on what might be involved is provided in brief description below, but for more detailed information visit http://www.genetics.edu.au the website for the Centre for Genetics Education.

**Trisomy 21 or Down syndrome**

Babies with Down syndrome will be slow to develop and will have intellectual disability. Problems with the heart and bowel are also common. Most people with Down syndrome will live independent lives.

**Trisomy 18 or Edwards syndrome**

Most babies with trisomy 18 will have serious and widespread problems. Most die soon after birth.
**Trisomy 13 or Patau syndrome**
Most babies with trisomy 13 will have serious and widespread problems. Most die soon after birth.

**XXY or Klinefelter syndrome**
Boys with XXY may be slow to develop and will often be shy. Their intelligence is usually normal, although they may have learning difficulties. They are usually infertile and tend to be tall. They have a normal lifespan.

**45X or Turner syndrome**
Girls with 45X syndrome are short, usually infertile and may have problems with their heart and kidneys. Their intelligence is usually normal, but they may have learning difficulties. They have a normal lifespan.

**XXX or triple X syndrome**
Girls with XXX may have reduced intelligence and learning difficulties. They tend to be tall. They have a normal lifespan.

**XYY syndrome**
XXY syndrome only affects males. Boys with XYY syndrome tend to be tall. Their intelligence is usually normal, but they may have some learning difficulties. They have a normal lifespan.

**Are chromosomal alterations inherited?**
Usually not, but sometimes they are, particularly if the chromosomal alteration affects the way the chromosome is structured. If a child in your family is diagnosed with a chromosomal alteration, or if there is a history of miscarriages, then it is worth seeing a genetics service to discuss the possibility of the alteration being inherited.

**What to do?**
If you have or are having a child with chromosomal alterations, much more information is available from support groups and from genetics services. You should seek specialist help and advice.
Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- National Organisation for Rare Disorders at [http://www.rarediseases.org](http://www.rarediseases.org)
- Trisomy 18 Registry and Research Society at [http://www.chromosome18.org](http://www.chromosome18.org)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on [free call Australia-wide 1800 631 276](tel:1800631276) or email [gtis-australia@unimelb.edu.au](mailto:gtis-australia@unimelb.edu.au) or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
### A. Hereditary thrombophilias

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### B. Haemophilias

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Patient and family fact sheets:
- Clotting disorders
- Haemophilias
A. Hereditary thrombophilias

GP’s role
- Identify individuals with a personal or family history of thromboembolism.
- Include:
  - Age of onset
  - Site and extent of thrombosis
  - Precipitating/contributing factors
- Perform a risk assessment – should patient be screened for thrombophilia?
- Arrange screening if indicated.
- Factor V Leiden and prothrombin variant genetic testing is available on the MBS only if the patient has:
  - A personal history of deep vein thrombosis (DVT), or
  - A family history of a diagnosed inherited thrombophilic condition
- Refer family to relevant support group (see Contacts, Support and Testing).

Features
- Normal haemostasis results from a balanced interaction between platelets and plasma clotting proteins (see Figure 1).
- Predisposition to thrombosis or ‘thrombophilia’ may be due to an excess of procoagulant factors, a deficiency of anticoagulant factors, or abnormal fibrinolysis. ‘Toxic’ effects on the endothelium may also predispose to thrombus formation.
- There are a number of different types of hereditary thrombophilia conditions which are distinguished by their different causes (see Table 1).
Table 1. The major hereditary thrombophilia conditions

<table>
<thead>
<tr>
<th><strong>Group 1 conditions</strong></th>
<th>Antithrombin deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to a defect or deficiency of an anticoagulant protein.</td>
<td>Protein C deficiency</td>
</tr>
<tr>
<td></td>
<td>Protein S deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Group 2 conditions</strong></th>
<th>Activated protein C resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to genetic mutations that result in an increased tendency towards thrombosis.</td>
<td>Factor V Leiden</td>
</tr>
<tr>
<td></td>
<td>Prothrombin gene variant</td>
</tr>
<tr>
<td></td>
<td>Elevated levels of factors VIII, IX and XI</td>
</tr>
<tr>
<td>Other conditions</td>
<td>Hyperhomocysteinaemia</td>
</tr>
</tbody>
</table>

- The risk of thrombosis is higher for patients with group 1 conditions than group 2 conditions.
- Group 2 conditions occur approximately 5 times more frequently than group 1 conditions.

**Genetics**

### Group 1 conditions

**Antithrombin deficiency**
- Antithrombin is a naturally occurring inhibitor of the coagulation cascade. It binds to and inactivates thrombin and factors Xa, IXa, XIa and XIIa.
- Antithrombin deficiency occurs in approximately 1 in 500 in the healthy population and in 4 to 5% of individuals with venous thromboembolism (VTE).
- Antithrombin deficiency is a strong thrombophilic condition, with approximately 60% of heterozygous carriers developing VTE by age 60 years.

**Protein C deficiency**
- Protein C is a natural anticoagulant that inactivates factors Va and VIIIa in a reaction requiring its cofactor, protein S.
- Protein C deficiency occurs in approximately 1 in 500 in the healthy population and in 2 to 4% of individuals with VTE.
- Heterozygous protein C deficiency is a moderate to strong thrombophilic condition, with up to 50% of people developing VTE by age 60 years.
- Individuals with heterozygous protein C deficiency commenced on warfarin without heparin cover may develop skin necrosis.
- Homozygous protein C deficiency is a severe thrombophilic condition characterised by the development of neonatal purpura fulminans and disseminated intravascular coagulation.

**Protein S deficiency**
- Protein S is an essential cofactor in the inactivation of factors Va and VIIIa by protein C.
- Protein S deficiency occurs in 3 to 13 in 1000 in the healthy population and in 2 to 4% of patients with VTE.
- Heterozygous protein S deficiency is a moderate thrombophilic condition, with approximately one third of carriers developing thrombosis by age 60 years.
- Like protein C deficiency, skin necrosis may occur in heterozygous carriers commenced on warfarin, while homozygous deficiency results in neonatal purpura fulminans.
Group 2 conditions

Factor V Leiden and activated protein C resistance

- Activated protein C (APC) mediates its anticoagulant activity via inactivation of factors Va and VIIIa.
- Resistance to APC is defined by failure of prolongation of the activated partial thromboplastin time (APTT) following the addition of APC to patient plasma.
- Approximately 90% of cases of APC resistance are due to the presence of an abnormal factor V gene, factor V Leiden.
- Factor V Leiden is characterised by a single amino acid change at one of the sites of cleavage of factor V by APC, which renders the protein resistant to inactivation by APC.
- Factor V Leiden heterozygosity is present in approximately 1 in 20 of the healthy Caucasian population. It is rare in people of Asian or African descent.
- Factor V Leiden is present in 10% of individuals with VTE and 30 to 50% of individuals investigated for thrombophilia.
- Factor V Leiden is a weak thrombophilic condition, with approximately 6% of individuals developing thrombosis by age 65 years.
- APC resistance due to mechanisms other than factor V Leiden may also result in mild thrombophilia, due to other mutations in the factor V gene, raised factor VIII levels or other disturbances of the APC pathway.

Prothrombin gene variant

- Prothrombin is the precursor to thrombin, which drives the formation of fibrin in the final common pathway of the coagulation cascade.
- A common variant in the prothrombin gene results in an increase in prothrombin synthesis.
- This prothrombin gene variant is present in 2 in 100 to 3 in 100 of the healthy Caucasian population and is rare in people of Asian or African descent.
- It is present in 5 to 10% of patients with VTE and 15% of patients investigated for thrombophilia.
- Heterozygosity for the prothrombin gene variant results in a weak thrombophilic condition, with less than 5% of carriers developing thrombosis by age 60 years.
- Homozygosity for the prothrombin gene variant or combined heterozygosity for factor V Leiden and the prothrombin gene variant increases the risk of thrombosis into the moderate range.

Hyperhomocysteinaemia

- High levels of homocysteine in the blood have been associated with both arterial and venous thrombosis, through poorly defined mechanisms.
- Hyperhomocysteinaemia may be due to congenital or acquired causes.
  - Acquired causes include folate, vitamin B12 or vitamin B6 deficiency
  - Congenital causes include abnormalities affecting either the cystathione β-synthase or genes in folate metabolism
- Genetic mutations causing severe deficiency of these proteins are rare and result in profound hyperhomocysteinaemia and premature vascular disease.
- The most common mutation, MTHFR C677T, has a prevalence in the Australian population of 10% for homozygotes. However, its relationship with venous thrombosis remains controversial and it is not currently recommended as part of a screen for thrombophilia.
Identifying individuals at risk of thrombophilia

- Screening for thrombophilia should be considered in individuals with these characteristics:
  - DVT at <50 years
  - Spontaneous thrombosis in absence of recognised risk factors
  - Recurrent thrombosis
  - Family history of thrombosis
  - Thrombosis in unusual sites, eg CNS, abdominal veins, upper limb
  - Stillbirth or fetal death in utero

- Factor V Leiden and prothrombin variant genetic testing is available on the MBS only if the patient has:
  - A personal history of DVT, or
  - A family history of a diagnosed inherited thrombophilic condition

### Table 3. Tests available for hereditary thrombophilias

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Group 1 conditions</th>
<th>Group 2 conditions</th>
<th>Other conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antithrombin deficiency</td>
<td>Activated protein C resistance</td>
<td>Hyperhomocysteinaemia</td>
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<tr>
<td></td>
<td>Protein C deficiency</td>
<td>Factor V Leiden</td>
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<td>Protein S Deficiency</td>
<td>Prothrombin gene variant</td>
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<td></td>
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<td>Elevated levels of factors VIII, IX and XI</td>
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<table>
<thead>
<tr>
<th></th>
<th>Conditions</th>
<th>Tests Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>Functional/antigenic assay</td>
<td></td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Functional/antigenic assay</td>
<td></td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>Functional/antigenic assay</td>
<td></td>
</tr>
<tr>
<td>Activated protein C resistance</td>
<td>Clotting assay</td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>DNA test</td>
<td></td>
</tr>
<tr>
<td>Prothrombin gene variant</td>
<td>DNA test</td>
<td></td>
</tr>
<tr>
<td>Elevated levels of factors VIII, IX and XI</td>
<td>Clotting assay</td>
<td></td>
</tr>
<tr>
<td>Hyperhomocysteinaemia</td>
<td>High performance liquid chromatography</td>
<td></td>
</tr>
</tbody>
</table>
Contraception and thrombophilia

- Oestrogen-containing oral contraceptives or hormone replacement therapy increase the risk of VTE by 2 to 4-fold and are relatively contra-indicated in women with hereditary thrombophilia.
- Third generation combined pills are more thrombogenic than second generation preparations.
- Decisions regarding oestrogen use should be made on an individual basis, after a risk-benefit analysis has been performed.
- Factors that should be considered when prescribing the combined oral contraceptive pill include:
  - Past or family history of VTE
  - Other risk factors for VTE
  - Suitability of alternative means of contraception
  - Patient preference
  - Patient compliance
- Advice should be sought from a specialist haematologist and/or family planning expert if required.

Note:
Screening all women for hereditary thrombophilias before commencing oestrogen has not been shown to be cost effective. With regard to factor V Leiden, 20,000 women would need to be screened in order to prevent one DVT, while 2 million women require screening to prevent one death from pulmonary embolism. Rather, prior to prescribing oestrogens, practitioners should take a careful history with respect to past medical and family history and additional risk factors for thrombosis. Screening can then be targeted to those women who appear to be most at risk of thrombophilia.

Management of thrombophilia

- Individuals with hereditary thrombophilia are at increased risk of VTE due to the following acquired risk factors:
  - Obesity
  - Increasing age
  - Prolonged immobilisation (>10 days)
  - Surgery or trauma
  - Pregnancy and the puerperium
  - Smoking
  - Combined oral contraceptive pill or hormone replacement therapy
  - Active cancer
  - Antiphospholipid antibodies
  - Acquired activated protein C resistance
- At least 50% of thrombotic episodes in individuals with hereditary thrombophilia occur during periods of increased thrombotic risk.
  - Periods of increased thrombotic tendency due to a risk factor, such as pregnancy, immobilisation or surgery, temporarily increase the baseline risk
  - Age and other permanent or temporary risk factors should be taken into account in determining the need for thromboprophylaxis
- Primary prophylaxis for individuals with hereditary thrombophilia is not recommended, as the lifetime risk of death from bleeding on anticoagulants is greater than the risk of death from thrombosis in previously asymptomatic individuals.
**Pregnancy and thrombophilia**

- Decisions regarding the management of hereditary thrombophilias in pregnancy should be made in consultation with a specialist haematologist, obstetric physician or obstetrician.
- Most asymptomatic women with Group 1 thrombophilic conditions will require thromboprophylaxis during the antenatal period and for 6 weeks post-partum.
- Asymptomatic women with Group 2 thrombophilias may require post-partum thromboprophylaxis.
- Factors to consider when deciding individual management include:
  - Past and family history of thrombosis
  - Presence of other risk factors for thrombosis
  - Patient preference
- Once a woman with hereditary thrombophilia has developed VTE, subsequent pregnancies will probably require antenatal and post-partum thromboprophylaxis.
- Recent studies have demonstrated an association between hereditary thrombophilias and adverse outcomes of pregnancy including fetal loss, growth restriction, placental abruption, pre-eclampsia and stillbirth. The majority of women who are carriers of hereditary thrombophilias do not experience these complications. Although there is little evidence regarding the effect of thromboprophylaxis on subsequent pregnancy outcome in these women, increasingly obstetricians are screening for hereditary thrombophilias in women with pregnancy complications.

**Implications for other family members**

- The patient should be encouraged to:
  - Inform family members that they may be at risk of inheriting a thrombophilic condition.
  - Advise family members to discuss their risk with their own GP and/or ask for a referral to a haematologist.
**B. Haemophilias**

**GP’s role**
- Identify children who potentially have haemophilia.
- Consider referral of those children for further assessment to a haematologist or haemophilia clinic.
- Assess family history for haemophilia.
- Provide support.
- Manage co-existing conditions.
- Identify carriers of haemophilia and/or refer to Genetics Services.

**Features**
- Haemophilia A and B are clinically similar and can only be distinguished by assays of factor VIII and IX activity.
- Males with moderate or mild haemophilia A or B are more difficult to diagnose as they may only present with haemorrhage after trauma, including teeth extraction.
- The severity of haemophilia A is directly related to the residual amount of factor VIII activity in the blood. Symptoms only occur once levels of factor VIII drop to 5% of normal or below.
- The severity of haemophilia B is directly related to the residual amount of factor IX activity in the blood. Symptoms only occur once levels of factor IX drop to 50% of normal or below.

Table 4. The severity of haemophilia A and B

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Haemophilia A Factor VIII levels (% of normal)</th>
<th>Haemophilia B Factor IX levels (% of normal)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt; 1%</td>
<td>&lt; 1 - 2%</td>
<td>Frequent spontaneous bleeding; abnormal bleeding after <em>minor</em> injuries, surgery, or tooth extractions</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 - 5%</td>
<td>2 - 5%</td>
<td>Spontaneous bleeding is rare; abnormal bleeding after <em>minor</em> injuries, surgery, or tooth extractions</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt; 5%</td>
<td>5 - 50%</td>
<td>No spontaneous bleeding; abnormal bleeding after <em>major</em> injuries, surgery, or tooth extractions</td>
</tr>
</tbody>
</table>
• Severe haemophilia A or B is characterised by:
  > Frequent episodes of bleeding, often spontaneously or after minimal trauma
  > Deep muscle haematomas
  > Prolonged oozing or renewed bleeding after initial bleeding stops, following tooth extractions, mouth injury, or circumcision
  > Menorrhagia, especially at menarche
  > Prolonged nosebleeds, especially recurrent and bilateral
  > Excessive bruising, especially with firm, subcutaneous haematomas
  > Bleeding into the brain in the absence of major trauma is a frequent cause of death
  > Haemarthrosis occurs commonly and repeated bleeding into joints can lead to chronic damage often producing severe disability and requiring joint replacement

Genetics

• Both haemophilia A and B follow an X-linked recessive pattern of inheritance.
  > Therefore females who are carriers have a 50% risk of passing the mutation on to their sons (who would then be affected with the condition) and daughters (who would then be carriers)
• Haemophilia A is caused by low or absent factor VIII.
• Haemophilia B is caused by low or absent factor IX.
• The factor VIII and factor IX genes are found on the X chromosome, very close to each another.
• A large number of different mutations occur in these genes and unrelated families with haemophilia A or B generally have different mutations.
• Different mutations in the factor VIII or factor IX genes have been identified that cause differing severity of haemophilia A or B respectively.
• The inheritance pattern may appear to look autosomal dominant in some families as up to 10% of women who are carriers can have mild bleeding symptoms.

Prevalence

Haemophilia A

• Affects approximately 1 in 4,000 to 1 in 10,000 males.
• The number of females affected is approximately 1 in 25,000,000 due to the inheritance of homozygous alleles for haemophilia A.
• Female carriers of haemophilia A:
  > Most have levels of factor VIII that are 50% of normal and are therefore unaffected.
  > Approximately 10% have low enough factor VIII activity levels to have mild bleeding themselves. This may be due to skewed X inactivation.

Haemophilia B

• Affects approximately 1 in 20,000 males.
• Female carriers of haemophilia B:
  > Most have levels of factor IX that are 50% of normal and are therefore unaffected
  > Approximately 10% have low enough factor IX activity levels to have mild bleeding themselves. This may be due to skewed X inactivation.
Investigations

- Those at risk include:
  - Males presenting in adulthood with unexplained bleeding could have moderate or mild haemophilia A or B.
  - Females who have a male relative affected with haemophilia A or B are at risk of being a carrier.
  - Children whose mother is a carrier, or daughters of an affected father.
- Specialist services can provide advice regarding appropriate testing.
- For individuals suspected of having haemophilia A or B, investigations include:
  - Partial thromboplastin time (PTT)
  - Activated partial thromboplastin time (APTT)
  - Prothrombin time (PT)
- In severe and moderately severe haemophilia A or B, the PTT is prolonged.
- In mild haemophilia A or B, the PTT is often normal.
- Individuals with a history of a lifelong bleeding tendency should have specific coagulation factor assays performed even if all the coagulation screening tests are in the normal range.

DNA testing

- Patients requiring DNA testing should be referred to a specialist centre.
- DNA testing is indicated to assist in prenatal testing in pregnancies at risk for haemophilia A or B.
- DNA testing can be time consuming and, if possible, couples should be referred prior to pregnancy.
- Even in individuals with clinical haemophilia, a specific mutation may not be found thus prohibiting cascade testing for carrier status.
- Testing can be offered prenatally to women using chorionic villus sampling or amniocentesis.

Management

- Haemophilia A and B are treated by infusion of the deficient factor to restore levels to normal.
- In some severe cases of haemophilia A, infusion may have to be done twice a day.
- Infusions to treat haemophilia B may be required twice a week.

Implications for other family members

- If an individual tests positive for the mutation causing haemophilia A or B, the family should be referred to Genetics Services for counselling, and testing should be offered to the extended family.
- Detection of mutation carriers allows families to make informed decisions regarding family planning.
- The patient/parents should be encouraged to:
  - Inform family members that they may be at risk of inheriting or passing on haemophilia A or B
  - Give their family members written information about haemophilia A or B
  - Advise family members to discuss their risk with their own GP and/or contact Genetics Services
Clotting and bleeding conditions

Referral information

- Refer to specialist and Genetics Services.

Further information

- Haemophilia Foundation Australia.
  http://www.haemophilia.org.au

Bibliography


Geneclinics, National Institutes of Health
http://www.geneclinics.org


Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD).

Blood is meant to clot. If you nick yourself, blood seeps out and then clots.

But it is only meant to clot outside the body. If it clots inside the body, there is a problem.

If blood clots in a vein in the calf, for example, then the person affected might get a sore swollen leg. This is known as a deep venous thrombosis or DVT.

If the clot stays where it is, it can feel uncomfortable. But if parts of the clot break off, they can travel through the bloodstream to other parts of the body, such as the lung or the brain. This condition, known as venous thromboembolism, can be quite dangerous.

Most people with DVT and/or venous thromboembolism do not have a genetic alteration that caused it.

But some do. Some have an altered gene which affects normal clotting. People with this gene alteration are said to have hereditary thrombophilia.

There are many different types of hereditary thrombophilia, all caused by different gene alterations, all of which affect people in slightly different ways.

Hereditary thrombophilias are passed on through an autosomal dominant pattern of inheritance (see fact sheet on ‘How do genetic conditions occur?’). This means they are likely to be present in other members of the family.

It also means that any child of an affected person has a 1 in 2 chance of having the gene alteration and a 1 in 2 chance of not having it.

In general, these gene alterations don’t cause blood clots on their own, but give people a high likelihood of getting blood clots.

Other indicators
People with hereditary thrombophilia are more likely to develop clots if they:

- Are overweight
- Stay in bed for 10 days or more
- Have surgery or a serious injury
- Are pregnant or have just given birth
- Smoke
- Take the oral contraceptive pill or hormone replacement therapy
- Have cancer

People with hereditary thrombophilia are more likely to develop clots as they get older.
**Contraception and pregnancy**

Oral contraceptive pills containing oestrogen increase the risk that a woman with hereditary thrombophilia will develop a clot. Women with hereditary thrombophilia should talk to their doctor about whether or not other forms of contraception may be better.

Any woman with hereditary thrombophilia who becomes pregnant is at higher risk than usual of developing a clot.

Any woman with hereditary thrombophilia also has a slightly higher than usual risk of having problems with the pregnancy, such as miscarriage, poor growth of the baby and problems with the placenta. However, most women with hereditary thrombophilia who become pregnant still have normal pregnancies.

Women with hereditary thrombophilia who become pregnant should see a specialist obstetrician for advice.

**What to do?**

People should be assessed to see whether they may have a hereditary thrombophilia if they have a venous thrombosis or thromboembolism:

- Before the age of 50
- With nothing obvious that could have caused it
- And others in the family have had the same problem
- In an unusual position, such as the brain, the abdomen or the arm.

People with a close relative who has been shown to have a hereditary thrombophilia, or who has had a thrombosis or thromboembolism, should ask their doctor about testing for a hereditary thrombophilia.

**Testing**

Tests are available to detect the common forms of hereditary thrombophilia.

**Contacts and further information**

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtil-australia@unimelb.edu.au or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
Haemophilia is a condition in which the affected person’s blood doesn’t clot properly. People with haemophilia can bruise or bleed internally after a minor injury and, if cut, bleed easily and find it hard to stop the bleeding.

Haemophilia can be mild or it can be severe, or anywhere in between.

There are two main types of haemophilia – A and B. Each type is caused by a specific gene alteration that leads to a shortage, or absence, of one of the proteins needed to make blood clot.

In haemophilia A, there is a shortage or absence of the protein called factor 8. Haemophilia A is also known as classical haemophilia.

In haemophilia B, there is a shortage or absence of the protein called factor 9. Haemophilia B is also known as Christmas disease.

Haemophilia is a genetic condition. It has an X-linked pattern of inheritance (see fact sheet on 'How do genetic conditions occur?').

Men who have the altered gene on their X chromosome have the condition. Any sons they have will not be affected and any daughters they have will be carriers.

Women who have the altered gene are carriers for haemophilia. Any sons they have will have a 1 in 2 chance of inheriting the altered gene and having the condition; and a 1 in 2 chance of not inheriting the altered gene and not having it. Any daughters they have will have a 1 in 2 chance of being a carrier and a 1 in 2 chance of not being a carrier. A few women who are carriers actually have a mild form of the condition.

People with haemophilia in the family should contact a genetics service for advice. Blood tests and genetic testing may be recommended.
Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- Haemophilia Foundation Australia at http://www.haemophilia.org.au
- Australasian Genetic Alliance at http://www.australasiangeneticalliance.org.au
- The Centre for Genetics Education at http://www.genetics.edu.au
- HealthInsite at http://www.healthinsite.com
- MedicineNet at http://www.medicinenet.com
- MyDr at http://www.mydr.com.au
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
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**Patient and family fact sheet:**

Cystic fibrosis
Cystic fibrosis

GP’s role

- Be aware of newborn screening procedures for CF in your State or Territory, and be ready to inform families when further testing is required or results from tests need to be discussed (see Newborn screening).
- Refer to a paediatrician/respiratory physician for a sweat test where there is clinical suspicion of CF regardless of the result of newborn screening.
- Discuss carrier testing, pre-implantation genetic diagnosis (PGD) and prenatal testing options as appropriate as part of pre-conceptual/early antenatal care (see Testing and pregnancy).
- Discuss the importance of cascade testing for immediate and extended family members after a diagnosis of CF or CF mutation carrier status (see Contacts, support and testing).
- Refer to Genetics Services for genetic counselling and more detailed discussion of issues such as recurrence and carrier risks, genetic testing and family planning (see Contacts, support and testing).
- Refer where appropriate to local Australasian Genetic Alliance Peak Body who will assist in direction to a Support Group (see Contacts, support and testing).

Clinical features

- The clinical features and clinical course of cystic fibrosis (CF) are variable, even within families who carry the same mutations.
- Clinical features and their prevalence in CF patients include:
  - Chronic suppurative lung disease, 95%
  - Pancreatic exocrine insufficiency, leading to malabsorption, 85%
  - Sweat gland salt loss, 100%
  - Male infertility (absent or altered vas deferens), 99%
  - Meconium ileus, 20%
  - Distal intestinal obstruction syndrome, 20%
  - CF-related diabetes, 20%
  - CF liver disease, 20%
  - Nasal polyps, 10%
- Some clinical features of CF seem to be mediated by the specific mutations in the CFTR gene that an individual inherits.
Genetics

- CF follows an autosomal recessive pattern of inheritance and is caused by mutations in the CFTR (cystic fibrosis transmembrane regulator) gene.
- As is common with autosomal recessive conditions, when a family member is diagnosed with CF there is often no family history of the condition since the mutation has previously only been present in healthy carriers on each side of the family (see Genetics in practice).
- CFTR regulates chloride and sodium transport in the epithelial surfaces of the airway, pancreatic and biliary ducts, the gastrointestinal tract, sweat ducts and the vas deferens. Pathogenic mutations either remove or reduce the function of CFTR gene.
- There are more than 1500 known CFTR mutations, but not all will be associated with classical CF.
- A carrier for CF, that is a person carrying only one mutated copy of the CFTR gene, will still produce sufficient amounts of the salt-transport protein for normal body function.
- Where multiple family members are affected with CF they may appear to be scattered among or within generations depending upon whether two carriers for CF have had children.
- Parents who are both carriers for a CFTR mutation associated with classical CF have a 1 in 4 chance of having a child with CF, in each pregnancy.
- If only one parent is a carrier for a CFTR mutation, each child has 1 in 2 chance of being a carrier like the parent, and unaffected.
- Carrier testing is accurate if the CFTR gene mutation in the family is known.
- The most common mutation in the CFTR gene is known as ΔF508 (also written as delF508) that accounts for approximately 70% of all CF gene mutations in those of Northern European ancestry.
- Laboratories test for varying numbers of the common mutations. Testing for 12 or more mutations covers at least 80% of possible mutations in Australian Caucasians. The rest of the mutations are extremely rare. Mutations that are common in populations other that those whose ancestry is Northern European may not be included in the panel of mutations that are routinely tested by laboratories.
- In the absence of a family history of CF, a negative screen for CFTR gene mutations is reassuring, but cannot absolutely rule out the possibility of being a carrier as not all mutations can be tested. Therefore if a couple chooses screening for CF there is still a small risk of having a baby with CF if their carrier test is negative.

Prevalence

- One in every 2,500 Australian babies, male or female, of Northern European ancestry.
- About 1 in 25 Australians of Northern European ancestry are carriers for a CFTR gene mutation.
- CF is less frequent in Southern European and Middle Eastern populations, and is rare or absent in Asian populations.

Investigations

- The sweat test is the principle test for diagnosis of CF.
- If there is clinical suspicion that a person has CF (regardless of whether the person was screened at birth) a sweat test should be requested.
Newborn screening

- Newborn screening will detect the majority (95%) of babies with CF.
- The newborn screening protocol for CF is outlined in Figure 1 below (see Newborn screening for more details):

Figure 1: Newborn screening for CF

- Newborn screening is performed on all babies 48 to 72 hours after birth.
- Immunoreactive trypsinogen (IRT) is measured in a dried bloodspot from a heel-prick test (Guthrie test, newborn screening card). Raised IRT is an indication for DNA testing for CFTR mutations, which is also performed on the heel-prick sample. Each State in Australia screens for a different number of mutations depending on the frequency of the mutations in those States.
- The presence of two CFTR gene mutations is diagnostic of CF.
- A repeat blood sample may be collected to confirm the diagnosis and a sweat test may also be performed.
- If one CFTR gene mutation is present, the baby is considered at increased risk and a sweat test is performed. Eleven babies out of every 12 requiring a sweat test, on the basis of newborn screening results, do not have CF, but are simply carriers (have one mutation, ie heterozygotes).
• If no CFTR gene mutations are detected, the baby is considered to be at low risk of having CF and no further testing is performed. Babies with CF caused by mutations other than those tested in the screening program(s) will be in this group and will therefore be missed by newborn screening.

• The Newborn Screening Programme in each State/Territory coordinates or recommends referral for sweat testing and genetic counselling.

• If a sweat test is required, the GP or paediatrician will be contacted if their details are on the newborn screening card or held by the hospital that delivered the baby. GPs then have the option of informing the family themselves or asking the genetic counsellor to do so. Feedback from families suggests they prefer to be contacted with results by someone known to them.

• CF may be missed by newborn screening for one of the following reasons:
  > Screening sample not collected
  > IRT is not raised
  > Condition caused by mutations other than those tested in screening
  > The sweat test is negative

Sweat tests
• Sweat tests measure chloride and sodium levels in sweat. They can be performed at any time from 1 week of age, but adequate sweat volumes may not be obtained before 6 weeks of age.

• Sweat test results are usually available within 24 hours and often on the same day.

• If there is clinical suspicion of CF, a sweat test should be arranged, even if the patient has had newborn screening, since approximately 5% of CF cases are not detected by newborn screening.

• Occasionally, sweat test results will be equivocal and a repeat will be required.

• Sweat tests can be difficult to perform and interpret, and should only be performed by an experienced clinician and laboratory staff.

• Sweat electrolyte values in adults are often higher than children and need to be interpreted by an expert.

• Patients who live in the country may need to travel to a CF centre for a sweat test.

DNA tests (see Contacts, support and testing)
• DNA testing for CF is performed during newborn screening or as a result of a positive sweat test or clinical suspicion.

• Genetic testing may be considered as a starting point for diagnosis if access to sweat testing is difficult. Discussion of such cases with a CF physician may be helpful.

• When a couple have had a baby with CF it is helpful to know the CFTR gene mutations to facilitate genetic counselling for subsequent pregnancies and accurate carrier testing for family members (cascade testing).

• Contact Genetics Services to find out which CFTR mutations are commonly tested for in your State or Territory (See Contacts, support and testing).

• Knowledge of ancestry can assist the detection of gene mutations.

• CF mutation screening can diagnose at least 80% of people with CF. Sweat testing is more definitive.

• Carrier testing can be offered to couples who have no family history, currently on a user-pays basis.


**Management**

**Respiratory symptoms**

- Management focuses on assisting mucus clearance and treatment of chest infections.
- Daily chest physiotherapy is usually performed.
- Under-treated bacterial infection is responsible for destruction of the airways in CF patients. Antibiotics are usually started early and continued until symptoms improve. Prolonged therapy might be required in some patients. Sputum culture is important in guiding antibiotic therapy.
- There is a low threshold for the use of antibiotics during common viral infections, during which bacteria may colonise the lower airway. In young children, *Staphylococcus aureus* and *Haemophilus influenzae* are common infecting organisms. *Pseudomonas aeruginosa* becomes the predominant organism with time.
- Lung transplantation is currently the only available, efficient treatment for life-threatening CF, and can improve quality of life and long-term survival.
- The major selection criterion for lung transplantation is a life expectancy predicted to be 50% or less at 2 years. This can be indicated by increasing decline in respiratory function, quality of life, weight, and more frequent need for IV therapy.
- The outlook for patients receiving lung transplants within Australia has improved significantly since the first transplant in 1986. Regardless of the form of transplant (single lung, double lung, or heart and double lung), the majority of patients (~90%) will live at least a year or more following their transplant and 80% live 4 or more years. Quality of life measured by ability to exercise and attend educational courses is significantly improved.
- GPs have a role in supporting patients and their families as they deal with these issues.

**Growth, nutrition and bone mass**

- Most patients with CF have pancreatic exocrine insufficiency that presents with steatorrhoea and failure to thrive. In these patients, pancreatic enzyme replacement is necessary prior to all meals and snacks.
- In addition, patients with CF have an increased basal metabolic rate requiring 120 to 150% of the recommended daily calorie intake. This requirement increases if there are additional persistent lung infections. A diet high in fat and protein is required.
- Feeding gastrostomy may be beneficial to supplement feeds, if growth is seriously compromised according to standard growth charts. Body image is a significant issue for people with CF.
- Most patients require fat-soluble vitamin supplements (principally vitamins A and E, and some will require vitamin D). Serum levels should be measured annually.
- A DEXA scan should be performed during puberty to determine bone mineral density.
- Salt replacement is necessary during periods when there is a risk of salt depletion.

**Fertility**

- Men with CF virtually always have congenital bilateral absence of the vas deferens (CBAVD) and require assisted conception to have children (sperm can be aspirated from the epididymis).
- Fertility in women is linked to nutritional status and its role in ovulation, and the potential for abnormal cervical mucus.
- Lung function may deteriorate during and after pregnancy, probably because of the physical demands of child rearing and reduced time for the patient’s own care.
- Respiratory failure may occur in women with CF and low lung function.
- Adolescents with CF may benefit from referral to a local Adolescent Health Service to answer concerns about reproductive and sexual health issues.
**Carrier testing**

- The purpose of CF carrier testing is for couples to identify if they are both carriers and therefore have a 1 in 4 chance of having a baby with CF. In this situation, it is important that carrier testing be performed prior to pregnancy, where possible.

- If a couple know they are both carriers prior to pregnancy, they are able to consider reproductive options, such as having prenatal diagnosis or pre-implantation genetic diagnosis, or to prepare themselves and their obstetric team for the possibility of having a child with CF (see *Testing and pregnancy*).

- Routine carrier testing detects the most common mutations. The panel of mutations that are commonly screened for varies amongst the Australian States/Territories. See *Contacts, support and testing* for contact details.

- The frequency of particular mutations varies between populations; therefore, knowledge of ethnicity assists carrier testing.

- Results are usually available in three to four weeks.

**Who should be offered carrier testing?**

- All 1° relatives of an individual with CF and, if positive, other relatives (see Table 1 for risk of being a carrier).

- Partners of individuals with CF.

- Partners of carriers for a CFTR mutation.

- Couples in close consanguineous relationships, particularly in ethnic groups where the CF carrier rate is high (eg Northern European, Ashkenazi Jewish).

- Men who are infertile due to, or suspected to be due to CBAVD, and their partners if they are planning a family.

**Carrier testing in the general population**

- CF carrier screening is now available in all states in Australia even where there is no family history of CF.

- There is currently no Medicare rebate available and there are out-of-pocket costs for the tests, which may be performed by a self-administered cheek brush test.

- Information regarding CF screening is available from Genetics Services.
Implications for other family members

Table 1. Risks that an unaffected individual is a carrier for cystic fibrosis prior to genetic testing for those of Northern European or Ashkenazi Jewish ancestry

<table>
<thead>
<tr>
<th>Relationship to person with CF</th>
<th>Risk of being a carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern European or Ashkenazi Jewish ancestry and no relatives with CF</td>
<td>1 in 25 (4%)</td>
</tr>
<tr>
<td>Parent</td>
<td>Obligate carrier (100%)</td>
</tr>
<tr>
<td>Brother or sister</td>
<td>At least 1 in 2 (≥50%)*</td>
</tr>
<tr>
<td>Half brother or half sister</td>
<td>1 in 2 (50%)</td>
</tr>
<tr>
<td>Uncle or aunt</td>
<td>1 in 2 (50%)</td>
</tr>
<tr>
<td>Cousin</td>
<td>1 in 4 (25%)</td>
</tr>
</tbody>
</table>

* Note: The risk given for the sibling of an affected individual takes into account both ‘classical’ CF and atypical CF. The chance that a sibling is a carrier is 1 in 2 at conception, but rises to 2 in 3 in healthy adult siblings of patients with disease severe enough to be diagnosed as children.

- To ensure that the correct mutations will be tested and that the risk figures given are accurate if testing does not detect a gene mutation, requests for carrier testing of blood relatives of an affected individual must include:
  - Either the mutations causing CF in that family or the name and date of birth of the affected individual
  - The degree of relationship to the closest affected family member
  - Ethnic background

Reproductive options

- Couples who are both carriers wishing to discuss their reproductive options should be referred to genetic counselling (see Contacts, support and testing).
- Reproductive options for carrier couples include prenatal testing by chorionic villus sampling from 11* weeks gestation, amniocentesis from 15* weeks and pre-implantation diagnosis (PGD) with IVF technology (see Testing and pregnancy).
- The approach of prenatal testing, whether by mutation testing or linkage, is best established prior to pregnancy (see Contacts, support and testing). Prenatal diagnosis for CF requires pre- and post-test genetic counselling and coordination between Fetal Medicine services and laboratory services. Screening for rarer mutations can take weeks.
- A referral to a genetic counsellor should be made as soon as pregnancy is confirmed.
  * Timing varies in different States and Territories. See Testing and pregnancy.

Atypical CF

- There are over 1500 mutations within the CFTR gene that are known to be associated with CF. Some combinations of mutations may result in a milder phenotype. For example, isolated cases of CBAVD can result from various combinations of uncommon mutations and polymorphisms (a common variation in the sequence of DNA among individuals) within the CFTR gene.
- It is highly recommended that carriers for these rarer mutations or polymorphisms, or families affected with atypical CF, be referred to Genetics Services for genetic counselling (see Contacts, support and testing).
**Referral information**

- Contact Genetics Services for details of specialty clinics in your area.

- See *Contacts, support and testing* for a list of the Peak Bodies in each State or Territory that can direct you to other CF and associated support groups in your area.

**Further information**

Cystic Fibrosis Australia.

Cystic Fibrosis Medicine.


The Australian Lung Foundation.

**Bibliography**


Cystic fibrosis is a genetic condition, which affects many parts of the body.

People with cystic fibrosis can have a range of different problems. The most common ones are lung disease (thick mucus that is difficult to cough up and lung infections), a problem with the pancreas (food is not digested and absorbed properly), loss of excessive amounts of salt in the sweat and, in males, infertility.

Other less common problems include bowel obstruction, diabetes and liver disease.

Cystic fibrosis is a serious condition which usually shortens the life of the person affected. As recently as two decades ago, a person with cystic fibrosis was unlikely to reach their twenties. Now, with improved treatment, the average lifespan is about 30 years and is expected to increase even further.

Cystic fibrosis comes about as a result of an alteration to the CFTR gene on chromosome 7. There are about 1000 known CFTR gene alterations.

Cystic fibrosis is an autosomal recessive condition (see fact sheet on 'How do genetic conditions occur?'), which means that somebody with one altered gene will be a carrier and somebody with two altered genes will have the condition.

An altered gene is found in 1 in 25 people of northern European ancestry and is slightly less common in people of southern European or Middle Eastern ancestry. An altered gene is rare in people of African or Asian ancestry.

If two people who are carriers have children, then each child has a 1 in 2 chance of being an unaffected carrier, a 1 in 4 chance of having the condition; and a 1 in 4 chance of not having the altered gene and not being affected.

Newborn screening tests (see fact sheet on 'Newborn screening') aim to detect cystic fibrosis. They do so in more than 90 out of 100 cases.

But the newborn screening tests are not perfect and 5 or 10 in every 100 people with cystic fibrosis do not have the condition picked up on those tests.

The main test for cystic fibrosis is called a sweat test. This measures the salt content of sweat. Children with the condition have a higher than normal amount of salt in their sweat.
What about other family members?

If someone in the family has cystic fibrosis, then both parents are automatically carriers for the altered gene for cystic fibrosis.

All members of the close family – parents, brothers, sisters, children, uncles and aunts – should see their doctors to discuss cystic fibrosis.

If the particular gene alteration causing the cystic fibrosis in the family is known, then blood tests to detect carriers will be highly accurate.

If the particular gene alteration is not known, it may still be possible to do a carrier test, but it will be more difficult.

If someone is a carrier for cystic fibrosis and they and their partner are planning to have children, the partner should consider having carrier testing before pregnancy. Testing will pick up only about 85 in 100 carriers for cystic fibrosis – the test can not check for all 1000 gene alterations. If no gene alteration is found, the chance that the partner is a carrier will be much lower than before the test, but the chance will not have been removed altogether.

Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- Cystic Fibrosis Medicine at [http://www.cysticfibrosismedicine.com](http://www.cysticfibrosismedicine.com)
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email [gtis-australia@unimelb.edu.au](mailto:gtis-australia@unimelb.edu.au) or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
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Patient and family fact sheet:
Diabetes
Diabetes

**GP’s role**

- Screen for diabetes every 3 years for:
  - People over 45 years with a 1° relative with type 2 diabetes
  - All people aged >55 years
  - Women with past history of gestational diabetes
- Screen for diabetes every 12 months for:
  - Aboriginal and Torres Strait Islander people over 35 years
  - People of Pacific Islander, Indian subcontinent or Chinese origin over 35 years
- Consider MODY if:
  - Early mild hyperglycaemia
  - Non-ketotic
  - No association with obesity
  - Autosomal pattern of inheritance

**Types of diabetes**

Based on recommendations from the Australasian Working Party on Diagnostic Criteria for Diabetes Mellitus the condition has been divided into four aetiological types, with impaired glucose tolerance and impaired fasting glycaemia as stages in the natural history of disordered carbohydrate metabolism.

**Type 1 diabetes**

- **Clinical features**
  - As symptoms (thirst, frequent urination and sugar in the urine) are usually first seen in childhood or adolescence, type 1 diabetes is often called juvenile diabetes.
  - This term can be misleading as type 1 diabetes can occur at any age and, in 50% of cases, onsets after the age of 20 years.
  - At least 90% of cases that are absolutely insulin dependent from diagnosis have an autoimmune destruction of the insulin-producing beta cells of the pancreas.

- **Genetics**
  - The genetic component appears to be a ‘susceptibility’ factor, rather than a direct cause of the condition. However, the majority of those who are genetically predisposed do not develop diabetes.
  - There are four confirmed susceptibility genes involved, which have a possible role in the breakdown of immune tolerance to pre-proinsulin, two of these are:
    - insulin
    - HLA (human leukocyte antigen) class II complex – HLA-DR and HLA-DQ contribute to both genetic susceptibility and protection
  - Siblings with identical forms of these HLA regions (haplotype) have around double the usual sibling risk shown in Table 1.
  - Those with a completely different haplotype have a risk of only around 1%.
  - Genetic testing is still in the research phase.
  - Understanding of the environmental triggers where there is a genetic susceptibility is still limited. However, viral infections may be an important trigger.
Prevalence

- Type 1 diabetes accounts for 10 to 15% of all diabetes in Australia.

Implications for family members

- The general population risk for developing type 1 diabetes is around 1 in 300.
- The risk that relatives of a family member with type 1 diabetes will also develop the condition has been estimated from empirical observation (see Table 1).

Table 1. Approximate genetic risks in type 1 diabetes mellitus (European data)

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Type 1 diabetes</th>
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</thead>
<tbody>
<tr>
<td>General population</td>
<td>1 in 300</td>
</tr>
<tr>
<td>Sibling of isolated case</td>
<td>1 in 14</td>
</tr>
<tr>
<td>Sibling, no shared HLA haplotype</td>
<td>1 in 100</td>
</tr>
<tr>
<td>Sibling, two or more shared haplotypes</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Sibling and another relative 1° affected</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Child of isolated case</td>
<td>1 in 25</td>
</tr>
<tr>
<td>Identical twin</td>
<td>1 in 3</td>
</tr>
</tbody>
</table>

Type 2 diabetes

Clinical features

- This form of diabetes most often occurs after the age of 40 so it has been referred to as maturity-onset diabetes.

Genetics

- Genetic predisposition for type 2 diabetes is stronger than for type 1, but the magnitude of genetic contribution is unknown and probably involves several genes.
- Recent research has identified that several polymorphisms in the hepatocyte nuclear factor 4 alpha (HNF-4α) gene is associated with increased susceptibility to type 2 diabetes by about 30%.
- Genetic testing is still in the research phase.

Prevalence

- 7.5% of the Australian population aged 25 years and older have diabetes, 8.0% of males and 7.0% of females. In people 75 years and over, 23.6% has diabetes.
- Type 2 diabetes accounts for more than 85% of people with diabetes in Australia.
- Increasing incidence of diabetes parallels the increase incidence of obesity.
- The frequency of the condition, and the most common age of onset, is different in different populations. The condition is epidemic in some countries.
- The lowest prevalences are seen in less developed countries (up to 2% in China and Africa).
- The highest prevalence can be found in certain ethn groups around the world:
  - Greater than 50% prevalence in Australian Aboriginal people.
  - Increased prevalences of diabetes in Pima Indians in the USA, South Sea Islanders and Pacific Islanders, all of whom develop type 2 diabetes early in their lives and quite severely.
**Management**

- For at-risk family members, diet and exercise may postpone the onset of the condition, or diabetes may not develop at all.

**Implications for family members**

- Risk that relatives of a family member with type 2 diabetes will also develop the condition has been estimated from observations of families with a history of the condition, not genetic testing (Table 2).  

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>Variable</td>
</tr>
<tr>
<td>Sibling of isolated case</td>
<td>1 in 10</td>
</tr>
<tr>
<td>Sibling and another 1° relative affected</td>
<td>1 in 5</td>
</tr>
<tr>
<td>Child of isolated case</td>
<td>1 in 10</td>
</tr>
<tr>
<td>Identical twin</td>
<td>1 in 2</td>
</tr>
</tbody>
</table>

**Maturity onset diabetes of the young (MODY)**

**Clinical features**

- MODY is the diabetic state associated with abnormality of the function of beta cells (still produce some insulin).
- The condition is frequently characterised by:
  - Onset of mild hyperglycaemia at an early age (generally before age 25 years)
  - No association with obesity
  - Non-ketotic disease
- Affected individuals have impaired insulin secretion with minimal or no defect in insulin action.
- There is variable severity and age of onset but symptoms usually are present before 25 years of age.

**Genetics**

- Autosomal dominant pattern of inheritance.
- There is a 1 in 2 risk for children of an affected parent.
- Changes in 1 of 6 different genes have been identified that are associated with up to around 87% of the different forms of MODY. All play a crucial role in insulin production and insulin secretion.
- Causative mutations have been identified in several MODY types.
Table 3. Some gene mutations and clinical features associated with MODY

<table>
<thead>
<tr>
<th>Gene</th>
<th>Age of onset</th>
<th>Family history</th>
<th>Fasting blood glucose</th>
<th>Response in glucose tolerance test</th>
<th>Insulin dependency</th>
<th>Other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluco-kinase (GCK)</td>
<td>Children, young adults</td>
<td>None, or one parent has mild type 2 diabetes or mild fasting hyperglycaemia</td>
<td>Persistent, stable, mild hyperglycaemia (5.5-8 mmol/L)</td>
<td>Small increment (&lt;3.5 mmol/L)</td>
<td>Not dependent, poor response to insulin</td>
<td>None</td>
</tr>
<tr>
<td>HNF-1α</td>
<td>Children, young adults</td>
<td>Strong – may be type 1 diabetes with later onset</td>
<td>Relatively normal</td>
<td>Very large increment (&gt;5 mmol/L)</td>
<td>Not dependent, although 1/3rd become insulin-dependent later in life</td>
<td>Extremely sensitive to sulphonylureas</td>
</tr>
<tr>
<td>HNF-4α</td>
<td>Children, young adults, although onset may be later than in MODY due to HNF-1α</td>
<td>Strong</td>
<td>Relatively normal</td>
<td>Very large increment (&gt;5 mmol/L)</td>
<td>Not dependent, although 1/3rd become insulin-dependent later in life</td>
<td>Extremely sensitive to sulphonylureas</td>
</tr>
</tbody>
</table>

Prevalence

- MODY comprises 2 to 5% of the diabetic population, although MODY due to mutations in HNF-4α are considerably less common.

Investigations

- Diagnostic genetic testing for MODY should be performed where it is going to change clinical management. This is likely to be in cases where there is uncertainty either in the diagnosis or in how a patient should be treated.
- Genetic testing may be available in Australia with out-of-pocket expenses.
- Predictive genetic testing for MODY may be available if the family specific mutation has been identified in an affected family member (see Contacts, support and testing). Such testing should only be considered after genetic counselling.
- Refer to Genetics Services for counselling and genetic testing if appropriate (see Contacts, support and testing).

Management

- The identification of the mutation can assist in guiding management.
Gestational diabetes

**Clinical features**
- Gestational diabetes risk factors include:
  - Glycosuria
  - Age over 30 years
  - Obesity
  - Family history of diabetes
  - Past history of gestational diabetes or glucose intolerance
  - Previous adverse pregnancy outcome
  - Belonging to an ethnic group with a high risk for gestational diabetes

**Genetics**
- Patients with MODY due to a mutation in the glucokinase gene (GCK, described above) have mild fasting hyperglycaemia throughout life and may present during pregnancy when routine testing is performed.
- Since these patients have a consistently raised fasting blood glucose they will have macrosomic children (as long as their child does not have the mutation).
- The diagnosis of a GCK mutation is important because:
  - The child may subsequently be picked up as having a raised fasting blood glucose associated with type 1 diabetes
  - Different guidelines will be given to the mother

**Prevalence**
- Ethnicity is a particularly important factor determining the incidence of gestational diabetes.
- Very high risk: Australian Indigenous, Polynesian and South Asian/Indian groups
- Moderate to high risk: Middle Eastern and other Asian groups.

**Investigations**
- The following criteria identify when GCK testing may be considered:
  - Persistently raised fasting blood glucose in the range of 5.5 – 8 mmol/L before, during and after pregnancy
  - An increment of <4.6 mmol/L on at least one oral glucose tolerance test (either during or after pregnancy)
  - A parent may have mild type 2 diabetes but often this has not been detected and so the absence of family history should not exclude the diagnosis
- Genetic testing may be available in Australia with out-of-pocket expenses.


Diabetes Research Department and the Centre for Molecular Genetics at the Peninsula Medical School and Royal Devon and Exeter Hospital, Exeter, UK. Maturity onset diabetes of the young (MODY). http://www.projects.ex.ac.uk/diabetesgenes/index.htm


Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, United Kingdom. http://www-gene.cimr.cam.ac.uk/todd/index.shtml


Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), March 2006. http://www.ncbi.nlm.nih.gov/omim/


Diabetes runs in families to some extent, but not too much is known about the genetic alterations involved.

There are four main types of diabetes:
- Type I, which usually comes on in children or young adults
- Type II, which usually comes on in middle age
- Maturity onset diabetes of the young, which is like type II in character but comes on in younger people
- Gestational diabetes, which appears in pregnancy.

The genetic involvement varies between the four types of diabetes. There is no genetic testing available for types I or II diabetes. Genetic testing is available in some circumstances for people with maturity onset diabetes of the young.

**Type I diabetes**
Type I diabetes can start at any age – about half the people who develop it are over 20 when they do so.

It seems that there is an inherited likelihood of getting type I diabetes. The child of someone with type I diabetes has a 1 in 15 chance of developing the condition. This is much higher than the average person’s chance of 1 in 500. Still, most people in the family of someone with type I diabetes do not develop the condition.

**Type II diabetes**
This is the most common type of diabetes, affecting about 1 in 20 people. Type II diabetes usually starts some time after the age of 40. It is far more common in people of certain ancestry, such as Indigenous Australians, and is more common in people who are overweight.

There is an inherited likelihood of getting type II diabetes. The child of someone with type II diabetes has a 1 in 5 chance of having the condition themselves.

Type II diabetes can be prevented, to some extent, with a good diet and regular exercise.

People who have type II diabetes in the family should ensure they eat a healthy diet, maintain a healthy weight and exercise regularly. They should also see their doctors to talk about their risk of developing diabetes and what they can do to reduce that risk.
Maturity onset diabetes of the young

This condition looks like type II diabetes in some ways, but it usually comes on before the age of 25 and is not more common in people who are overweight.

Maturity onset diabetes of the young is an inherited condition with an autosomal dominant pattern of inheritance (see fact sheet on 'How do genetic conditions occur?'). Alterations to at least six different genes can cause the condition.

People who have maturity onset diabetes of the young in the family, or who have type II diabetes in the family in someone who developed it while under the age of 25, should talk to their doctor about a referral for genetic counselling.

Gestational diabetes

Gestational diabetes is diabetes that comes on during pregnancy. It is more common in women:

- Over the age of 30
- Who have diabetes in the family
- Who are overweight
- Who have certain ancestries – Indigenous Australian, Polynesian, Indian, Middle Eastern and Asian.

Most women with gestational diabetes can look after themselves with a healthy diet and regular exercise. A few women may need insulin injections.

Gestational diabetes usually goes away soon after the child is born, although woman who have it are left with a higher than normal chance of developing type II diabetes. Babies do not develop diabetes as a consequence of their mother having gestational diabetes.

Diabetes and pregnancy

Women with diabetes have a higher than normal chance of having a baby with problems. The chances are highest if insulin is needed to control the diabetes. Risks are reduced if there is good control of diabetes in the lead up to, and during, pregnancy. Women with diabetes who are planning to become pregnant should discuss their situation with the doctor treating their diabetes.

Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- Diabetes Australia at http://www.diabetesaustralia.com.au
- Australasian Genetic Alliance at http://www.australasiangeneticalliance.org.au
- MyDr at http://www.mydr.com.au
- HealthInsite at http://www.healthinsite.com
- MedicineNet at http://www.medicinenet.com
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
Fragile X syndrome and other causes of developmental delay
Fragile X syndrome

Features

Males with a full mutation

Females with a full mutation

Individuals with a premutation

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Implications for other family members

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Further Information

Autism

Underlying genetic conditions in children presenting with autistic features

At-risk individuals

Bibliography

Patient and family fact sheet:

Developmental delay and intellectual disability
**Fragile X syndrome and other causes of developmental delay**

**GP’s role**
- Identify people who may have developmental delay, intellectual disability and/or dysmorphic features and consider referral to a relevant specialist and/or Genetics Services for assessment.
- Consider testing children or adults with developmental delay, intellectual disability, dysmorphic features or autistic-like features by karyotype and fragile X DNA testing.
- Assess family history for X linked developmental delay, including fragile X syndrome and undiagnosed developmental delay.
- Refer to Genetics Services for cascade testing of relatives.
- Manage co-existent conditions.
- Facilitate access to allied health services.
- Refer family to relevant support group (see *Contacts, support and testing*).

**Developmental delay and intellectual disability**

- Developmental delay/intellectual disability (DD/ID) is categorised as mild, moderate or severe and diagnosis is dependent on adaptive behaviour as well as IQ.
- There are many conditions such as Down syndrome and fetal alcohol syndrome that are diagnosed at birth and are associated with DD/ID.
- The majority of individuals are diagnosed with DD/ID due to a delay in reaching age-related milestones.
- When DD/ID is caused by an underlying condition, knowledge of this condition may inform the ongoing management of the child’s condition. It will also inform parents regarding the risks to future children and other family members, and enable family members to have better access to services and support.
- Although there is no cure for developmental delay or intellectual disability, early diagnosis allows for early intervention, which can improve learning outcomes.

**Genetic causes of DD/ID**

- **Chromosomal conditions** *(see Chromosomal conditions)*
  - Aneuploidy, eg trisomy 21 (Down syndrome)
  - Chromosome deletion syndromes, eg Wolf-Hirschhorn syndrome, 5p- syndrome (Cri-du-chat syndrome)
  - Chromosome microdeletion syndromes, eg Williams syndrome, Prader-Willi syndrome, Angelman syndrome

- **Single gene conditions**
  - Autosomal dominant inheritance, eg tuberous sclerosis
  - Autosomal recessive inheritance, eg metabolic conditions, including phenylketonuria (PKU) *(see Newborn screening)*
  - X-linked inheritance, eg fragile X syndrome, Rett syndrome, X-linked lissencephaly, ARX gene mutations
**Congenital infections/ teratogens**

- Congenital cytomegalovirus, congenital HIV
- Fetal alcohol syndrome
- Fetal anticonvulsant syndrome

*Individuals with conditions that can cause developmental delay may present at different ages:*

**Prenatally**
- Detected by ultrasound, eg fetal brain abnormality
- Detected by chorionic villus sampling or amniocentesis, eg Down syndrome (see *Testing and pregnancy*)

**At birth or during the neonatal period**
- Dystrophic features/birth defects, eg many chromosomal conditions or genetic syndromes
- Neurological abnormality, eg hypotonia in Prader-Willi syndrome
- Identified by newborn screening, eg PKU (see *Newborn screening*)

**In infancy**
- Marked delays, eg congenital brain malformations, Rett syndrome
- Regression in psychomotor skills

**During early childhood**
- Mild/moderate ID/DD with speech or language delay and/or behavioural difficulties, eg fragile X syndrome, Williams syndrome

**During school age years**
- Learning/socialisation problems
- Mild ID or borderline ability or specific learning disability, eg velocardiofacial syndrome with 22q11 deletion
Fragile X syndrome

Features

• Fragile X syndrome is the most common known inherited cause of intellectual disability and it has a wide variety of presentations. It is the second most common genetic cause of intellectual disability (Down syndrome is the most frequent).
• Intellectual problems can vary from mild learning difficulties through to severe intellectual disability.
• Emotional and behavioural problems may be present.
• Females show varying degrees of the condition.
• Early diagnosis can facilitate strategies that will enable individuals to achieve their maximum potential

Males with a full mutation

(see ‘Genetics’ below)
Typical features may not always be present, and may vary in severity.
• Developmental delay:
  > Intellectual disability (100% of males)
  > Speech delay
  > Fine and gross motor delay
  > Co-ordination difficulties
  > Hypotonia
• Behavioural or emotional problems:
  > Attention-deficit disorders with or without hyperactivity
  > Speech disturbances including variable pitch, perseverative speech (repetition of word or phrase) and cluttering (rapid speech with repetitions and tangential remarks)
  > Autistic-like features, eg hand flapping and biting, gaze aversion, repetitive speech mimicry (echolalia) and preoccupation with objects
  > Sensory defensiveness (aversion to touch, loud noises, bright lights and strong smells)
  > Hyperarousal or anxiety
  > Mood instability with aggression and depression, especially in post-pubertal male
• Medical conditions:
  > Up to 20% have epilepsy
  > Mitral valve prolapse
  > Recurrent ear infections
  > Eye problems, eg strabismus
• Physical characteristics (may be subtle in childhood)
  > Large prominent ears
  > Long face
  > Large testicles
  > High, broad forehead
  > High arched palate
  > Connective tissue problems, eg:
    – Flat feet
    – Loose joints
    – Scoliosis
Females with a full mutation
(see ‘Genetics’ below)
- Around 60% of females with a full mutation have cognitive deficiencies with IQ in borderline (70-84) or mild disability range.
- Females may also present with hyperactivity or a shy personality and some will present with selective mutism.
- Females may also have the emotional and behavioural characteristics seen in affected males.
- Generally speaking, affected females have a milder phenotype than affected males.

Individuals with a premutation
(see ‘Genetics’ below)
- Premature ovarian failure
  - Female premutation carriers have approximately 20% risk of developing premature ovarian failure (menopause before the age of 40 years).
- Fragile X tremor/ataxia syndrome (FXTAS)
  - FXTAS is a progressive neurological disorder that usually starts after 50 years of age. It is characterised by intention tremor, cerebellar ataxia, Parkinsonism, peripheral neuropathy and dementia.
  - Both male and female premutation carriers may develop FXTAS.
  - The risk increases with age and in males is approximately 50% by age 79 years. Female premutation carriers are less likely to develop FXTAS; the risk is not quantifiable at this time.

At-risk individuals
- Individuals of either sex with:
  - Intellectual disability
  - Developmental delay
  - Autistic-like characteristics
  - Learning disabilities of unknown cause, including borderline cases
  - A family history of fragile X syndrome or relatives of a person with developmental delay of unknown cause.
  - A previous fragile X cytogenetic test result that was inconclusive
- Consider offering fragile X DNA testing to:
  - All individuals at risk.
  - Adults (>50 years of age) who present with unexplained ataxia and/or intention tremor, Parkinsonism and dementia.
  - Preconceptionally or during pregnancy to any woman with a family history of fragile X syndrome or intellectual disability of unknown cause or a family history of premature ovarian failure.
  - Offer prenatal testing to females who are known to have a fragile X premutation or full mutation (see ‘Genetics’ below for details). Where the cause of intellectual disability has not been determined in the affected member(s) in the family, prenatal testing should be discussed and may be offered concurrently with testing of family members if time allows.
Genetics

- Fragile X syndrome follows an X-linked pattern of inheritance.
- However, due to the type of genetic alteration involved, the pattern of X-linked inheritance is atypical.
- It is caused by a mutation in a gene on the X chromosome (the FMR1 gene: fragile X mental retardation 1). The FMR1 gene codes for a protein, FMRP, which is thought to be necessary for normal neurological functioning.
- Fragile X syndrome results from an increase in the number of copies of a tri-nucleotide sequence within the gene (see Table 1). Most people have between 6 and 54 repeats, with an average of 30. Copy numbers between 55 and 200 or 230 (depending on how it is reported by the laboratory) are said to be ‘premutations’ and copy numbers of 200 or 230 and above are said to be ‘full mutations’. Genes with premutations and full mutations contain an expansion. Full mutations cause FMRP to be switched off, resulting in an individual having fragile X syndrome.

Inheritance pattern

- The size of the expansion in the FMR1 gene is unstable and can change through generations. Both men and women with an expansion may pass it on to their children:
  - Mother to child transmission is unstable, and the expansion may increase in size
  - Mothers of affected males carry either a premutation or a full mutation
  - Father to daughter transmission is stable within a small variation for premutations; that is, the expansion will not increase to a full mutation
  - There is limited data on men with full mutations; however, it appears that daughters usually inherit a premutation from their affected fathers
- Women who are carriers of a premutation or a full mutation have a 50% chance of passing it on to each of their children.
- The risk of a female premutation carrier having a child with the full mutation is related to the size of her premutation.
- Men pass a premutation or a full mutation on to all their daughters but to none of their sons, as the sons receive only their father’s Y chromosome.

Table 1. Repeat numbers and variable presentation of fragile X syndrome

<table>
<thead>
<tr>
<th>No. of repeats</th>
<th>Gene Status</th>
<th>Effect</th>
<th>Estimates of frequency in the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 - 54 (average 30)</td>
<td>Normal (including grey zone)</td>
<td>Unaffected</td>
<td></td>
</tr>
<tr>
<td>55 - 200 or 230</td>
<td>Premutation</td>
<td>Females usually unaffected carriers</td>
<td>1 in 100 - 1 in 500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males usually unaffected carriers</td>
<td>1 in 800</td>
</tr>
<tr>
<td>&gt;200 or 230</td>
<td>Full mutation</td>
<td>Females: at least half are affected</td>
<td>Approximately 1 in 8,000 females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males: generally affected</td>
<td>Approximately 1 in 4,000 males</td>
</tr>
</tbody>
</table>
A male diagnosed with fragile X syndrome could have inherited this from:

- A mother with a full mutation

  OR

- A mother with a premutation

Family studies are likely to identify individuals with premutations and may identify individuals with full mutations. Genetic counselling is important and allows families to make informed decisions about family planning (see Contacts, support and testing).

It is difficult to distinguish between a normal version of the gene and a small premutation.

The number of repeats of an intermediate size (so called ‘grey zone’ in the upper end of normal range) can change into a premutation when passed on to children.

## Prevalence

- Approximately 1 in 4,000 males has fragile X syndrome.
- Between 1 in 100 and 1 in 500 females are estimated to carry the premutation for fragile X syndrome and be variably affected.
- Between 1 in 5,000 and 1 in 8,000 females have fragile X syndrome.

## Investigations

- Fragile X DNA testing should be considered for all people with an unknown cause of developmental delay. DNA studies offer a definitive result for affected individuals and carriers.
- The DNA test is available on the MBS, and requests must specify fragile X syndrome. The MBS criteria for testing are:
  - A patient with one or more of the clinical features of fragile X syndrome
  - A patient who has a relative with a fragile X mutation
- Testing should always be performed with appropriate pre- and post-genetic test counselling.

### Preconception testing

- DNA studies to determine carrier status for those with a family history of fragile X syndrome.

### Prenatal testing

- DNA studies can be offered using specimens obtained via chorionic villus sampling or amniocentesis.
- A positive result for fragile X syndrome does not indicate the degree of intellectual disability, which varies greatly between individuals.
- Depending on test results, termination of pregnancy may be considered by the parents.
- Referral for specialist genetic counselling is recommended (see Contacts, support and testing)
Figure 1: Family pedigree of fragile X syndrome showing genotype

- **Premutation female**: eg 32,126 refers to 32 repeats on one X chromosome and 126 repeats on the other.

- **Full mutation female**: 278 refers to 278 repeats on X chromosome.

- **Premutation male**: 32,126 refers to 32 repeats on one X chromosome and 126 repeats on the other.

- **Full mutation male**: 278 refers to 278 repeats on X chromosome.
Management

- While there is no cure for fragile X syndrome, a wide range of specific treatment and management strategies are available, which involve multiple health professionals as well as the parents and carers, and are of great benefit to affected individuals and their families. These include:
  - Genetic counselling
  - Grief and anger counselling
  - Support for families, including the assistance of a community worker or social worker
  - Early intervention, ongoing speech and occupational therapies
  - Management of behavioural issues (sensory defensiveness, hyperarousal and attention problems)
    - Some clinicians find that behavioural symptoms may respond well to SSRIs (selective serotonin re-uptake inhibitors) and psychostimulants
  - Educational strategies
  - Maximising strengths
  - Pharmacological management of medical issues including epilepsy, attention disorders, aggression and mood disorders

Implications for other family members

- If an individual tests positive for a fragile X full mutation or premutation, their family should be referred to Genetics Services for counselling.
- The individual and their family should be supported in discussing fragile X syndrome with their extended family, as counselling and genetic testing should be offered to those relatives at risk of having the fragile X mutation.
- Detection of fragile X carriers allows families to make informed decisions regarding family planning

Referral Information

- Refer to paediatric and Genetics Services for assessment. Genetics Services will provide information regarding availability of multidisciplinary clinics for fragile X syndrome (see Contacts, support and testing).
- Refer to your local AGA Peak Body (see Contacts, support and testing) to find a relevant support group.

Further Information

FRAXA. http://www.fraxa.org (includes the very helpful listserver)
Autism

- Autism is characterised by impairment in verbal and nonverbal communication, imaginative play activity and social interaction.
- Between 3 in 1,000 and 4 in 10,000 individuals have autism.
- Onset is prior to 30 months of age.
- Around 80% have learning disability.
- Categorised within pervasive developmental conditions which also includes Asperger syndrome, childhood disintegrative disorder and Rett syndrome.
- May co-exist with other conditions including: intellectual disability, speech and language conditions, anxiety and depression, epilepsy, attention disorders, Tourette syndrome and Down syndrome.
- It is important to exclude specific genetic developmental conditions, specifically minor chromosomal changes and fragile X syndrome, and autistic-like features of ID.
- Autistic features can be the presenting symptoms in ID and other genetic conditions.
- Early diagnosis and intervention for a child with autism has been shown to improve outcomes and maximise learning opportunities. While there is no cure, a wide range of specific treatments and management strategies are available. Early diagnosis also ensures families and carers have better access to services and professional support.
- There is no clear inheritance pattern, however family and twin studies have shown there is a familial component to autism and pervasive developmental delay conditions.
- As yet there is no known single gene that causes autism and therefore genetic testing is not available.

Underlying genetic conditions in children presenting with autistic features

- Tuberous sclerosis, characterised by epilepsy, DD, depigmented macules
- Fragile X syndrome
- Chromosomal abnormalities, eg inversions, duplications, 15q deletions
- Metabolic conditions
- Rett syndrome, characterised by language and motor regression, loss of purposeful movement

At-risk individuals

- Individuals, especially males with:
  > A close family history of autism or related pervasive developmental delay disorder
  > Autistic-like features
- Tests that may be relevant for individuals with autistic features include:
  > Karyotype
  > Fragile X DNA testing
  > Repeat tests for newborn screening
- Refer to:
  > Paediatrician for assessment of autistic features
  > Genetics Services if the individual is dysmorphic
  > Neurologist if regression of psychomotor skills occurs
  > AGA Peak Body for an appropriate support group (see Contacts, support and testing)
- It is estimated that there is a 5% recurrence risk for siblings of children affected with autism.
http://www.genetics.com.au


http://www.racgp.org.au

Developmental delay and intellectual disability are similar phrases. They describe aspects of a person who is either slow to develop, or has not fully developed, in some of the following areas: speech, language, mental capacity or physical capacity.

Developmental delay and intellectual disability can be extremely mild or they can be quite severe. Some people with developmental delay or intellectual disability lead normal lives, while others have very restricted lives and need care outside the family.

Sometimes children with developmental delay and intellectual disability are picked up soon after birth. Sometimes the problems are noticed when children are slow to learn to talk. Sometimes problems are not detected until the child starts school. Quite often, the parents have suspected there is a problem well before it is diagnosed by doctors.

There are many different causes of developmental delay and intellectual disability. Some of the causes include infections, injuries, difficult births and autism.

Genetic conditions can also cause developmental delay or intellectual disability. The most common ones are:

- Chromosomal conditions, such as Down syndrome
- Single gene conditions, such as fragile X syndrome (which causes intellectual disability and a range of behavioural problems) or phenylketonuria (where the body lacks a specific enzyme, which causes abnormal metabolism that may result in brain damage).

In some cases, when someone in the family has developmental delay or intellectual disability, it is wise to discuss whether or not other family members need to be assessed. It is also wise to see whether or not any genetic testing is available.

While there is no cure for any form of developmental delay or intellectual disability, finding out the cause early and getting help from a wide range of professionals, can help. Some young children with developmental delay can catch up.
Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- National Organization for Rare Disorders at [http://www.rarediseases.org](http://www.rarediseases.org)
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
GP’s role

- Haemoglobinopathy carrier testing is recommended and should be discussed as part of pre-conceptional/antenatal care in the following individuals:
  > With a family history of anaemia/thalassaemia/abnormal haemoglobin variant
  > With any of the following ethnic backgrounds: Southern European, Middle Eastern, African, Chinese, South East Asian, Indian subcontinent, Pacific Islander, New Zealand Maori, South American and some northern Western Australian and Northern Territory Australian Indigenous communities
  > Partners of known or identified haemoglobinopathy carriers
  > When MCV <80fL or MCH <27pg

- Test partners of pregnant at-risk women at the same time as the pregnant woman where possible.

- Investigate with the following:
  > FBE
  > Iron studies (ferritin)
  > Haemoglobin electrophoresis

- Indications for DNA testing:
  > Possible carrier for α-thalassaemia (low-borderline MCV or MCH, normal ferritin and normal haemoglobin electrophoresis).
  > Proven carrier for β-thalassaemia and partner is also a carrier for thalassaemia or other haemoglobinopathy.
  > Confirmation of carrier status for a haemoglobin variant.

- Where a DNA test is positive, refer to specialist service (haematology clinic, Genetics Services, thalassaemia clinic).

- If both partners of a couple are carriers, refer to Genetics Services and/or haematology clinic for genetic counselling and testing. **This is particularly urgent for pregnant couples** (see Contacts, support and testing).

- Cascade genetic testing is recommended and should be discussed (see Contacts, support and testing).

- Refer the family to a relevant support group (see Contacts, support and testing).
Prevalence of haemoglobinopathies

- Figure 1 illustrates the global distribution of haemoglobin conditions in terms of number of affected infants per 1,000 births.
- The World Health Organization (WHO) estimates that globally at least 5% of adults are carriers for a haemoglobin condition: approximately 2.9% for thalassaemia and 2.3% for sickle cell disease.
- Most countries have an uneven distribution of carriers because their populations include different ethnic groups (with different carrier rates, types of haemoglobinopathy and mutations) that have become co-located as a result of migration.

In investigations

Investigations of carriers for haemoglobinopathies in general

- Genetics Services and haematologists can provide advice regarding appropriate testing.
- It is considered good practice to investigate all women of childbearing age with FBE and ferritin, and Hb electrophoresis for women from an at-risk group (see Figure 2).
- Investigation for haemoglobinopathy carrier state is usually a multi-step process, with results of FBE, ferritin studies and clinical picture influencing decisions regarding haemoglobinopathy testing and DNA analysis.
- All indications for investigation should be given, including pregnancy, gestation, ethnicity and family history, to assist the laboratory in interpreting test results.

It is not always possible to assume ethnicity from country of birth or surname. More information can be obtained by asking patients where their parents, grandparents or great-grandparents were born.

Figure 1. Global distribution of haemoglobin disorders, in terms of births of affected infants per 1000 births (WHO)
**FBE and ferritin**

- FBE and ferritin identify individuals who require further investigation; however, not all carriers for a haemoglobinopathy will be identified. For example, carriers for \( \alpha \)-thalassaemia with a one-gene deletion will usually have **borderline to normal** red cell indices, while carriers for sickle cell disease will usually have normal red cell indices.

- Ferritin is ordered to identify iron deficiency. Iron deficiency may mask thalassaemia carrier status. If the woman is not pregnant, FBE should be repeated when iron stores are replete. If the woman is pregnant, her partner should be investigated before iron stores are corrected. If the partner is shown to be a carrier for a haemoglobinopathy, DNA studies on both partners may be appropriate.

**Possible results**

- The majority of carriers for \( \alpha \)-thalassaemia and individuals with two or three copies of the \( \alpha \)-globin gene deleted will have:
  - MCV <80fL
  - MCH <27pg
  - Slightly low or normal Hb

- The majority of carriers for sickle cell disease will have normal MCV and MCH, but these could be reduced in the presence of another underlying haemoglobinopathy (eg \( \beta \)-thalassaemia carrier status) and/or iron deficiency.

**Haemoglobinopathy testing**

- Haemoglobinopathy testing determines the types, quantity and proportions of haemoglobin in the blood (see ‘Genetics’ below). Techniques for this may include haemoglobin electrophoresis and High Pressure Liquid Chromatography (HPLC) analysis. Blood films and HbH (see ‘Genetics’, under ‘\( \alpha \)-thalassaemia’) preparations identify HbH inclusions found in HbH disease and in carriers for two-gene deletion \( \alpha \)-thalassaemia (-/- \( \alpha \) \( \alpha \) or -\( \alpha \)-\( \alpha \)).

- Ideally, haemoglobinopathy testing should be performed six months after iron replacement and when iron stores are replete. However, testing should not be delayed if the woman is pregnant. If the woman is pregnant and has low red cell indices, her partner should be investigated.

- Consult a haematologist or thalassaemia service for advice.

- In general, haemoglobinopathy testing should be performed after FBE and ferritin investigations.

Haemoglobinopathy testing should be performed **concurrently** with FBE/ferritin for:

- Pregnant woman with low red cell indices
- Pregnant woman from a high-risk ethnic background
  - Partners of the pregnant woman should be tested at the same time as the pregnant woman
- Partners of individuals who are carriers for thalassaemia or a haemoglobin variant
- A family history of haemoglobinopathy or haemoglobinopathy carrier state
- Individuals from ethnic groups with a high prevalence of haemoglobinopathy
- Consanguinity
**Interpretation of results**

- A haematologist or thalassaemia service should be consulted for assistance in interpreting haemoglobinopathy testing results, as interpretation is influenced by the clinical picture.
- β-thalassaemia carrier state is characterised by the presence of increased HbA₂ (see ‘Genetics’), but this can be masked in some circumstances, such as low iron stores.
- α-thalassaemia carrier states are characterised by low red cell indices, with normal HbA₁c and/or haemoglobin electrophoresis results. Individuals with a three-gene deletion and two-gene deletions may be identified by presence of HbH bodies on HbH preparation; however, a normal HbH preparation does not exclude α-thalassaemia carrier state, especially one-gene deletion forms where the MCV & MCH are also usually in the normal range.

- Definitive identification of α-thalassaemia with one- and two-gene deletions requires DNA testing.

---

**Figure 2. Suggested protocol for targeted carrier testing of high risk populations**

1. For patients in ANY ONE of the categories below:

   - **Family history**
     - Family history of anaemia, thalassaemia or other abnormal haemoglobin variant
   
   - **Ethnic origin**
     - Southern Europe, Middle East, Africa, China, South East Asia, the Indian subcontinent, Pacific Islands, New Zealand (Maori), South America and some northern Western Australian and Northern Territory Indigenous communities

   - **Abnormal FBE**
     - MCV ≤ 80 fL and/or MCH < 27 pg

---

Arrange blood tests for person and, if applicable, partner

**Order the following:**

- FBE
- Haemoglobin electrophoresis
- Iron studies (if indicated)
- Blood for DNA studies

---

Any abnormality or diagnosis or suggestion of carrier state in couple

---

**Potential risk for couple:**

- Both carriers, or status unclear

   - Referral for counselling and risk assessment

   - Urgent if woman is pregnant

---

**No risk for couple:**

- One partner is a carrier and the other has been tested and is not a carrier

---

- One partner only is a carrier

   - Health professional, eg GP, midwife to disclose carrier status

   - Consider referring to genetic counselling service to discuss issues raised with carrier status

---

**Couple counselling:**

- Both partners are carriers: discussion about risk to pregnancy from haemoglobinopathy and available options

---

1 Petrou V, Bowden D, 2005. *Suggested protocol for targeted testing of high risk populations*, Medical Therapy Unit, Monash Medical Centre, Victoria, Australia (adapted).
Table 1. Interpretation of haemoglobinopathy carrier testing results

<table>
<thead>
<tr>
<th>MCH (pg)</th>
<th>Ferritin</th>
<th>Haemoglobin electrophoresis</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; or ≥ 27</td>
<td>Normal</td>
<td>Normal</td>
<td>Thalassaemia unlikely but one-gene deletion α-thalassaemia not excluded</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Hbs present</td>
<td>Carrier for sickle cell disease</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Normal</td>
<td>Reduced iron stores or iron deficiency, thalassaemia unlikely but one-gene deletion α-thalassaemia not excluded</td>
</tr>
<tr>
<td>&lt;27</td>
<td>Normal</td>
<td>HbA₂ increased HbH present</td>
<td>Carrier for β-thalassaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA₂ normal HbH present</td>
<td>Carrier for α-thalassaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbS present</td>
<td>Carrier for sickle cell disease Possible co-existent thalassaemia carrier state</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td></td>
<td>Possible carrier for α-thalassaemia DNA testing indicated</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Normal</td>
<td>Iron deficiency Thalassaemia may coexist If woman is pregnant, seek advice about DNA testing; test partner for full haemoglobinopathy screen</td>
</tr>
</tbody>
</table>

DNA testing

**Indications for DNA testing**

- Possible carrier for α-thalassaemia (low-borderline MCV or MCH, normal ferritin and normal haemoglobin electrophoresis).
- Proven carrier for β-thalassaemia and partner is also a carrier for thalassaemia or other haemoglobinopathy.
- Confirmation of carrier status for a haemoglobin variant.
- Patients requiring DNA testing should be referred to specialist services.

DNA testing of couples who are both carriers is necessary for prenatal diagnosis to be available. Testing can be time-consuming and, if possible, couples should be tested and referred prior to pregnancy.
### Prenatal diagnosis

- Prenatal diagnosis is available to couples where:
  - There is a risk of having a child affected by a haemoglobinopathy
    **and**
  - The causative globin mutations carried by the parents are known
- Due to the time-consuming nature of DNA testing to identify causative gene mutations, it is important that, wherever possible, DNA studies are carried out pre-pregnancy.
- Prenatal diagnosis is performed on a sample collected by chorionic villus sampling (see *Testing and pregnancy*). This is usually performed in the first trimester but, under certain circumstances, may be performed in the second trimester.

### Referral

- If both members of a couple are found to be carriers for a haemoglobinopathy, they should be immediately referred to specialist services for information regarding their risk of having a child with a severe form of thalassaemia, and to discuss the need for DNA studies. Some combinations of thalassaemia and haemoglobin variants can result in a clinically affected child.
- Pregnant couples at risk of having a child with a major thalassaemia syndrome or sickle cell disease should be urgently referred to a specialist service for counselling and possible prenatal diagnosis.

### Condition-specific information

#### β-Thalassaemia

**Clinical features**

- The common clinical features of β-thalassaemia major manifest after birth, usually within six to 12 months and include:
  - Pallor
  - Lethargy
  - Poor appetite
  - Developmental delay
  - Failure to thrive
  - Irritability, difficulty settling
  - Splenomegaly, growth failure with bone changes, fractures and leg ulcers also develop during childhood
  - Haemolytic anaemia
- Carriers for β-thalassaemia are usually asymptomatic but may have mild hypochromic anaemia.
Genetics

- Haemoglobin A (HbA) contains two α-globin chains and two β-globin chains (α₂β₂).
- HbA₂ is a normal variant of haemoglobin and is composed of two α-globin and two δ-globin chains (α₂δ₂). It usually represents 2 to 3.5% of normal total adult haemoglobin.
- HbF refers to fetal haemoglobin, a normal variant in fetal development that persists in small amounts postnatally. It is composed of two α-globin and two γ-globin chains (α₂γ₂) and usually represents less than 1% of normal total adult haemoglobin.
- β-thalassaemia is caused by reduced or absent production of the β-globin chain of the haemoglobin molecule.
- The β-globin gene (HBB) encodes the β-globin chain. Each individual has two copies of this gene, one from each parent.
- β-thalassaemia major is caused by mutations in both copies of the β-globin gene, resulting in virtually no functional β-globin chains being produced. This is a severe medical condition requiring frequent blood transfusions and iron chelation therapy.
- β-thalassaemia minor (also called β-thalassaemia trait) is the carrier state and is caused by a mutation in one copy of the β-globin gene. While this is not a serious medical condition, it manifests as reduced red cell indices and elevated concentrations of HbA₂, and can be mistaken for iron deficiency.
- β-thalassaemia major follows a pattern of autosomal recessive inheritance. Carriers have a 50% chance of passing the mutated β-globin gene to their children. Couples who are both carriers have a 25% chance of having an affected child. This risk applies for every pregnancy of that partnership.
- Co-inheritance of β-thalassaemia minor and a haemoglobin variant (for example, Hb Lepore, HbC or HbE) may result in a form of β-thalassaemia major (see 'Other haemoglobinopathies caused by structural change'). This is known as compound heterozygosity, as the two types of gene mutations are different.
- Couples where one partner is a carrier for β-thalassaemia and the other is a carrier for α-thalassaemia are not at risk of having children with thalassaemia major.

Prevalence

- There are particular sub-groups of the population who are at increased risk of being a carrier for α-thalassaemia:
  - 1 in 5 people of high-risk ethnic background (from the Middle East, Southern Europe, Indian subcontinent, Central and South East Asia and Africa) may carry a β-thalassaemia mutation
  - An individual with an MCH <27pg and/or MCV <80fL is at increased risk of having a thalassaemia minor carrier state. Some labs consider MCH ≤ 27pg and MCV ≤ 81fL
  - Individuals with a family history of β-thalassaemia major and/or β-thalassaemia minor
- Also see 'Prevalence of haemoglobinopathies' above.

Investigations

- See 'Investigations of carriers for haemoglobinopathies in general' above.
- Genetics Services or haematologists can provide advice regarding appropriate testing.

For affected individuals

- FBE usually shows significant anaemia, microcytosis, hypochromia and abnormal red cell morphology, including target cells. Nucleated red blood cells are usually present.
- Haemoglobin electrophoresis testing to determine HbF and HbA₂ levels is usually diagnostic of β-thalassaemia. Affected children over the age of six months usually have markedly elevated levels of HbF and elevated HbA₂.
- Compound heterozygous states result in a variety of abnormal results on haemoglobinopathy testing. Contact a haematologist for advice.
For potential or identified carriers

- It is considered good practice to investigate all women of childbearing age with FBE and ferritin, and Hb electrophoresis for women from an at-risk group (see Figure 2).
- Investigation for β-thalassaemia carrier state is usually a multi-step process, with results of FBE, ferritin studies and clinical picture influencing decisions regarding haemoglobinopathy testing and DNA analysis.
- All indications for investigation should be given, including pregnancy, gestation, ethnicity and family history, to assist the laboratory in interpreting test results.

Management

- Treatment and management is performed by specialist services.
- Patients with β-thalassaemia major require regular blood transfusions every three to four weeks for their whole life.
- Excess iron is eliminated from the body by iron-chelating agents (eg desferrioxamine, administered by subcutaneous infusion pump), with oral chelating agents now available to supplement or replace desferrioxamine.
- A ‘no added iron’ diet is recommended.
- The majority of complications associated with β-thalassaemia major are due to iron build-up, despite chelation therapy, or marrow expansion.
- Splenectomy may be performed because of enlargement. These patients require the same immunisation as other children and prompt treatment of infections.
- Bone marrow transplantation may cure β-thalassaemia major but has a significant risk of complications and mortality.
- The life expectancy of well-treated, compliant patients is not known but is likely to be normal or near normal.
- Carriers for β-thalassaemia should have folic acid (5 mg) daily throughout all pregnancies.
- Carriers for β-thalassaemia must not have long-term iron treatment to attempt to cure microcytosis, unless they are also iron deficient.

α-Thalassaemia

Clinical features

- Clinical features of α-thalassaemia can manifest in pregnancy or after birth and include:
  > Hydrops fetalis, resulting from deletions of all four α-globin genes, is fatal in the fetus or neonate.
  > Haemoglobin H (HbH) disease is an intermediate form of α-thalassaemia caused either by deletions or other mutations of three copies of the α-globin genes. It causes life-long anaemia of mild to moderate degree.
  > Carriers for α-thalassaemia are usually asymptomatic but may have a mild hypochromic microcytic anaemia.
Genetics

- α-thalassaemia is caused by decreased or absent production of the α-globin chains.
- Two identical α-globin genes encode the α-globin chains.
- Each individual therefore has four α-globin gene copies: two gene copies inherited from each parent.
- **Hydrops fetalis** is caused by deletion of all four copies and results in early fetal or neonatal death. In addition, the mother of an affected fetus is at risk of severe early pre-eclampsia, ante-partum or post-partum haemorrhage, and pre-term delivery.
- **Haemoglobin H disease (HbH disease)** is caused by deletion of three copies of the α-globin genes, which results in the presence of HbH (β4), an abnormal form of haemoglobin caused by excessive β-globin chains. HbH disease is an intermediate form of α-thalassaemia, which varies in severity. HbH disease can cause life-long anaemia of mild to moderate degree and sometimes requires transfusion support. Medical management is advised.
- Individuals with **α-thalassaemia minor** have one or two copies of the α-globin genes deleted. This is not clinically significant; however, haemoglobin is often in the low end of the normal range and MCV and MCH may be reduced.
- In general, α-thalassaemia major follows an autosomal recessive pattern of inheritance, but the genetics is complex.

Prevalence

- The carrier state is common in certain ethnic groups. Those who are at increased risk for having α-thalassaemia carrier state (α-thalassaemia minor or trait) include individuals:
  - With an MCH <27pg and/or MCV <80fL.
  - Who are most commonly of Chinese and South East Asian origin but the disorder occurs in many other ethnic groups, including those from Southern European countries, the Middle East, the Indian subcontinent, Pakistan, Africa, the Pacific Islands and New Zealand (Maori), and some Indigenous Australian communities in the Northern Territory and northern Western Australia.
  - With a family history of α-thalassaemia major and/or α-thalassaemia minor.
  - Have a history of severe pre-eclampsia in association with early fetal death.
- Also see ‘Prevalence of haemoglobinopathies in general’ above.

Investigations

- See ‘Investigations of carriers for haemoglobinopathies in general’ above.
- Genetic Services or haematologists can provide advice regarding appropriate testing.

For affected individuals

- FBE usually shows significant anaemia, microcytosis, hypochromia and abnormal red cell morphology, including target cells and fragmented cells.
- Haemoglobinopathy testing demonstrates normal HbA2 and abnormal haemoglobin electrophoresis. In younger individuals HbH preparation demonstrates presence of varying amounts of HbH.
Haemoglobinopathies

For potential or identified carriers

- It is considered good practice to investigate all women of childbearing age with FBE, ferritin and Hb electrophoresis for women from an at-risk group (see Figure 2).
- Investigation for α-thalassaemia carrier state is usually a multi-step process, with results of FBE, ferritin studies and Hb electrophoresis and clinical picture influencing decisions regarding further haemoglobinopathy testing and DNA analysis.
- All indications for investigation should be given, including pregnancy, gestation, ethnicity and family history, to assist the laboratory in interpreting test results.
- In couples where both people are carriers for α-thalassaemia or another haemoglobinopathy, referral to a specialist service for information about their risk of having an affected pregnancy should be arranged.

Where an α-thalassaemia carrier state is identified it is essential that the partner be investigated. Testing the partner is an urgent priority if the woman is already pregnant.

Management

- Some individuals with HbH diseases require regular blood transfusion and folic acid.
- Patients should receive regular medical care from their GP.

Sickle cell disease (also known as HbS disease)

Clinical features

The common features include:
- Anaemia
- Failure to thrive
- Repeated infections
- Painful swelling of the hands or feet
- Infarction
- Asplenia
- Abdominal pain
- Chest pain

Genetics

- Haemoglobin contains two α-globin chains and two β-globin chains. Each individual has two copies of the β-globin gene, one from each parent.
- Sickle cell disease is caused by a mutation in both copies of the β-globin genes resulting in changes to the structure of the β-globin chain of haemoglobin, ie haemoglobin variant. This results in red blood cells that form an irreversible sickle shape after repeated cycles of deoxygenation.
- Individuals with sickle cell disease usually have chronic anaemia due to increased destruction of red blood cells.
- They may also experience sickle cell crises due to blockage of blood vessels by these cells, causing bone and chest pain and damage to other organs.
- They usually autosplenectomise within the first ten years of life.
- Individuals with sickle cell disease who have crises require medical management, which may include regular blood transfusions.
- Sickle cell trait (term to describe the carrier state) is caused by a mutation in one copy of the β-globin gene. Carriers are usually healthy. In some very rare instances (eg anaesthesia or long distance air travel), the red blood cells of a carrier can undergo partial sickling.
• Sickle cell disease is an autosomal recessive condition. Carriers have a 50% chance of passing the mutated gene to their children. Couples who are both carriers have a 25% chance of having an affected child. This risk applies for every pregnancy of that partnership.

• Co-inheritance of sickle cell trait (or other haemoglobin variant) and β-thalassaemia minor may result in a form of sickle cell disease. This is known as compound heterozygosity, as the two types of gene mutations are different.

## Prevalence

• Sickle cell disease is one of the most common inherited conditions of haemoglobin worldwide and is seen in many populations including people from Africa, the Middle East, Southern Europe, India, Pakistan, South America and the Caribbean.

• The WHO estimates that 1 in 500 African-American births and 1 in every 1,000 to 1,400 Hispanic-American births are affected by sickle cell disease, and that 1 in 12 African-American people carry the mutated sickle cell allele.

• In Australia, sickle cell disease has been most commonly seen in individuals of Southern European and Middle Eastern origin (especially Lebanese and Turkish). However, with increasing immigration from sub-Saharan Africa and the Indian subcontinent, HbS is becoming more prevalent.

• Individuals who are carriers for sickle cell disease may be clinically and haematologically silent, with normal red cell indices.

• Individuals at increased risk of being a carrier for sickle cell also include those with a family history of sickle cell disease and/or sickle cell carrier state.

• Also see ‘Prevalence of haemoglobinopathies in general’ above.

## Investigations

• See ‘Investigations of carriers for haemoglobinopathies in general’ above

• FBE and ferritin tests generally do not show abnormalities.

• Haemoglobinopathy testing results are abnormal and indicate sickle cell disease (homozygosity) or sickle cell trait (heterozygosity – sickle cell disease carrier state)

• It is important to identify couples who are both carriers for sickle cell disease or other haemoglobin variants and/or thalassaemia in order to offer information about their risk of having a severely affected child and, where possible, prenatal diagnosis.

• The best time to identify carriers is prior to pregnancy.

Where the sickle cell carrier state is identified it is essential that the partner be investigated. Testing the partner is an urgent priority if the woman is already pregnant.

## Management

• Sickling of red blood cells can occur in any organ and affect its function.

• Individuals with symptoms of sickle cell crisis should be sent immediately to the emergency department of a hospital for administration of:

  ▶ IV fluids
  ▶ Pain relief
  ▶ Other treatment if indicated

• Patients should receive regular medical care from their GP.

• Women with sickle cell disease who are pregnant should be referred to a specialist centre for management.

• Carriers for sickle cell disease are healthy and are not affected by anaemia. In some very rare instances, (eg anaesthesia), the red blood cells of a carrier can undergo sickling. Anaesthetists should be informed when a patient is a carrier for sickle cell disease.
Other haemoglobinopathies caused by structural change

- Individuals from certain ethnic backgrounds have an increased risk of carrying a globin chain gene mutation causing a structural variant.
- Only a small number of variants capable of causing a severe condition in the homozygote or in compound heterozygotes are encountered in Australia. These include HbS (sickle cell disease), HbC, HbD, HbE, HbO and Hb Lepore.
- Testing for haemoglobin variants requires haemoglobin electrophoresis as it is common for no other haematological abnormality to be present.
- Partners should have FBE and haemoglobinopathy testing to investigate carrier status for β-thalassaemia and/or haemoglobin variants.

Table 2. Examples of states causing clinically significant haemoglobinopathies

<table>
<thead>
<tr>
<th>Haemoglobin types</th>
<th>Disease status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous HbS</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>HbS/β-thalassaemia</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>HbS/HbC disease</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>HbS/HbD</td>
<td>Sickle cell disease of variable severity</td>
</tr>
<tr>
<td>Homozygous HbE</td>
<td>Behaves as a mild β-thalassaemia mutation</td>
</tr>
<tr>
<td>HbE/β-thalassaemia</td>
<td>Mild to severe condition equivalent to β-thalassaemia major</td>
</tr>
<tr>
<td>HbC/β-thalassaemia</td>
<td>Sickle cell disease (mild to severe, depending on causative mutations)</td>
</tr>
<tr>
<td>Homozygous Hb Lepore</td>
<td>β-thalassaemia intermedia (moderate to severe β-thalassaemia)</td>
</tr>
<tr>
<td>Hb Lepore/β-thalassaemia</td>
<td>β-thalassaemia major</td>
</tr>
<tr>
<td>Hb Lepore/HbS</td>
<td>Sickle cell disease of variable severity</td>
</tr>
</tbody>
</table>
Further information


Bibliography


http://www.genetics.com.au


Petrou V, Bowden D, 2005. Suggested protocol for targeted testing of high risk populations. Medical Therapy Unit, Monash Medical Centre, Victoria, Australia (adapted).


http://www.who.int/genomics/public/Maphaemoglobin.pdf


Haemoglobin is an important protein in the blood. Haemoglobin is found in red blood cells and carries oxygen from the lungs to all the tissues.

Various genetic conditions affect haemoglobin, making it less able to carry oxygen, or causing damage to the red blood cell it is in.

The most common problems are thalassaemia (a genetic disorder inherited from both parents resulting in a reduction in the amount of haemoglobin produced by the body) and sickle cell anaemia (a genetic disease in which red blood cells may change shape under certain circumstances; this causes problems when the cells become stuck in blood vessels that carry oxygen and nutrients to individual cells). About 5 in every 100 people throughout the world are carriers for one of these conditions. Haemoglobinopathies are more common in some parts of the world than in others, particularly where malaria is common.

Haemoglobinopathies may be mild or they may be severe. They can cause a range of illnesses from slight tiredness, to severe anaemia (not enough red blood cells) needing regular blood transfusions, to episodes of severe pain.

You should consider having a blood test to see if you are a carrier for one of these conditions and possibly see a genetic counsellor if you:

- Have a relative with one of these conditions, or have a relative who is a carrier for one of these conditions
- Have unexplained anaemia or have people in the family with unexplained anaemia
- Have ancestry from where these conditions are common – southern Europe, the Middle East, South-East Asia, Africa, the Indian subcontinent, South America, the Caribbean and the Pacific Islands.

This is particularly important if you are pregnant or could become pregnant.
Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- Thalassaemia Society of Victoria at http://www.tsv.org.au
- National Organization for Rare Disorders at http://www.rarediseases.org
- Australasian Genetic Alliance at http://www.australasiangeneticalliance.org.au
- MyDr at http://www.mydr.com.au
- The Centre for Genetics Education at http://www.genetics.edu.au
- HealthInsite at http://www.healthinsite.com
- MedicineNet at http://www.medicinenet.com
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
Hereditary haemochromatosis

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**GP’s role**
- Order iron studies (fasting transferrin saturation and serum ferritin).
- Consider HFE gene testing or referral to gastroenterologist if: transferrin >45%, ferritin >250µg (pre-menopausal female) or >300µg (post-menopausal female/male).
- Organise regular monitoring of iron indices in people being treated for iron overload.
- Discuss the importance of cascade testing (see Contacts, support and testing) for 1° and 2° relatives when an individual has been diagnosed with HH or has been found to be heterozygous.
- Refer to Genetics Services if appropriate for genetic counselling and discussion regarding issues such as testing (see Contacts, support and testing).
- Refer family to a relevant support group (see Contacts, support and testing).
- The MBS covers HFE gene testing for patients with:
  - Raised ferritin or transferrin levels on more than one occasion, or
  - A 1° relative diagnosed with HH

---

**Clinical features**
- Hereditary haemochromatosis (HH) is a common condition in which excessive iron absorption leads to greatly increased body iron stores. The deposition of iron occurs in parenchymal cells of the liver, heart, pancreas and other organs.
- In the majority of patients with overt HH, the first symptoms develop between the ages of 30 and 60 years.
- Clinical expression in children with HH is extremely uncommon before the late teens.
- Antenatal diagnosis is not necessary as HH is an adult onset condition.
- Menstruation and pregnancy account for the delayed presentation of the condition in women.
- Common clinical features include one or more of the following:
  - Lethargy and weakness
  - Arthralgia
  - Loss of libido
  - Upper abdominal discomfort
  - Hepatomegaly
  - Grey/brown skin pigmentation
  - Testicular atrophy
  - Joint swelling/tenderness
- Liver function tests (LFTs) are frequently normal in asymptomatic patients, but may be abnormal in symptomatic patients.
- Early diagnosis and treatment of HH is associated with a normal life expectancy.
- Untreated HH can lead to serious complications and death. The complications include:
  - Liver condition with fibrosis or cirrhosis
  - Arthritis/osteoarthritis at the metacarpal heads, particularly in the second and third MCP joints
  - Impotence
  - Diabetes mellitus – usually seen in the advanced stages of the condition
  - Cardiomyopathy and arrhythmias
  - Hepatocellular carcinoma in about 30% of patients with cirrhosis
Genetics
• The gene involved in HH is called the HFE gene.
• Mutations in the HFE gene can lead to impaired regulation of iron storage and are believed to be the most common cause of HH.
• Frequencies of HFE genotypes in the Australian population are shown in Table 1.
• About 90% of people of Northern European ancestry with symptoms of HH have the C282Y mutation in both copies of their HFE gene - homozygotes (see Contacts, support and testing for an explanation of terminology).
• About 2% of people with HH have a C282Y gene mutation in one of their copies of the HFE gene, and the H63D gene mutation in their other copy (compound heterozygotes).
• Compound heterozygotes have inherited one copy of the C282Y gene mutation from one parent and one copy of the H63D gene mutation from the other parent.
• HH follows an autosomal recessive pattern of inheritance.
• Therefore there is often no family history of the condition, or affected family members may appear to be scattered amongst or within generations.
• Where both parents are heterozygous (carriers for a mutation in the HFE gene), there is a 25% chance that each of their children will inherit a gene mutation in both copies of their HFE gene, and be genetically predisposed to HH.
• If only one parent is a carrier for a mutation in the HFE gene, there is a 50% chance that each of their children will be an HFE mutation carrier.

<table>
<thead>
<tr>
<th>HFE genotype</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>No gene mutation found</td>
<td>2/3</td>
</tr>
<tr>
<td>Homozygous C282Y</td>
<td>1/200</td>
</tr>
<tr>
<td>Compound heterozygote (C282Y/H63D)</td>
<td>1/50</td>
</tr>
<tr>
<td>Heterozygous C282Y</td>
<td>1/10</td>
</tr>
<tr>
<td>Heterozygous H63D</td>
<td>1/6</td>
</tr>
<tr>
<td>Homozygous H63D</td>
<td>1/100</td>
</tr>
</tbody>
</table>

Prevalence
• More common in people of Northern European backgrounds:
  > Affects about 1 in 250 people of Northern European background
  > Approximately 1 in 8 people with this same ancestry are carriers for a mutation for haemochromatosis (heterozygotes)
• Uncommon in Asian and African populations.

Investigations
• Assess risk by taking a family history (see Genetics in practice).
• Note ancestry.
• If there is a family history of HH, perform iron studies and an HFE gene test for 1° and 2° relatives of an index case if they are your patients and of an appropriate age.
• If there is no family history but HH is suspected, the most useful tests are fasting transferrin saturation and serum ferritin.
Iron studies

- The transferrin saturation (ratio of serum iron and iron binding capacity) reflects increased absorption of iron, which is the underlying biological defect in HH.
- A fasting transferrin saturation >45% is the most sensitive test for detecting early iron overload but a raised fasting transferrin saturation or ferritin is not diagnostic of HH.
- HH is also unlikely if the ferritin is very high and the transferrin saturation is normal.
- An elevated serum ferritin reflects an increase in body iron stores:
  - Serum ferritin is also an acute phase reactant and can be elevated non-specifically in the presence of alcohol consumption, inflammation and other liver conditions
  - Serum ferritin is abnormal when it is >250 µg/L in pre-menopausal women and >300 µg/L in men and post-menopausal women
- If the fasting transferrin saturation or serum ferritin is increased on more than one occasion, HH should be suspected, even if there are no clinical symptoms or abnormal LFTs. In this situation, the HFE gene test should be ordered.
- Some C282Y heterozygotes will have minor abnormalities in iron studies, but this has not been proven to be associated with the development of HH.
- Iron studies may be normal in individuals with a genetic predisposition to HH who have not developed iron overload. Up to 40% of homozygotes have normal iron studies, which may be due to overt (blood donation) or covert (gynaecological or gastrointestinal) blood loss.

HFE gene test

- The MBS covers HFE gene testing for patients with:
  - Raised ferritin or transferrin levels on more than one occasion, or
  - A 1° relative diagnosed with HH
- Most laboratories test for the HFE gene mutations C282Y and H63D (see Contacts, support and testing).

Interpreting the results of the gene test

- All patients with iron overload require follow-up regardless of the HFE gene test result, because in a small percentage of cases of HH a different, rarer gene mutation may be responsible.
- Where no mutation is found in the HFE gene, and iron studies are normal, HH is exceedingly unlikely to develop.
  - C282Y homozygote:
    - 90% of Australians with HH have this genetic test result
    - However, not all individuals with this genotype will develop HH
    - It is estimated that 60 to 70% of C282Y homozygotes will develop iron overload during their lifetime
  - Compound heterozygote:
    - Only about 1% of people with this genotype develop HH
    - Iron status should be monitored every 2 to 5 years
  - C282Y and H63D heterozygote or H63D homozygote:
    - The risk of developing HH is extremely small
    - Some patients may have minor abnormalities in iron studies
    - There is no need to monitor iron status unless levels are abnormal or symptoms are present
Management

- Follow up all patients with iron overload regardless of the HFE gene test result.
- If HFE gene test shows a patient to be C282Y homozygote and iron overload is absent, perform iron studies every 2 to 5 years.
- If HFE gene test shows a patient to be C282Y homozygote and iron overload is present or the patient has other complications of HH:
  - Lifelong venesection is required
  - An initial course of 1 or 2 venesections per week is performed until the excess iron stores are removed
  - The response to venesection treatment depends on the presenting symptoms and the stage of the condition at the time of diagnosis (see Table 2)
  - Therapeutic venesection can still be arranged even if a patient is not eligible to donate blood for other reasons
  - Once iron levels are at low normal levels, patients usually require one venesection every 3 to 4 months to keep levels low without rendering the patient iron-deficient
  - A high red meat intake may increase the frequency of venesections required to maintain normal iron stores and therefore patients may choose to reduce their red meat intake
  - Diet modification may help if patients cannot undergo venesection, but it is not nearly as effective
  - Vitamin C (ascorbic acid) supplements should be avoided, since vitamin C increases iron absorption
  - Patients should abstain from alcohol consumption until iron levels are normalised through venesection
  - Fibrosis does not reverse following venesection therapy
  - It is rare for patients not to tolerate venesection therapy
  - Non-cirrhotic patients diagnosed and treated early have a normal life expectancy provided they continue treatment
  - Cirrhosis is unlikely
    - If the ferritin level is <1000 µg/L, the AST level is normal and there is no hepatomegaly
    - If the patient is non-cirrhotic at diagnosis and is adequately treated
  - Cirrhosis rarely develops, but if cirrhosis does develop, it does not regress to normal despite treatment
  - Patients with cirrhosis have a risk of primary liver cancer even when complete iron depletion is achieved. These patients should be screened every six months with hepatic ultrasound and serum a-fetoprotein levels
  - Liver biopsy may be performed to either confirm or exclude the presence of cirrhosis if blood tests are suggestive of cirrhosis

Table 2. Response to venesection

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Good</th>
<th>Variable</th>
<th>Poor</th>
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<tbody>
<tr>
<td>Fatigue</td>
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<td>Skin pigmentation</td>
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<td>Abdominal pain</td>
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<td>Cardiomyopathy</td>
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<td>Diabetes</td>
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<td>Hypogonadism</td>
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<td>Hepatic fibrosis</td>
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<td>Arthropathy</td>
<td>•</td>
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<tr>
<td>Cirrhosis</td>
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</table>
Implications for other family members

- The family members of individuals with HH, unaffected C282Y homozygotes, compound heterozygotes and C282Y heterozygotes may be at increased risk of also having HH (see Table 3).
- Individuals known to carry these gene mutations should be encouraged to:
  - Inform family members that they may be at increased risk of HH
  - Give family members written information about HH
  - Advise family members to discuss their risk of HH with their GP or Genetics Services
- Since all individuals inherit one copy of the HFE gene from each of their parents, an individual’s risk of inheriting a predisposition for HH depends on the genotype of their parents.
- It is recommended that 1° and 2° relatives of individuals who have HH or are homozygous for the C282Y gene mutation are tested with iron studies and the HFE gene test.
- Siblings of individuals with HH, or siblings of unaffected C282Y homozygotes, have at least a 25% chance of having the same genotype, and 50% chance of being a carrier for the HFE mutation. Where possible, parents should also be tested.
- Genetic screening of adult children of a patient with HH is not required if the other parent is tested and does not have an HFE gene mutation.
- The most appropriate age for screening at-risk children should be decided on a case-by-case basis by the treating specialist.
- Predictive genetic testing of asymptomatic children should generally be delayed at least until the age of 18 years.
- The Human Genetics Society of Australasia recommends that predictive genetic testing of children should be carried out only when a specific treatment intervention is available and delay is inappropriate.
- If parents are worried, explain that the partner of the homozygote can be tested and if they test negative for an HFE gene mutation, then the children can only be carriers.
- Pre-test genetic counselling should occur if parents insist on testing their children.

Table 3. Parents’ HFE genotype and probability of HFE genotypes for offspring

<table>
<thead>
<tr>
<th>Parent 1 HFE genotype</th>
<th>Parent 2 HFE genotype</th>
<th>Probability offspring C282Y homozygote</th>
<th>Probability offspring C282Y heterozygote</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y heterozygote</td>
<td>C282Y heterozygote</td>
<td>25%</td>
<td>50%</td>
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<tr>
<td></td>
<td>Compound heterozygote</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>No gene mutation</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>C282Y homozygote</td>
<td>C282Y heterozygote</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Compound heterozygote</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>No gene mutation</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>Compound heterozygote</td>
<td>Compound heterozygote</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>No gene mutation</td>
<td>0%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Referral information

- Patients or families requiring more detailed genetic counselling can be referred to Genetics Services.
- Venesection can be performed in a number of settings, including:
  - The Australian Red Cross Blood Service which offers a therapeutic venesection service for patients with HH, provided that they do not suffer from a transfusion transmissible condition. The referring doctor is required to review the ongoing need for venesection at least every 12 months.
  - In association with a hepatology clinic.
  - Some private pathology services.
  - Some medical practitioners (a Medicare item number applies).

Bibliography


Hereditary haemochromatosis is a common condition in which too much iron is absorbed from food and stored in the body. It is usually picked up between the ages of 30 and 60 – earlier in men than in women.

The condition can cause tiredness, sore joints, loss of sex drive, impotence, abdominal pain, heart disease, diabetes, an enlarged liver and even, occasionally, cirrhosis of the liver and liver cancer.

If it is not detected for many years, hereditary haemochromatosis can be a severe condition.

But if picked up early and treated, the condition can be mild. People with treated hereditary haemochromatosis usually have a normal lifespan.

Haemochromatosis arises from an alteration to a particular gene known as the HFE gene. It follows an autosomal recessive pattern of inheritance (see fact sheet on 'How do genetic conditions occur?'). This means that someone with the condition has an alteration in both copies of their HFE gene. The parents of an affected person will be carriers and there are likely to be other family members who are carriers. There may also be relatives with alterations in both copies of the gene who are healthy at present, but will develop the disorder in the future.

It is worth noting that having alterations in both HFE genes does not give you haemochromatosis – it only indicates that you have a high likelihood of getting the condition. At least a third of people with alterations in both their HFE genes will have no problems from it.

If someone in the family has hereditary haemochromatosis, then all members of the immediate family should have blood tests known as iron studies, which measure the amount of iron in the body. They should also have tests to see if they have two, one or no alterations in HFE.

Those who have abnormal iron studies will usually be referred to a specialist for follow up and treatment. Those with alterations in both HFE genes but normal iron studies need follow up by their doctor.

Depending on these results, your doctor may recommend that other adult family members also be tested. Because the condition does not generally affect children, it is usually best to wait to test until they are adults.

A word of caution about the gene test. The test picks up both HFE gene alterations in most people with hereditary haemochromatosis. But it does not always do so and it is possible to have hereditary haemochromatosis, but not have it show up on a genetic test.

Anybody with hereditary haemochromatosis, and their close relatives, should have genetic counselling, which may involve referral to a genetics service.
Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on [free call Australia-wide 1800 631 276](tel:1800631276) or email [gtis-australia@unimelb.edu.au](mailto:gtis-australia@unimelb.edu.au) or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
Neurofibromatosis
Neurofibromatosis type 1 (NF1)

Also known as Von Recklinghausen’s disease; Peripheral Neurofibromatosis; Von Recklinghausen’s Neurofibromatosis; Recklinghausen’s Phakomatosis; Multiple Neurofibroma.

GP’s role

• Where possible confirm or rule out a diagnosis in the parents of an affected individual using the clinical diagnostic criteria listed below. If unsure of a diagnosis, refer to Genetics Services (see Contacts, support and testing).
• Refer as appropriate to specialist paediatric or adult neurology, dermatology, ophthalmology and/or orthopaedic services.
• Refer to Genetics Services for discussion of prenatal genetic testing (see Contacts, support and testing).
• Refer family to relevant support groups (see Contacts, support and testing).

Clinical features

• NF1 is characterised by the development of multiple café-au-lait spots, inguinal/axillary freckling and multiple neurofibromas.
• Symptoms usually appear during childhood and may become more pronounced during puberty, pregnancy, or when hormonal changes take place.
• Range and severity of symptoms can vary greatly among affected individuals even between family members.
• Rate of progression is not predictable.
• Diagnosed when two of the following clinical features are present:
  > Six or more café-au-lait spots, >0.5cm diameter before puberty, or >1.5cm in adults
  > Two or more neurofibromas of any type or one plexiform neurofibroma
  > Freckling under the arms or in the groin area
  > Benign tumour of the optic nerve (glioma)
  > Two or more Lisch nodules (iris hamartomas)
  > A distinctive osseous lesion such as a sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis
  > A 1st relative (parent, sibling or offspring) with NF1 by the above criteria
• Additional but not diagnostic features:
  > Precocious puberty or delayed sexual development may occur
  > About 50% have specific learning disabilities in reading, spelling or mathematics
  > Growth may be reduced
  > Macrocephaly
  > Scoliosis
  > Hypertension
  > Epilepsy
Genetics
• NF1 is caused by mutations in the NF1 gene that encodes a protein called neurofibromin, which functions as a tumour suppressor.
• Many different mutations in the NF1 gene have been identified in individuals with the condition.
• The condition follows a pattern of autosomal dominant inheritance.
• Approximately 50% of NF1 cases are inherited from a parent.
• About 50% are due to new mutations in the NF1 gene occurring randomly at or around conception for unknown reasons.

Prevalence
• NF1 affects about 1 in 3000 people.
• There is a wide range of severity of symptoms.
• Many people with the condition will only be affected mildly.
• For most people, NF1 does not significantly affect their health but for a few, NF1 can cause major health problems at certain stages of their lives.

Investigations
• Genetic testing is not needed to diagnose the condition after birth because most people with NF1 will have enough signs of the condition by age 5 years for a specialist to diagnose them with confidence.
• Genetic testing for NF1 is not widely available and is currently expensive, but it can be helpful in some situations, such as where prenatal diagnosis is requested.
• Prenatal genetic testing can be done where one of the parents is affected and wants to know if the fetus is affected, provided the specific NF1 mutation in the affected parent has been identified.

Management
• An annual review by GP for complications of the condition and for management advice (eg referral to plastic surgeon) should be undertaken.
• Be aware that:
  > Neurofibromas can cause cosmetic problems and wrap around or penetrate the nerves causing pain.
  > There is about a 5% increase in risk for various cancers, including brain tumour. Sometimes plexiform neurofibromas and, very rarely, simple neurofibromas can become malignant.
  > Hypertension is more common in NF1 patients than in the general population. At least annual blood pressure should be undertaken on all individuals with this condition. If hypertension is identified, then investigations for a secondary cause such as renal artery stenosis and phaeochromocytoma should be undertaken.
  > There is also an increased rate of scoliosis in NF1. This should be looked for and there should be a low threshold for referral to an orthopaedic surgeon for investigation and management. As with scoliosis in other conditions, it most commonly presents and progresses around the time of puberty.
• Areas of surveillance should include:
  > Ophthalmology for optic gliomas; growth of these is rare over 10 years of age.
  > Education, as specific learning disabilities in reading, spelling or mathematics may be present. Children also may have short attention span, low muscle tone, reduced co-ordination and emotional immaturity.
  > Monitoring of any rapid changes in the growth or symptoms of a neurofibroma.
Neurofibromatosis type 2 (NF2)

GP’s role
- Take and update the family history (see Genetics in practice).
- Inform adult patients with NF2 of the familial nature of the condition and risks to future children and relatives.
- Manage co-existent conditions.
- Provide referral as appropriate to neurology and ophthalmology specialists for assessment and surveillance.
- Provide referral to Genetics Services for discussion of predictive genetic testing (see Contacts, support and testing).

Clinical features
- NF2 is a rare genetic condition that is primarily characterised by vestibular schwannomas.
- Symptoms may include:
  - Gradual hearing loss
  - Tinnitus
  - Balance problems
- The condition is diagnosed in individuals with one of the following:
  - Bilateral vestibular schwannomas
  - A first-degree relative with NF2 and unilateral vestibular schwannomas or any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
  - Unilateral vestibular schwannoma and any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
  - Multiple meningiomas and unilateral vestibular schwannoma or any two of schwannoma, glioma, neurofibroma, cataract
- Café-au-lait spots may be present but are usually fewer in number than in NF1.
- Benign tumours may also occur in or around the spinal cord.
- Other tumours of the central nervous system may also develop including schwannomas, meningiomas, gliomas and rarely neurofibromas.
- Posterior subcapsular cataracts may develop at a younger age than would otherwise be expected, with symptoms including impaired and/or progressive loss of vision.
- Other features include:
  - Facial spasms
  - Generalised muscle weakness, numbness, pain, and/or partial paralysis
  - Difficulty swallowing and/or impaired speech
  - Other neurological problems including headaches and/or seizures
- Symptoms usually develop around the time of puberty or during early adulthood from the presence of benign tumours on both auditory nerves (acoustic neuromas/vestibular schwannomas) with 90% being symptomatic by age 45.
- Up to 30% of patients present in the first two decades of life with a non-vestibular tumour such as intracranial meningioma, astrocytoma or spinal tumour.
- 10% present under the age of 10 years. Early presentation with a non-vestibular tumour is an adverse prognostic indicator.
Genetics

- NF2 is caused by mutations in the NF2 gene that regulates the production of the merlin/schwannomin protein which functions as a tumour suppressor.
- Merlin/schwannomin is related to a class of proteins (ezrin-radixin-moesin proteins) that serve to link the internal, supportive system within a cell (cytoskeleton) to proteins in cell membranes.
- Many different mutations in the NF2 gene have been identified in individuals with the condition, and may contribute to the wide variability of symptoms and findings in affected individuals.
- The condition follows a pattern of autosomal dominant inheritance.
- Approximately 50% of NF2 cases are inherited and about 50% are due to new mutations in the NF2 gene.

Prevalence

- NF2 has an estimated birth frequency of 1 in 33,000 to 40,000.

Investigations

- Genetic testing is rarely required for diagnosis.
- The main utility for genetic testing of the NF2 gene is to enable predictive testing and to facilitate prenatal testing where this is requested.
- Following genetic counselling, genetic testing is first done on a family member with NF2 and germ-line mutations can be detected in about 60% of those affected. This can take some months. (See Contacts, support and testing).
- Once the family mutation has been identified, presymptomatic testing is then available to blood relatives and results are available in a much shorter time frame.

Management

- Early detection of vestibular schwannomas is associated with better outcome.
- The diagnosis is confirmed by a thorough clinical evaluation and specialised testing such as magnetic resonance imaging (MRI).
- Vestibular schwannomas are surgically removed when possible. The surgical procedure that is performed is based upon the size and precise location of the tumours.
- Radiation therapy may be considered for those who are not candidates for surgery.
- Tumour surveillance in carriers for an NF2 mutation, affected individuals and at-risk individuals.

Implications for other family members

- Testing for the NF2 mutation in asymptomatic family members can identify those who may be at risk of developing tumours and would benefit from regular screening.
- If a relative is found not to have inherited the family NF2 mutation then no further screening is necessary. The emotional and financial costs can therefore be avoided.


Neurofibromatosis Association of Australia (NFAA) Inc. http://nfaa.org.au
Neurological conditions
<table>
<thead>
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<th>Neurological and Neuromuscular Conditions</th>
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Patient and family fact sheet:

Neurological conditions
Neurological Conditions

**GP’s role**
- Discuss familial risks of common neurological conditions.
- Refer to neurological services for **diagnostic** genetic testing for Huntington disease and early onset familial Alzheimer disease.
- Refer to neurological/Genetics Services for **predictive** and **pre-symptomatic** genetic testing for Huntington disease and early onset familial Alzheimer disease.
- Refer family to relevant support group (see **Contacts, support and testing**).

**Overview of neurological and neuromuscular conditions**

- Most common adult-onset neurological conditions are multifactorial in cause.
- A minority of adult-onset neurological conditions are inherited and due primarily to a mutation in a single gene (eg Huntington disease).
- Some genetic variations (polymorphisms) may be associated with a higher risk of developing certain neurological conditions.
- Testing for polymorphisms is currently only on a research basis and neither recommended nor available for routine use (eg ApoE4 in Alzheimer disease predisposition).

Table 1. Examples of inherited adult onset neurological and neuromuscular conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance Status</th>
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<tbody>
<tr>
<td>Creutzfeldt-Jakob disease and other prion diseases <strong>a</strong></td>
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<tr>
<td>Early-onset Parkinson disease</td>
<td></td>
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<tr>
<td>Familial Alzheimer disease <strong>a</strong></td>
<td></td>
</tr>
<tr>
<td>Familial epilepsy <strong>a</strong></td>
<td></td>
</tr>
<tr>
<td>Familial motor neurone disease <strong>a</strong></td>
<td></td>
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<tr>
<td>Friedreich ataxia <strong>b</strong></td>
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<tr>
<td>Hereditary peripheral neuropathies (Charcot-Marie-Tooth disease) <strong>a</strong></td>
<td></td>
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<tr>
<td>Hereditary spastic paraparesis <strong>a</strong></td>
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<td>Huntington disease <strong>b</strong></td>
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<td>Muscular dystrophies <strong>a</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Spinal muscular atrophy <strong>b</strong></td>
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<tr>
<td>Spinocerebellar ataxias <strong>a</strong></td>
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</tr>
</tbody>
</table>

**a** Genetic testing may be available for some familial forms of this condition.

**b** Genetic testing is available for this condition.

**These conditions may present earlier in life.**
Indications for referral

- Take a family history, noting family members believed to have the neurological condition or suggestive neurological symptoms. Where possible, the family history should cover three generations and include grandparents, uncles, aunts and cousins.
- Refer individuals or family members to Genetics Services or specialist neurogenetic services where there are:
  - Proven (clinically or by genetic testing) personal or family history of an inherited neurological or neuromuscular condition
  - Personal features consistent with an inherited neurological or neuromuscular condition
  - A suspicious family history:
    - Two or more family members affected with apparently the same condition
    - A significantly earlier age of onset than average
  Not all States have a neurogenetics service or clinic. Contact Genetics Services to discuss the most appropriate clinic to refer to (see Contacts, support and testing).

Management of symptomatic individuals

- Diagnostic genetic testing for some conditions may be performed to confirm a clinical suspicion and/or to identify the causative mutation, enabling at-risk individuals to have predictive genetic testing (see Contacts, support and testing).
- Genetic testing can be complex and is often best arranged by a clinical geneticist or clinicians in a neurogenetics clinic after detailed neurological assessment.
- Depending on the condition, referral of the individual to a neurogenetics clinic or Genetics Services before or after genetic testing for information, counselling and/or case management is important to ensure people have access to the best range of supports to meet their needs and also so that the family implications of the diagnosis can be considered.
- Contact Genetics Services for details of the most appropriate clinic for referral.
- Consider referral to a support group for the condition, as it may be a useful and supportive contact for the person (see Contacts, support and testing).

Management of asymptomatic at-risk individuals

- Predictive testing may be available through Genetics Services or specialist neurogenetics clinic.
- In some cases a family-specific mutation has to be identified in an affected family member before predictive testing can be offered.
- Consider referral to a support group for the condition they are at risk for, as it may be a useful and supportive contact for the person (see Contacts, support and testing).
Huntington disease

Clinical features

- Huntington disease (HD) is an inherited condition that gives rise to progressive, selective, neuronal cell death.
- Symptoms can be classified into three basic groups:
  - **Physical** – involuntary, jerky movements or ‘chorea’, abnormal gait, bradykinesia, hyperflexia, abnormal eye movements, dysarthria and dysphasia
  - **Cognitive** – impairment including disturbances in verbal fluency, cognitive speed, the retrieval of memories, ability to persist at a task or change cognitive sets, therefore causing difficulties with judgment, planning, problem solving and eventually dementia
  - **Emotional** – including personality changes such as impulsiveness, perseveration, disinhibition, depression, mood swings and aggression
- These symptoms usually commence between the ages of 30 and 50 years, and become progressively worse over time.
- However, onset can occur in children and people in their later years.
- Not all people will experience all the symptoms, nor will the symptoms appear in any particular order.
- An individual with HD lives on average for 15 to 20 years after developing the first symptoms.

Genetics

- HD follows an autosomal dominant pattern of inheritance. Each child of an individual with HD has a 50% risk of inheriting the mutated gene.
- HD is caused by a mutation in the gene called huntingtin.
- The mutation is the result of an increase in size (expansion) of a certain part of the gene where a tri-nucleotide sequence, CAG, is repeated over and over again (known as a triplet repeat).
- The huntingtin gene normally contains the triplet CAG repeated up to 26 times.
- In people with HD, or those who will develop HD during their lifetime (if they live long enough), the CAG triplet is repeated 40 times or more in one copy of their huntingtin gene.
- Where an individual has the CAG triplet in one copy of their huntingtin gene repeated between 27 and 39 times (intermediate range), careful interpretation is required when assessing the meaning of this result for the individual and their family.
- It is not possible to predict at what age symptoms will appear based on the number of repeats in the mutated huntingtin gene. However, on average the larger the gene expansion the earlier the age of onset.

Prevalence

HD has a population frequency of approximately 1 in 10,000.
Investigations

- Genetic testing is available for the diagnosis of a symptomatic individual or for predictive testing of an asymptomatic at-risk individual.

**Symptomatic individuals**

- Refer symptomatic patients to a neurologist or neurogenetics service for neurological assessment and genetic testing to confirm diagnosis.

**Asymptomatic at-risk individuals**

- Refer to Genetics Services for discussion and counselling around predictive genetic testing.

Management of symptomatic individuals

- There is currently no cure for HD.
- Symptomatic treatment is available for some of the features of HD, such as chorea and depression.
- Discuss informing other family members of the diagnosis with the individual (see Genetics in practice).
- Suggest/encourage contact with the Australian Huntington Disease Association in their State/Territory (see Contacts, support and testing) for information, support, counselling, advocacy and ongoing monitoring of the patient’s/family’s support and service needs.

Management of asymptomatic at-risk individuals

- Explore and document the family history of HD, including age of onset of affected family members.
- If the individual wishes to explore their risk further, discuss direct referral to Genetics Services or neurogenetics service, or contact with a support group for information and counselling.
- An appointment with Genetics Services or a neurogenetics service will involve:
  > Detailed assessment of risk and discussion of availability of genetic testing
  > Support during decision making regarding testing
  > Pre- and post-test counselling
- Up to 80% of people at risk of HD choose not to have genetic testing prior to onset of symptoms (predictive testing) as they feel that knowledge of their genetic status would not be helpful and may increase anxiety.
- If the individual does not wish to discuss genetic testing with the predictive testing service, they may still benefit from ongoing support and contact with an HD support group.
Alzheimer disease

- The great majority of people with Alzheimer disease will have developed the condition for unknown reasons but **not** due to inheriting a familial form of the disease.
- Alzheimer disease:
  - Can be familial or sporadic and, in either instance, can have early (<60 years) or late onset
  - Is the most common cause of dementia in people older than 40 years
  - Is a pathological diagnosis based on the presence of amyloid plaques and neurofibrillary tangles and cannot be diagnosed with certainty by clinical assessment
- The risk of developing the condition increases with age, like other forms of dementia.

Non-familial late-onset Alzheimer disease

- There is no discernible increase in risk for the individual if the family history comprises:
  - No relatives with Alzheimer disease, or
  - Grandparent only with Alzheimer disease, or
  - Parent with Alzheimer disease diagnosed before the age of 65 years, and the patient is asymptomatic and current several years older than 65
- For individuals with a family history of Alzheimer disease, the risk of Alzheimer disease depends on the degree of relationship and number of relatives affected. In most cases, the individual is more likely not to develop Alzheimer disease.
- The risk of late-onset Alzheimer disease among 1st relatives of individuals with probable or definite Alzheimer disease by age 85 years is approximately a 2.5 fold increase over that of the general population.

Familial Alzheimer disease

There are two forms:
- Early-onset familial Alzheimer disease (EoFAD)
- Late-onset familial Alzheimer disease (LoFAD)

Early-onset familial Alzheimer disease (EoFAD)

- Clinical features
  - Typically occurs in middle age (less than 60 years) but is otherwise indistinguishable from sporadic early-onset Alzheimer disease.

- Criteria for EoFAD:
  - A family with two or more affected people with onset age <65 years in more than one generation of a family, with clinically suggestive symptoms or pathologically proven Alzheimer disease in at least one individual.
  - An individual or family member with a disease-causing genetic mutation in one of the genes causing early-onset familial Alzheimer disease.
Genetics

- Represents 1% of all cases of Alzheimer disease.
- Follows a pattern of autosomal dominant inheritance.
- The vast majority of individuals affected are sporadic cases where there is no family history of the condition.
- Mutations in the gene presenilin-1 (PS-1) are implicated in over 50% of families with EoFAD.
- Other genes that are known to cause EoFAD are amyloid precursor protein (APP) and presenilin-2 (PS-2).

Late-onset familial Alzheimer disease (LoFAD)

Clinical features

- Typically has an onset >65 years and is indistinguishable from non-familial late-onset Alzheimer disease.

Genetics

- No single causative genes have been recognised for LoFAD.
- A susceptibility gene, ApoE, which has three forms (alleles) - ApoE2, ApoE3 and ApoE4 - has been identified for Alzheimer disease.
  - An individual's risk of developing late-onset Alzheimer disease is related to the combination of ApoE alleles they carry
  - Those individuals with one or two copies of the ApoE4 allele are at increased risk of developing Alzheimer disease
  - However, 50% of all people with late-onset Alzheimer disease do not have a copy of ApoE4. It is possible to have this form of the gene and not develop dementia despite living to old age

Prevalence

- The prevalence of dementia in individuals over the age of 85 years is estimated to be 25 to 45%.
- Approximately 10% of all persons over the age of 70 years have significant memory loss and more than half of these individuals have Alzheimer disease.
- About 25% of all Alzheimer disease is familial.
- About 1 to 6% of all Alzheimer disease is early-onset (<60 years) and about 60% of EoFAD.
- LoFAD is responsible for up to 10% of late-onset cases.

Investigations

- Predictive genetic testing is available for at-risk relatives of individuals identified with EoFAD due to mutations in PS-1, APP and PS-2.
  - However, the testing is only available when a specific mutation has been identified in an affected family member
- Testing for ApoE status for Alzheimer disease has been the subject of debate. To date, local collaborative groups and international bodies have recommended that ApoE not be used for diagnostic or predictive testing for Alzheimer disease.

Management

- Refer to neurogenetics or Genetics Services for the following:
  - Any individual with a personal or family history consistent with early-onset familial Alzheimer disease (see ‘Criteria for EoFAD’).
  - Any individual with two or more affected family members with late-onset Alzheimer disease over one generation within the same parental line.
  - While ApoE testing for Alzheimer disease risk is not recommended, individuals requesting ApoE testing for Alzheimer disease risk may benefit from referral to a neurogenetics clinic for further discussion.
Motor neurone disease

Clinical features
- Motor neurone disease is also known as amyotrophic lateral sclerosis (ALS) or Lou Gehrig disease.
- It is a rapidly advancing condition characterised by progressive muscle weakness due to the death of motor neurons in the brain, brain stem and spinal cord.
- This affects movement of the limbs, speech, swallowing and respiration.

Genetics
- Inherited motor neurone disease shows:
  - Familial aggregation
  - An earlier age of onset than average (40s or younger)
  - Clinical features essentially the same as the sporadic form
- Approximately 10% of cases of motor neurone disease are thought to be due to mutations in a single gene.
- About 20% of cases all inherited motor neurone disease is due to mutations in the SOD1 gene
  - In these cases, the inheritance pattern is autosomal dominant
  - However, some causative mutations in SOD1 are not fully penetrant so the person may remain asymptomatic despite having the mutation
- Other genes in which mutations can cause motor neurone disease include:
  - ALS2 which follows a pattern of autosomal recessive inheritance
  - ALS4 which follows a pattern of autosomal dominant inheritance and is associated with variations in the SETX gene

Investigations
- Diagnostic and predictive genetic testing if appropriate may be available through a neurogenetics service or Genetics Services.

Management
- Consider referral to a neurogenetics service or Genetics Services where:
  - More than one member of a family has motor neurone disease
  - A sporadic case has an early age of onset
Parkinson disease

Clinical features
- Individuals with onset before 20 years of age are considered to have juvenile-onset Parkinson disease.
- Those with onset before 50 years of age are classified as having early-onset Parkinson disease.
- Those with onset after age 50 years are considered to have late-onset Parkinson disease.

Genetics
- 70 to 90% of cases are sporadic.
- The majority of cases with a family history do not have a clear inheritance pattern and could be the result of exposure to common environmental factors and/or a genetic predisposition, or simply a chance familial aggregation.
- Some cases of juvenile/early-onset Parkinson disease have been shown to be due to mutations in the parkin gene which follow a pattern of autosomal recessive inheritance.
- A very few cases of the condition have been shown to be due to mutations in the α-synuclein gene and follow a pattern of autosomal dominant inheritance.

Prevalence
- Affects more than 1% of individuals 55 years of age and more than 3% of those over 75 years of age, but may also affect younger people.

Investigations
- Genetic testing for Parkinson disease is not currently available outside research protocols.

Management
- Referral to a neurogenetics service or Genetics Services may be considered for families with unusual features, such as familial aggregation and/or early-onset Parkinson disease.
Bibliography


National Organisation for Rare Disorders (NORD). http://www.rarediseases.org/

Neurological conditions

There are a number of neurological conditions which have a genetic basis. These include Huntington disease, myotonic dystrophy, Charcot-Marie-Tooth disease, Friedreich ataxia, muscular dystrophies and others.

These conditions tend to appear at varying times of life and get progressively worse, although there are exceptions.

All these conditions have a different genetic basis. If you or anybody in your family has one of these conditions, you should discuss seeing a genetic service with your doctor.

Most other neurological conditions – Alzheimer’s disease, Parkinson’s disease, stroke, motoneurone disease and others – are usually not based on a simple genetic alteration. But occasionally, genetics plays a part. You should talk to your doctor about the possibility of there being a genetic basis to these common conditions if:

- The condition comes on much younger than usual, or
- Two or more members of the family have the same condition.

In such cases, you would want to help your doctor understand your family history (see fact sheet on 'Your family history') and you may be referred to a genetics service for specialised advice.

Contacts and further information

- All states and the ACT have familial cancer services. Contact them through your local state or territory health department.
- Australasian Genetic Alliance at http://www.australasiangeneticalliance.org.au
- National Organization for Rare Disorders at http://www.rarediseases.org
- MyDr at http://www.mydr.com.au
- The Centre for Genetics Education at http://www.genetics.edu.au
- HealthInsite at http://www.healthinsite.com
- MedicineNet at http://www.medicinenet.com
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
Psychiatric conditions

GP’s role

• Discuss familial risks of common psychiatric conditions.
• Refer family to relevant support group (see Contacts, support and testing).

The schizophrenias

Clinical features

• This term is used because there is likely to be a number of different conditions under the ‘umbrella’ label of schizophrenia.
• Symptoms include hallucinations, delusions, paranoia, disorganisation of thoughts and feelings, and social withdrawal.
• The symptoms usually appear in late adolescence or early adulthood.
• Schizophrenia is a common condition with a lifetime prevalence of approximately 1%.

Genetics

• Many studies have demonstrated that schizophrenia has a clear genetic component but the genetics are complex and poorly understood.
• The risk of 1st relatives developing schizophrenia is based on empirical data (see Table 1).
• No genes causing schizophrenia have been identified or characterised to date.
• However, large regions of some chromosomes have been associated with schizophrenia, such as 22q11.
• Genetic testing is not available.
• Genetic counselling can assist in providing current information about the genetic basis of the condition to the family so that risks for the condition in other family members can be estimated correctly (see Contacts, support and testing).
Mood disorders

Clinical features

- Mood disorders may have a manic-depressive (bipolar) or purely depressive (unipolar) course.

Genetics

- Individuals with an affected 1st relative have an increased risk of a bipolar mood disorder (see Table 1).
- Genetic testing is not available.
- Genetic counselling can assist in providing current information about the genetic basis of the condition to the family so that risks for the condition in other family members can be estimated correctly (see Contacts, support and testing).

<table>
<thead>
<tr>
<th>Affected relative</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Schizophrenia</td>
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<tr>
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</tr>
<tr>
<td>Sibling</td>
<td>9</td>
</tr>
<tr>
<td>Parent</td>
<td>13</td>
</tr>
<tr>
<td>Sibling and one parent</td>
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<tr>
<td>Both parents</td>
<td>45</td>
</tr>
<tr>
<td>2nd relative</td>
<td>3</td>
</tr>
<tr>
<td>Monozygotic twin</td>
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<tr>
<td>Dizygotic twin</td>
<td>10</td>
</tr>
<tr>
<td>First cousin (3rd relative)</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Alcoholism

- While there appears to be a familial tendency to alcoholism, there is no consensus as to whether this is mainly due to genetic variation in alcohol metabolism or whether there are additional genetic predisposing factors.
- There is currently no genetic test to determine predisposition to alcoholism.
Bibliography

http://www.genetics.com.au


National Organisation for Rare Disorders (NORD).
http://www.rarediseases.org/

Mental illness

Mental illness is common. The most common serious mental illnesses are:

- Schizophrenia – in which the affected person may have hallucinations, delusions and disorganised thoughts, and withdraw from society.
- Depression – in which the person feels very down and may lose all appetite, energy and enjoyment of life.
- Bipolar disorder – in which depressed moods alternate with feelings of power, energy and elation.

The risk of developing such an illness is higher if somebody else in the family has the condition. The risk is much higher if both parents are affected. It is clear that genetics are involved.

But the genetic element in these conditions is not thoroughly understood. There seems to be no single genetic alteration associated with most forms of mental illness. There is no easy explanation for what causes these illnesses. And there is no single genetic test that can help diagnose them or provide advice on what such illnesses mean to the rest of the family.

If you have mental illness, or have mental illness in the family, it is worth talking to your doctor about the likelihood of other family members developing it.

Contacts and further information

- All states and the ACT have familial cancer services. Contact them through your local state or territory health department.
- Sane Australia at [http://www.sane.org](http://www.sane.org)
- National Organization for Rare Disorders at [http://www.rarediseases.org](http://www.rarediseases.org)
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- HealthInsite at [http://www.healthinsite.com](http://www.healthinsite.com)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
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- Where possible, take a three generational family history on both sides of the family, noting where appropriate:
  - Age
  - Age at diagnosis
  - Age and cause of death
  - Ancestry and cultural background
  - Birth defects
  - Step-relationships and adoption
  - Stillbirths
  - Miscarriages
  - Terminations of pregnancy
  - Children born of parents who are related

- This may be collected at the first visit, when a particular issue arises, or to provide information for preventive strategies. The patient should understand the reason for collecting this information, as some of it may be private, and may not be known by other members of the family.

- Ideally construct a pedigree, in either paper-based or electronic format where possible.

- Update patient’s pedigree including births, deaths and new diagnoses opportunistically.

- Be aware of, and able to discuss, possible risks of conditions that may be identified from the family history.

- Be aware of, and able to discuss, the ethical, legal and social issues arising when a genetic condition is identified in a family, including insurance implications.

- Consider the sensitivity of the language that you use in discussing genetic issues with families, eg different ways of explaining risk, mutation, and ethnicity.
Collecting a family history

- Drawing a pedigree is a method of documenting family history information, genetic relationships and medical information. For a guide to drawing pedigrees, see ‘Drawing a pedigree’ below.
- A three-generation family history should be collected, where possible, including first-degree (1st) relatives (children, siblings, parents) and second-degree (2nd) relatives (aunts, uncles and grandparents).
- Information collected should include the age at diagnosis of any medical conditions in the family.
- The medical information collected will depend to some extent on the condition or concerns of the individual.
- Some common health problems you may wish to explore:

<table>
<thead>
<tr>
<th>Birth defects</th>
<th>See Testing and pregnancy</th>
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<tbody>
<tr>
<td>Miscarriage</td>
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<td>Stillbirth</td>
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<table>
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<th>See Cancer in the family</th>
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<td>See Clotting and bleeding conditions</td>
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<td>See Fragile X syndrome and other causes of developmental delay</td>
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<td>Thalassaemia</td>
<td>See Haemoglobinopathies</td>
</tr>
<tr>
<td>Sickle cell anaemia</td>
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</table>

Ancestry - ethnicity and cultural issues

- Cultural background and ethnicity can influence people’s understanding and response to genetic conditions and risk. It is important to be aware of stereotypes and always attempt to individualise communication. Options discussed should not be limited or based on choices anticipated due to ethnicity, culture or religion.
- Genetic conditions are considered stigmatising in some cultures and familiarisation with some common cultural beliefs can assist in counselling. Ethnic agencies can help with this, and useful information regarding cultural beliefs, multilingual education material and services is available online (see ‘Further information’).
- Cultural beliefs can influence perceptions of kinship as not all follow the Anglo-Celtic concept of bilateral descent. The beliefs can also influence perception of cause of conditions in the family which may negate understanding or acceptance of the concept of genetics. Acknowledging rather than dismissing those beliefs is important.
Whenever possible, medically trained interpreters should be used to avoid burdening family members with translating medical information and the risk of misunderstanding or selective disclosure. Generally, people that have been in an English speaking country for less than two years will require an interpreter; however, language skills can be affected by distress and emotional situations. An interpreting service may be helpful.

- Interpreters have been made available via telephone by an Australian Government initiative. The Translating and Interpreting Service can be reached 24 hours a day, 7 days a week by telephoning 131 450.

- Be aware that certain conditions, which are rare in some populations, may be more prevalent in others (see Contacts, support and testing and ‘Rare conditions’ below).

- Cultural background can influence a person’s concept of family, kinship, patterns of descent and relationships to other people. As well, certain mutations are more common in particular populations. For example, mutations causing cystic fibrosis in Ashkenazi Jews differ from those found in people with Northern European ancestry.

- Ask separately about blood relatives on both sides of the family.

- Recognise the possibility of consanguinity that, whilst more common in certain cultural groups, occurs in all populations.

  - Ways of asking questions regarding the family and their health include:
    - ‘How many pregnancies did (name of relative) have?’
    - ‘How many children do they have?’ (Asking for pregnancy failure)
    - ‘How many [for example] brothers and sisters do you have altogether?’ ‘Have any died?’
    - ‘How is their health?’
    - ‘Did anyone attend an education support unit/centre whilst at school?’
    - ‘Are there any conditions you are worried about?’

- Pedigrees should be dated and then updated regularly.

- The accuracy of a medical family history that a patient provides will be dependent on both the patient’s recollection and the condition. For example, breast cancer amongst families is often more accurately reported than colorectal cancer.

- You may wish to give your patient a family history questionnaire so that more accurate information can be gathered.

Special considerations regarding family history collection and Indigenous Australians or Torres Strait Islanders

- It is important to note that for families with an Indigenous Australian or Torres Strait background, the concept of family history may hold a different meaning.

- When collecting a family history or drawing a pedigree for people with this background, consider issues pertaining to the Lost and Stolen Generations. In some cases, this historical background will mean that family history is unclear or unattainable.

- Kinship patterns within families of Indigenous Australian or Torres Strait heritage also require special attention. For the purposes of genetic risk assessment, it is important to take the time to clarify whether individuals within a family tree are biological relatives or not.

- Intra- and inter-familial adoptions should be considered when collecting a family history from someone of Aboriginal or Torres Strait Islander background.

- It is recommended to consult the Aboriginal Liaison officers based in hospitals or public health units in your State.

Under the Commonwealth’s Privacy Act 1988, a Temporary Public Interest Determination (No. 2001–1) allows health information to be collected from an individual about another individual (see http://www.privacy.gov.au/act/public_interest) in certain circumstances that include family history taking.
Health and life insurance issues

- Private health insurance is community rated and so does not take into account genetic information but will take into account any existing condition. However, an asymptomatic individual with a positive predictive genetic test result does not have a pre-existing condition.
- Genetic information that includes a family history and the results of predictive genetic tests are taken into account in applications for life insurance products. This includes cover for death, disability/income protection, trauma/crisis care, business and insurance relating to bank loans.
- The Investment and Financial Services Association Ltd (IFSA), an organisation representing most insurance companies in Australia, has a policy on genetic testing and life insurance products. This policy does not extend to General Insurers who offer travel insurance.
  
  - The IFSA policy states that an individual will not be required to undergo a predictive genetic test in order to obtain life insurance or to increase the cover in a policy.
  - However, under the Insurance Contracts Act 1984, a person applying for insurance has a duty "to disclose to the insurer every matter that you know, or could reasonably be expected to know, that is relevant to the insurer’s decision.”

- While some insurance companies will ask for more specific details than others, applicants must disclose all known genetic information about their relatives or themselves that would be relevant to the assessment of their risk, over and above the questions asked. This would include predictive test results of their relatives. Failure to do so may render a claim invalid.
- This information may have a range of consequences, depending on the condition involved and whether the genetic test was positive, uninformative or negative:
  > No effect on insurance premiums
  > Premiums previously that were non-standard (eg loaded) returning to standard (eg if a predictive genetic test is negative, it can remove the influence of a family history)
  > Lead to higher (non-standard) insurance premiums
  > Result in a reduced period of coverage
  > Result in an exclusion for one or more medical conditions
  > Lead to the offer of an alternate insurance product
  > Deferral or denial of an offer to insure an individual
- If an application is held or taken out before a genetic condition is diagnosed or before a risk is identified through a predictive genetic test, the applicant does not have to disclose this new information. Life insurance cover is guaranteed renewable and, so as long as the premiums are paid, that cover will apply.
- As costs of insurance and ability to obtain cover may vary from one insurance company to the next, patients may wish to make multiple applications to a range of companies at the same time.
Ethical issues

- The ethical principles that guide all medical care apply in genetics. However, ethical dilemmas arise when there is tension or conflict between the rights of different family members.

- Key ethical principles include:
  - Justice (all should be treated equally, and there should be equity of access to services regardless of place of residence, ethnicity, gender, religion, age or disability)
  - Respect for autonomy (the right of an individual to self-determination, including privacy and confidentiality)
  - Beneficence (taking positive action to do good)
  - Non-maleficence (do no harm)

- There can be tensions when these principles are considered with respect to the right of an individual to:
  - Know, or not to know, information relevant to their own health (autonomy)
  - Disclose, or not, personal information (privacy)
  - Make an informed decision regarding genetic testing

- Genetic counselling emphasises that an autonomous choice be made, ie a choice that is informed, reflective of the individual’s own values and made freely (without coercion). However, ethical dilemmas may arise, eg:
  - As a result of genetic testing, an individual’s result may disclose the genetic status of another family member who has not had testing (and may not wish to), eg identical twins
  - An individual refuses to disclose to other family members that they are at risk
  - Parents request that their child (under 18 years) be tested for an adult onset condition where there is no health benefit for the child, thus affecting the child’s future autonomy
  - In any of these situations, it is important to explore with the individual the potential harms and benefits and their reasons for their request. Referral to Genetics Services for counselling is strongly recommended (see Contacts, support and testing)
### Drawing a pedigree

#### Step 1
Draw the symbol for the family member being seen. (See Figure 1 for standard symbols used in drawing a pedigree). Indicate this person with an arrow, and enter any pertinent details (eg name, age):

![Symbol for family member]

#### Step 2
If the individual has had a child/pregnancy, draw a line directly across to a symbol for the partner:

![Line to symbol for partner]

#### Step 3
Ask about the number of pregnancies pertaining to the couple. Draw a reverse ‘T’ from the relationship line and add the symbol for each child and pregnancy:

![Reverse T with children]

#### Step 4
Add a line from each child/pregnancy to the reverse T:

![Lines from children to reverse T]

#### Step 5
Ask about brothers and sisters for each partner. Add the relevant symbols along side the corresponding person:

![Symbols for siblings]

#### Step 6
Indicate the relationship between siblings by drawing a vertical line stemming from each symbol and joining them together with a horizontal line:

![Vertical lines connecting siblings]

#### Step 7
Add a vertical line from this sibship line, and add parents:

![Vertical line from sibship to parents]

#### Step 8
Indicate deceased family members by drawing a line through the symbol:

![Line through symbol]

#### Step 9
Repeat steps 5-8 for each parent of the family member you are seeing to include the aunts, uncles and grandparents:

![Diagram showing repeated steps]

- At each step ask about the health of the family member being discussed.
- Record the date on which the pedigree is drawn and update it as new information becomes available.
- It may not always be possible to complete the pedigree due to complexities such as adoption, the lack of reliable information or family disruption. It is important to consider such issues in each family.
**Figure 1. Common pedigree symbols, definitions and abbreviations***

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Sex unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual</strong></td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>b. 1925</td>
<td>□ 30 y</td>
<td>□ 4 mo</td>
</tr>
<tr>
<td><strong>Affected individual</strong></td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>(define shading in key/legend)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affected individual</strong></td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>(more than one condition)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carrier</strong></td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>Multiple individuals, number known</strong></td>
<td>□ 5</td>
<td>□ 5</td>
<td>□ 5</td>
</tr>
<tr>
<td><strong>Multiple individuals, number unknown</strong></td>
<td>□ n</td>
<td>□ n</td>
<td>□ n</td>
</tr>
<tr>
<td><strong>Decreased individual</strong></td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>d. 35 y</td>
<td>□ d. 4 mo</td>
<td>□</td>
</tr>
<tr>
<td><strong>Stillbirth (SB)</strong></td>
<td>□ SB 28 wk</td>
<td>□ SB 30 wk</td>
<td>□ SB 34 wk</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>□ P SB 28 wk</td>
<td>□ P SB 30 wk</td>
<td>□ P</td>
</tr>
<tr>
<td><strong>Spontaneous abortion (SAB)</strong></td>
<td>△ male</td>
<td>△ female</td>
<td>△ ECT</td>
</tr>
<tr>
<td>If ecotopic pregnancy write ECT below symbol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affected (SAB)</strong></td>
<td>△ male</td>
<td>△ female</td>
<td>△ ECT</td>
</tr>
<tr>
<td><strong>Termination of pregnancy (TOP)</strong></td>
<td>△ male</td>
<td>△ female</td>
<td>△ ECT</td>
</tr>
<tr>
<td><strong>Affected (TOP)</strong></td>
<td>△ male</td>
<td>△ female</td>
<td>△ ECT</td>
</tr>
<tr>
<td><strong>Adoption</strong></td>
<td>□ Adoption in</td>
<td>□ Adoption out</td>
<td></td>
</tr>
</tbody>
</table>

* These symbols have been adapted from Bennett et al, 1995, and are presented above as they are used in The Royal Australian College of General Practitioners’ ‘Guidelines for Preventive Activities in General Practice’, 6th edition

**Abbreviations**

- If age at death is known, abbreviate with the letter “d” (deceased) followed by the age.
- If the age at diagnosis of a condition is known, abbreviate with “dx” (diagnosed) followed by the age.
Figure 2. Degrees of relationship

<table>
<thead>
<tr>
<th>Degree</th>
<th>% Genes shared</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td></td>
</tr>
<tr>
<td>Parent-child</td>
<td>50</td>
</tr>
<tr>
<td>Siblings</td>
<td>50</td>
</tr>
<tr>
<td>Dizygotic (non-identical)</td>
<td>50</td>
</tr>
<tr>
<td>Monozygotic (identical) twins</td>
<td>100</td>
</tr>
<tr>
<td>Second degree</td>
<td></td>
</tr>
<tr>
<td>Grandparent-grandchild</td>
<td>25</td>
</tr>
<tr>
<td>Aunt (uncle) - niece</td>
<td>25</td>
</tr>
<tr>
<td>Half-siblings</td>
<td>25</td>
</tr>
<tr>
<td>Third degree</td>
<td></td>
</tr>
<tr>
<td>First cousins</td>
<td>12.5</td>
</tr>
<tr>
<td>Great-aunt - nephew</td>
<td>12.5</td>
</tr>
<tr>
<td>Fourth degree</td>
<td></td>
</tr>
<tr>
<td>First cousins once removed</td>
<td>6.25</td>
</tr>
<tr>
<td>Fifth degree</td>
<td></td>
</tr>
<tr>
<td>Second cousins</td>
<td>3.125</td>
</tr>
</tbody>
</table>
Consanguinity

- Consanguinity describes a relationship between two people who are related to each other as a result of sharing a common ancestor.
- Consanguineous relationships occur in all population groups but may occur more frequently in certain cultures.
- It is important to be aware that the most common form of consanguineous relationships is between first cousins, and in some societies this can account for more than 50% of relationships.
- People who are blood relatives share a greater proportion of their genes than unrelated people, and thus potentially have the same mutated recessive gene(s).
- When people are first cousins and there is no family history of a specific condition, or of other consanguineous relationships in previous generations, the risk of them as a couple having a child with a genetic condition is approximately 5 to 6% (compared to 3 to 4% for all parents in the general population).
- Risk will increase in societies where there is a multi-generational tradition of first cousin marriages, rendering couples closer in genetic relationship.
- See Contacts, support and testing for a description of particular conditions that are more common in specific ethnic/ancestral groups, and may be relevant when discussing consanguinity.
Inheritance patterns – what to look for

- Once a pedigree has been drawn it is often possible to see patterns of inheritance of specific conditions and diseases among family members. This in turn can help in:
  > Diagnosing a medical condition
  > Deciding what medical tests to order
  > Identifying other members of the family who are at risk of developing certain diseases
  > Calculating individual risks of certain diseases
  > Calculating individual risks of passing certain conditions on to future generations
- Depending on the mode of inheritance of conditions present in families, patterns evident from family trees will differ. The following outline various characteristics that may be seen according to the most common modes of inheritance.

**Autosomal recessive inheritance**

eg cystic fibrosis, hereditary haemochromatosis

![Figure 3. Cystic fibrosis: autosomal recessive inheritance](image)

- When a family member is diagnosed with a condition that follows a pattern of autosomal recessive inheritance, there is often not a family history of the condition, since the mutation has previously only been carried through each side of the family. The pedigree above is an example of what could be obtained from the patient.
- Parents of a child with an autosomal recessive condition are almost always obligate carriers for the mutation involved. The recurrence risk is 1 in 4 for each pregnancy.
- Wide variability in clinical expression is common in many autosomal recessive conditions, even within the same family.
- If there is a family history of a particular autosomal recessive condition, it is likely that it has occurred amongst siblings or cousins, and on average will have occurred in 25% of these children.
- It is important to correct the common misunderstanding that conditions can ‘skip’ generations. In the case of autosomal recessive conditions, affected family members may appear to be scattered across a generation. Obviously this has occurred when two carriers for the condition have had children. The pedigree above in Figure 3 is an example of how carriers for autosomal recessive conditions (indicated by filled circles inside symbols) can produce offspring who are affected by that condition.
- Consanguinity is noted more often among the parents of individuals with rare autosomal recessive conditions. A consanguineous relationship noted in the parents of a patient with an unidentified genetic condition suggests the possibility of an autosomal recessive single gene condition.
- If you notice a family history of an autosomal recessive condition, and would like more information on the condition and/or recurrence risks, contact Genetics Services (see **Contacts, support and testing**).
Autosomal dominant inheritance

Eg Huntington disease, most familial cancers

Figure 4. Huntington disease: autosomal dominant inheritance

- When a condition follows an autosomal dominant pattern of inheritance, the family tree will usually reveal multiple affected members on one side of the family.
- The condition is usually inherited on one side of the family and present down multiple generations.
- Wide variability in clinical expression is common in many autosomal dominant conditions, even within the same family. Severely affected offspring may be born to minimally affected adults and thus careful examination of a child’s parents can be important (eg neurofibromatosis type 1 and type 2, see Neurofibromatosis).
- Early onset of conditions such as cancer can be indicative of autosomal dominant inheritance within a family.
- Not all autosomal dominant conditions show 100% penetrance (eg BRCA1 gene mutations; see Cancer in the family). Penetrance describes the extent to which characteristics controlled by the gene, or mutation within the gene, will be expressed. Consequently, people who carry the autosomal dominant mutation may not always develop the condition — this would demonstrate incomplete penetrance. Other genes and lifestyle factors such as diet, exercise and smoking may also affect the onset of some conditions.
- An autosomal dominant condition cannot be ruled out just because there is only one affected family member. Isolated cases of dominant conditions may be the result of a spontaneous (de novo) gene mutation.
- If you notice a family history of a dominant condition, and would like more information on the condition and/or recurrence risks, contact Genetics Services (see Contacts, support and testing).
X-linked recessive inheritance

eg haemophilia, muscular dystrophies, colour blindness

Since a male inherits only one X chromosome (from his mother), in a family affected by a condition that follows a pattern of X-linked recessive inheritance there will be more affected males than affected females. Males are usually more severely affected than females (see ‘X inactivation’ below).

In the family history there may be a pattern of transmission of the mutation from an affected grandfather to an affected grandson through an intermediate carrier female, who is usually unaffected by the condition (see ‘X inactivation’ below).

It is important to correct the common misunderstanding that conditions can ‘skip’ generations. In the case of X-linked inheritance, affected family members may appear to be scattered across generations.

Since a male only passes his Y chromosome to his son, there will be no male-to-male transmission present, as shown in the pedigree in Figure 5 above.

Females who are carriers for the mutation involved have a 1 in 2 chance, with each pregnancy, of passing on the mutation. Sons who inherit the mutation will be affected and daughters who inherit the mutation will be carriers like their mothers (indicated by filled circles inside symbols), as shown in the pedigree in Figure 5 above.

Daughters of affected males can only inherit the mutation from their father and are said to be ‘obligate carriers’.

If you notice a family history of an X-linked condition, and would like more information on the condition and/or recurrence risks, contact Genetics Services (see Contacts, support and testing).

X inactivation

Inactivation of most genes on the X chromosome in female somatic cells ensures that both males and females have the same number of X chromosome genes instructing the body to perform particular functions.

This is usually a random process, and thus a female’s body will contain a mixture of cells with respect to the inactivated X chromosomes being of maternal or paternal origin.

The usual random process of X inactivation means that female carriers for the mutation will not usually show any signs of the condition as there are enough cells with the correct copy of the gene to instruct the body to perform particular functions.

Rarely, some female carriers may be mildly symptomatic due to unequal or skewed inactivation of the X chromosomes.
Multifactorial inheritance

- Multifactorial inheritance, also called complex inheritance, can be attributed to a combination of genetic (a single gene or multiple genes), environmental, and lifestyle factors.
- The genetic contribution is susceptibility.
- The number of necessary factors, and the impact those factors will have on the presence or severity of a condition will vary for different conditions and different individuals.
- Often when there are multiple susceptibility genes involved, there is an additive effect on the outcome.
- Early onset of conditions such as cancer, cardiovascular disease or type 2 diabetes may be indicative of multifactorial inheritance within a family.
- This type of inheritance does not follow a characteristic pedigree pattern but may look like autosomal dominant inheritance with incomplete penetrance.

Rare conditions

- While individuals with rare conditions do not commonly present to GPs, collectively there are probably about 1.2 million Australians who have a rare condition.
- GPs may be the first point of call and it is acknowledged that management can be challenging.
- Individuals and their families have similar experiences despite their different diagnoses and GPs are well placed to help with these problems.
- The patient and their family as well as support groups can be an important source of information for GPs about the specific condition.
- Peer support can be helpful for individuals when a support group is not available.
Talking about genetics

When an individual is identified as affected by, or at risk of, a condition with a direct or contributory genetic basis, the impact ripples though the family. It is the family dimensions and impact that can make a genetic consultation different.

Consumers’ perspective

- A recent study exploring Australian consumers’ views regarding the management of genetic conditions by GPs highlights a number of key points related to counselling skills in the general practice:
  > The GP’s role is perceived as one that should manage the patient in a holistic manner. This encompasses the patient’s medical history, their family, as well as their emotional health
  > The GP is viewed as a health care provider with whom a long-term relationship is likely to develop. Given good interpersonal skills, this will allow a patient and their family to develop trust and confidence in the GP over time
  > Families living with rare genetic conditions often have considerable understanding of the condition. GPs need to consider the patients’ and families’ expertise, as consumers can be a useful source of information

Common misconceptions about genetics

An individual’s physical similarity to other relatives will indicate their risk of developing a condition, eg ‘My father has the condition, but I look like my mother, so I’m OK’.

Conditions affecting mostly women (eg breast cancer) can only be inherited through the maternal line.

A condition only affects one gender in a family eg when only men in a family have or had Huntington disease, the women are not at risk.

Tests are available for all inherited conditions.

The presence of a mutation means that an individual will definitely develop the condition, even though the risk is not 100% (incomplete or reduced penetrance), eg ‘I have the breast cancer gene, therefore I am going to get cancer’.

A ‘one in four’ risk means that after one child is affected, the next three will be unaffected.

If a condition is dominantly inherited, then the mutated gene is ‘stronger’ and will be passed on more often, so more people will be affected than unaffected.
Language considerations when talking about genetics

• Studies with consumers with genetic conditions suggest that, for some people, certain commonly used genetic terms may have negative connotations if used without explanation or out of context. While correct medical or scientific terms are accurate, they may often be misunderstood.

• It is important when discussing genetic issues to reflect how the words chosen may impact on a patient’s perceptions and understanding and consider the potential to offend by using insensitive language. Other studies have shown that language can impact on patients’ understanding of genetic information.

• Similar terms may be used to describe quite different situations.
  > eg ‘carrier’ can be used to describe a contagious person, such as with an HIV carrier
  > This has led to the term ‘CF carrier’ to be interpreted as cystic fibrosis also being an infectious disease

• The list below provides examples of some terms that, if not explained, may have potentially negative connotations or be misunderstood.

<table>
<thead>
<tr>
<th>Term</th>
<th>Possible alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic disease/genetic disorder</td>
<td>Genetic condition</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Bad or abnormal gene</td>
<td>Altered gene; changed gene</td>
</tr>
<tr>
<td>Mutation</td>
<td>Gene alteration; change in gene that affects its function; faulty gene</td>
</tr>
<tr>
<td>Sufferer, victim, afflicted with…</td>
<td>Affected by; living with</td>
</tr>
<tr>
<td>Normal/abnormal</td>
<td>Unaffected by/affected by</td>
</tr>
<tr>
<td>CF carrier/carrier of CF</td>
<td>Carrier for CF; carrier for the altered gene for CF; genetic carrier for CF</td>
</tr>
<tr>
<td>Wheelchair-bound or confined</td>
<td>Uses a wheelchair</td>
</tr>
<tr>
<td>An achondroplast, dwarf, midget</td>
<td>Person with achondroplasia</td>
</tr>
<tr>
<td>A ‘Downs’</td>
<td>Person with Down syndrome</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Characteristic group of symptoms</td>
</tr>
</tbody>
</table>

Communicating genetics issues

General strategies

• Sometimes people’s preconceived ideas about genetics and inheritance in their family are in fact misconceptions that may affect their understanding of genetic explanations.

Assess understanding

• Ask about the individual’s understanding of their situation before providing information. Use their understanding as a starting point for the discussion, ie start with what the family knows or believes then introduce new concepts or correct misunderstandings.

• As you explain genetic concepts, check the individual’s understanding of what they have been told before continuing.
**Use strategies to aid recall and understanding**

- Actively encourage questions.
- Write down key medical terms.
- Make use of simple diagrams and pictures where appropriate.
- Repeat and summarise important information.
- Improvement in an individual’s recall after receiving complex information can be assisted by:
  > Writing down relevant information
  > Sending the individual a summary letter as a follow-up
  > Providing brochures and fact sheets
  > The presence of a support person at the appointment

**Deliver genetic information in plain English**

- Give clear, specific information. Try to provide information about one issue completely before talking about the next issue. For example, when talking about testing during pregnancy, completely address one type of test (e.g., Down syndrome screening) before talking about the next.
- Explain medical terms or genetic terms and avoid jargon. Many people are familiar with words such as genes and chromosomes but may not have a complete understanding of what they mean.
- Feedback from genetic support groups shows that language commonly used to describe genetics can sound offensive and/or judgemental to people who are not familiar with genetic concepts. Avoid using terms that may unintentionally convey negative messages.

**Risk**

- Discussing genetics can involve explaining many different types of risk, including the risk of:
  > Receiving an ‘increased risk’ result from a screening test
  > Having a baby with a chromosomal abnormality (based on maternal age or screening test results)
  > Being a carrier for a genetic condition
  > Having a child affected by a genetic condition
  > Having a genetic predisposition to an adult-onset genetic condition
  > Developing a condition to which an individual has a genetic predisposition
- The term ‘risk’ can imply a negative outcome and sometimes ‘chance’ or ‘probability’ may be more appropriate terms.
- Many people find concepts of chance or risk difficult to understand and find numbers or percentages confusing. Graphs, pie charts or figures showing groups of people may be useful alternatives. Some people do not realise that risk gives an idea of how likely or unlikely a situation is, not that the situation will definitely happen. Describing risk in terms of individuals can assist this.
- Risk figures can be misunderstood and can be seen as being ‘used up’. For example, a one in four risk of an affected pregnancy is often (wrongly) interpreted as meaning once a child is affected, the next three will not be.
- Conversely, an individual who has experienced an uncommon event, such as the diagnosis of pregnancy with a fetal abnormality, can feel heightened vulnerability and find it difficult to believe that the event is unlikely to happen again.
- The significance of a given risk varies between individuals. The same risk figure may sound unacceptable (high risk) to one individual, but acceptable (low risk) to another. For this reason, it is important to clarify the individual’s reactions to a risk assessment and explore any apparent contradictions with open-ended questions or reflection (e.g., ‘You seem to feel these are pretty good odds’ or ‘It seems like too much of a risk to you’).
- The use of ‘high’ and ‘low’ to describe risk is therefore very subjective and it may be preferable to use ‘increased’ and ‘decreased’ risk.
Ways of explaining prenatal screening risk figures

Giving an increased risk result:

A 29-year-old woman receives an increased risk result for Down syndrome after a serum screen test. The risk is 1 in 100. Prior to the test her risk was based on maternal age alone and was 1 in 1002.

- Risk relative to maternal age:
  ‘Your risk is now similar to that of a 39 to 40 year old who has not had any screening. Women who have this level of risk are offered further testing to determine if the baby has Down syndrome.’

- Comparison to other women getting the same test result:
  ‘Of 100 women with this test result, on average, one will have a baby with Down syndrome and 99 will have babies who do not have Down syndrome.’

- Some people find it easier to understand numbers visually as diagrams (see below).

Counselling issues

- Individuals often have emotional reactions to their genetic situation that cannot be resolved by simply providing them with information and facts. Addressing these reactions can require the use of counselling skills such as active listening and a non-judgemental approach.

- As with all counselling, avoid stereotyping or making assumptions about the people’s level of understanding or emotional ability to deal with the situation.

- Counselling in consultations about genetics may address breaking difficult or bad news, anxiety, uncertainty, grief, guilt and blame. Counselling can assist individuals to adjust to their situation; however, in some instances people may have unresolved issues. Referral for specialist counselling may be appropriate (see Contacts, support and testing).

- Difficult or bad news in genetics can include:
  - A higher than anticipated risk shown by screening or clinical assessment
  - Diagnosis of a genetic condition, by testing or clinical assessment
  - Lack of a definitive diagnosis
  - Uncertainty regarding prognosis
  - Uninterpretable test results (eg no mutation/gene alteration found in cancer genetic testing)
  - News that is different from anticipated
  - Identification of carrier status
• Breaking difficult/bad news is complex due to:
  > The practitioner’s own emotional state
  > The degree of identification with the individual
  > Acceptance of the practitioner’s own mortality
  > The burden of truth telling
  > Continuing commitment to the individual
  > Uncertainty
• It is never easy to break difficult or bad news; however, there are sensitive ways to break such news that facilitate coming to terms with the news over time. A caring and empathic manner is important.

**When to tell the individual**
• Prepare the individual for the possibility of difficult/bad news as early as possible in the diagnostic/testing process.
• Plan a consultation for the time when all of the results will be available.
• Tell the individual as soon as the final result or diagnosis is available.

**Prior to giving the news**
• Ensure the news is given in person.
• Allow enough uninterrupted time in a comfortable place.
• Encourage a second person or family member to be present, if appropriate.
• Ensure you have the necessary information and appropriate referrals.

**When giving the news**
• Assess the individual’s understanding of their situation.
• Define the nature of the session. ‘You’ve come today to get the results …’
• Warn of the news and offer reassurance:
  > ‘Unfortunately this is probably not the news you wanted to hear’
  > ‘You may not hear or remember all that I will tell you’
  > ‘I will repeat it all later’
  > ‘You can ask questions’
• Provide the news simply and honestly. Use lay terms and avoid euphemisms.
• Work at the pace the family can cope with; however, avoid withholding further difficult news to other appointments.
• Be aware of the types of reactions individuals experience when receiving the news.
• After giving the news, allow silence to allow the individual to absorb and respond to the information.
• Work from what the individual knows and understands. At each stage, check understanding.
• Be aware of unhelpful self-protection strategies when giving news such as suppression of feeling, authoritarian style, and therapeutic zeal.
• Be aware of your own body language, actively listen and avoid closed questions.
Afterward

- Express empathy and the ability to help; however, avoid expressions such as ‘I know how you feel’.
- Prepare the individual for what they may experience after the appointment, e.g., a feeling of disbelief, physical reactions, a sense of unreality, an inability to concentrate, sleeplessness, moodiness, increased thoughts about the situation and anxiety.
- Provide a structure for the next step. This does not mean making a decision but providing support, another appointment or referral or other plan for the next contact.
- Provide appropriate written information, as recall of information presented in consultation is often poor.

Anxiety and living with uncertainty

- There are many potential areas of uncertainty in genetics that tend to diminish a sense of control over events and life. Anxiety and fear are often the result, or may be exacerbated.
- Potential areas of genetic uncertainty include:
  - An increased chance (risk) of occurrence of a genetic condition
  - An increased risk of a pregnancy affected by a chromosome abnormality
  - A risk that future pregnancies will be affected by a genetic condition
  - Clinical identification of a child with unusual physical features but no definite diagnosis
  - The diagnosis in a child of a condition where the level of ability and future health may be unknown
  - An increased risk of developing a condition at some time in the future
- In an attempt to obtain certainty, people may be motivated to search the Internet, visit many doctors, travel overseas for medical advice, and question the expertise of the original doctor.
- Family members may expect a genetic consultation or diagnosis to resolve uncertainty and decrease anxiety. This expectation is not always realistic and may lead to new uncertainties.
- Counselling for anxiety and uncertainty may be facilitated by:
  - Discussing the individual’s expectations prior to tests being conducted
  - Enabling the individuals to verbalise their concerns and fears. This can assist them to identify the underlying source of their anxiety
  - Discussing past experiences that involved uncertainty and their resolution
  - Being self-aware. Anxious individuals can unconsciously ‘transfer’ their feelings of anxiety and helplessness to the practitioner (transference). Practitioners need to be aware that their own feelings may reflect the emotional state of their patient
  - Avoiding false reassurance or expectations
  - Avoiding jargon
  - Discussing the individual’s expectations of a referral (e.g., to a clinical geneticist)
**Decision making**

- In many health settings, people expect advice and direction. In genetics, best practice is often unclear and the person may be faced with a range of options. Ultimately, the decision must be made by the person himself or herself.

- Choices that arise in genetics:
  - Choosing between medical options, eg whether to have a test, and which test
  - Deciding on prophylactic measures such as surgery
  - Deciding whether to terminate or continue an affected pregnancy

- The ‘best’ decision often rests on personal factors such as values, coping style and circumstances.

- Individuals may perceive that family, friends, society or the medical profession are applying pressure to make a particular decision.

- Individuals may ask ‘What would you do?’ This question may arise from uncertainty or from a desire to check the acceptability of a decision. It is not appropriate to offer a personal opinion as this can imply that other choices are not valid or acceptable.

- An appropriate response to the question ‘What would you do?’ might be to acknowledge that the decision is a difficult one and to offer support in reaching a decision. Highlight that there is no right or wrong decision, and it is important that the person consider what is best for them. Decision making may be facilitated by:
  - Using counselling skills that allow value-free and non-judgemental discussion of the issues and factors impacting on the decision
  - Providing correct, up-to-date and unbiased information from a variety of reliable sources
  - Allowing time and the opportunity for consultation with different sources of information
  - Asking the individual to consider different scenarios and the impact these may have on their life
  - Asking the individual to consider past decisions, including how they were made and what helped

**Grief and loss**

- When given genetic information, patients may grieve the loss or change in their lives, eg they may grieve the loss of a pregnancy, grieve the anticipated loss of a child, or grieve the loss of expectations for their child or themselves.

- Grief is not an illness but a normal response to loss, and reflects a healthy process of adjustment over time. An understanding of the physical, emotional and social reactions of grieving people is essential. All people do not grieve in the same way. A person may benefit from some outline of the grief process to realise that their reactions (current and future) are normal. Referral for grief counselling may be appropriate (see Contacts, support and testing).

**Guilt, shame and blame**

- Emotions commonly experienced after the diagnosis of a genetic condition or predisposition include guilt, shame and/or blame. These reactions are not confined only to parents or affected individuals, but can be experienced by other family members.

- Guilt is a very common reaction and can take the form of questions such as
  - ‘What did I do wrong?’
  - ‘Is this a punishment?’

- These questions may not always be verbalised. Instinctive rejection of a child or pregnancy affected by a genetic condition can also be a source of guilt. Guilt is a reflection of a feeling of responsibility for the condition and can be experienced by grandparents as well as parents.

- Shame is an expression of the (self-) perception that an individual or couple has failed to live up to their own or society’s expectations, eg by not having a ‘normal’ baby.
• Blame can be a defence against a potential threat to self-image, a way of stating ‘it can’t be me’. Family members may ‘blame’ the ‘other side of the family’ for a problem directly or by highlighting the absence of any ‘defects’ in their family history. Blame directed at specific individuals or between a couple may be a symptom, or the start, of underlying problems in the relationship.

• An intellectual understanding of genetics is not always sufficient to counteract these emotions.

• Guilt can be alleviated at the time of diagnosis or once feelings of guilt have been expressed, by stating or reinforcing the fact that the individual (couple) is not responsible. Permitting the individual/couple to talk about their feelings and using skills such as normalisation may be helpful.

• It is common for parents to look for a reason why their child has a condition. Taking a family and personal history may unintentionally convey that the parents contributed in some way. When taking a history, offer reassurance where possible that a factor has not contributed to the condition, e.g., social drinking during pregnancy has not caused a chromosomal condition.

• Shame may be expressed as the desire to hide the source of shame from the eyes of a judging world. Ridicule and rejection are anticipated, so it is important that they feel the practitioner is not judgemental. Helpful skills include enabling the individual to talk about their feelings, accentuating aspects in which the individual is doing well and bolstering self-esteem. Demonstrate that an affected child or baby is not rejected by referring to them by name, and by being inclusive of the affected child, e.g., holding the baby, or talking to the child.

Patient and further information

Support groups


Financial services


Counselling skills


Genetic counselling


Grief and loss

National Association for Loss and Grief (NSW) Inc. http://www.nalag.org.au

Australian Centre for Grief and Bereavement. http://www.grief.org.au

Psychological aspects of genetics


Breaking difficult/bad news

Cultural information
Centre for Culture, Ethnicity and Health. http://www.ceh.org.au

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http://www.genetics.com.au

http://www.genetics.com.au

http://www.genetics.com.au

http://www.genetics.com.au


http://racgp.org.au
A genetics service is a team of health professionals – including: counsellors, doctors, nurses, social workers and those who care for people who may have genetic conditions.

The people in a genetic service are able to:

- Discuss the possibility that you or someone in your family may have a genetic condition
- Offer counselling about the availability, appropriateness, benefits and risks of having genetic testing
- Carry out any tests that you agree to
- Talk about what the tests might mean for you, your family, your working life and so on
- Provide support and information after you have received the genetic test result and talk to you about what it now means for you and your family
- Provide on-going support to people with a genetic condition
- Refer you to a support group.

Genetic services are generally fairly small and fairly busy. You will need a referral from your doctor before attending.

If you are going to see a genetic service, you can prepare by:

- Learning as much as possible about your family’s health (see fact sheet on ‘How do genetic conditions occur?’)
- Taking along photos of as many family members as possible
- Taking along a list of questions you may have
- Taking along another family member, if possible.

There are a lot of other services which help people with genetic conditions. They include:

- Prenatal services
- Familial cancer services
- Specialist services for people with specific genetic conditions.

**Contacts and further information**

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
Genetic testing is common. Almost every baby born in Australia has a blood sample taken from their heel within a few days of birth to look for the genetic condition phenylketonuria (where the body lacks a specific enzyme, which causes abnormal metabolism that may result in brain damage) and a range of other conditions (see fact sheet on 'Newborn screening').

Testing is also done in many other situations:
- To make a diagnosis for someone who has a medical condition
- To look for altered genes in the relatives of people with a genetic condition
- To look for carriers of altered genes in people of certain ethnic groups
- To look at people with certain medical conditions such as breast cancer, to see if they have an altered gene, which indicates that they have a high likelihood of getting the condition
- To screen for, or diagnose, a genetic condition during pregnancy
- To work out if someone could develop a medical condition in the future
- To identify paternity and other important relationships in times of dispute or in coronial inquiries.

If you are considering having genetic testing, you should be aware that it has both advantages and disadvantages.

The advantages are that:
- You might clarify an uncertain situation
- You might find your fears were unfounded
- You might find that while you have a genetic condition or gene alteration you’d rather not have, at least you now know and can work out what to do
- What you learn might have implications for others in your family.

The disadvantages are that:
- You may learn something that, with hindsight, you’d rather not have learnt
- What you learn might have implications for others in your family
- What you learn might cause problems for you with issues like life insurance.

The limitations are:
- No test is perfect – sometimes results can give guidance only, sometimes the result will be unclear and, on rare occasions, the result can give false impressions
- A test can’t predict what will happen to a person – it can only give an idea of what might happen.
If you’re thinking about having a test for a genetic condition, then you need to talk to a doctor or genetic counsellor before the test. You need to find out:

- What it means for you and your family if the test is positive, or if it’s negative, or if the result is unclear
- Whether or not it might be wise to take out life insurance before the test, so premiums are not affected by test results. Note that you have to declare your family history, regardless of whether or not you have had genetic testing
- The cost – some genetic tests are provided free through public hospitals, some are covered by Medicare and some have to be paid for.

Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- The Centre for Genetics Education at [http://www.genetics.edu.au](http://www.genetics.edu.au)
- For other related fact sheets, you can contact the Gene Technology Information Service on [free call Australia-wide 1800 631 276](tel:1800 631 276) or email [gtis-australia@unimelb.edu.au](mailto:gtis-australia@unimelb.edu.au) or visit Biotechnology Australia’s website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
Support groups

Finding out that someone in the family has a genetic condition can raise a lot of issues. Different people will deal with the situation in different ways.

Some people will want to learn as much as possible and will need as much information as possible, as soon as possible.

Some people may need emotional support to get through what can be, for some, a difficult time.

Some people may want practical help and advice – what does this mean for work, for insurance, for the future, for others in the family?

Some people may want to talk to others who are going through, or have been through, a similar experience.

All this help is available through support groups. There is usually a support group for all but the rarest genetic conditions. Even where there is no particular group for your condition, the peak agency in each state may be able to help by putting you in contact with another family in similar circumstances.

Support groups operate in a number of different ways. Some have regular meetings. Some offer telephone support. Some provide information in printed form and/or via websites. Some keep members up to date with research. Some provide one-to-one contact with someone who has been there. While they vary in how they operate, the common theme is that they offer support and information to individuals and families dealing with genetic conditions and their families.

There is also a coordinating agency in most states for all these support groups.

<table>
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<tr>
<th>State/Territory</th>
<th>Coordinating Organisation</th>
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| Australian Capital Territory | Self-Help Organisations United Together (SHOUT)  
PO Box 717, Mawson ACT 2607  
Ph: (02) 6290 1984  
Fax: (02) 6286 4475  
Email: admin@shout.org.au  
Website: www.shout.org.au |
| New South Wales          | The Association of Genetic Support of Australasia (AGSA) Inc.  
66 Albion Street, Surry Hills NSW 2010  
Ph: (02) 9211 1462  
Fax: (02) 9211 8077  
Email: info@agsa-geneticsupport.org.au  
Website: www.agsa-geneticsupport.org.au |
| New Zealand | New Zealand Organisation for Rare Conditions (NZORD)  
PO Box 38-538, Petone. NZ 6008  
Ph: (+64) (0)4 566 7707  
Fax: (+64) (0)4 566 7717  
Email: exec.director@nzord.org.nz  
Website: www.nzord.org.nz |
| --- | --- |
| Queensland | Self Help Queensland (SHQ) Inc.  
PO Box 353, Sunnybank QLD 4109  
Ph/Fax: (07) 3344 6919  
Email: selfhelp@gil.com.au  
Website: www.selfhelpqld.org.au |
| Victoria | Genetic Support Network Victoria (GSNV)  
10th Floor, Royal Children’s Hospital  
Flemington Road, Parkville VIC 3052  
Ph: (03) 8341 6315  
Fax: (03) 8341 6390  
Email: info@gsnv.org.au  
Website: www.gsnv.org.au |
| Western Australia | Genetic Support Council WA (GSNWA)  
Level 1, Oasis Lotteries House  
37 Hampden Road, Nedlands WA 6009  
Ph: 08 9389 6722  
Fax: 08 9389 9377  
Email: info@geneticsupportcouncil.org.au  
Website: http://geneticsupportcouncil.org.au |

These coordinating organisations come together to form one group known as the Australasian Genetic Alliance, which you can find on the web (http://www.australiangeneticalliance.org.au).

Note that there are no coordinating organisations for support groups in South Australia, Tasmania or the Northern Territory. In these regions, please contact the Australasian Genetic Alliance or your nearest genetics service, teaching hospital or health department for advice.

Contacts and further information
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au
Emerging genetic technologies
Emerging genetic technologies

GP’s role

• Have up-to-date information about genetic technologies ready to give to patients who raise concerns.
• Refer patients to relevant and reliable sources for further information.

Personalised medicine: pharmacogenomics

• Small differences in genes between different population groups, or some families within a population group, can mean that individuals react differently to drugs.
• Knowledge of these genetic differences can be used to tailor drug therapy to ensure that an individual receives the most appropriate pharmacotherapy: maximizing the likelihood of therapeutic benefit while minimising adverse drug events.

Applications

• Genes can determine how many drug receptors are produced on or within cells. For example:
  > Women with metastatic breast cancer who over-express the protein product of the gene called HER2 have aggressive disease and a poor prognosis. When HER2 is over-expressed, extra protein receptors are produced on the cell surface. Twenty to 30% of all women with metastatic breast cancer over-express the HER2 protein
  > The drug Herceptin® is a monoclonal antibody against the HER2 gene product. It is thought that Herceptin® works by binding to the receptor sites on the cell surface, thereby limiting the amount of cell division that occurs and preventing the growth of the cancer.
• Some patients may metabolise drugs faster or slower than others, impacting on the drug efficacy and contributing to side effects. Genetics can influence how someone would react to a medicine prior to giving it. Genetic testing to guide drug prescription is still in its infancy but is a rapidly developing area.
  > For example, the enzyme in the liver which is produced by the gene CYP2D6, controls the metabolism of codeine to morphine, which is the active analgesic metabolite. Variations of the CYP2D6 gene can have an impact on enzyme production and activity
  > People who have low levels of the functioning enzyme metabolise codeine slowly. Codeine therefore remains in their bodies longer than if it was metabolised quickly
  > Slow metabolisers of codeine are more likely to have respiratory side effects
  > The amount of CYP2D6 produced will determine how effective codeine is. Patients who produce low levels of CYP2D6 in the liver will require smaller doses of the drugs that are metabolised by this enzyme, while fast metabolisers will need larger drug doses to get the same effects
  > The enzyme encoded by the CYP2D6 gene also plays a primary role in the metabolism of drugs used to treat severe depression, schizophrenia, bi-polar disorder, cardiovascular disease treated with beta blockers, ADHD, and others.
Gene therapy

- Gene therapy involves the introduction of new genes into targeted cells of the patient’s body. It is highly experimental, but has the potential to treat and cure inherited or acquired genetic conditions that are currently incurable.

- New genes can be introduced into human cells either *in vivo* or *in vitro*.
  - The new gene can be inserted into a patient’s cells *in vitro* and the modified cells are then transplanted back into the patient.
  - Genes that will modify the immune response to infectious disease or cancer can be targeted to a patient’s immune system (eg lymphocytes).

- There are two main methods of delivering therapeutic genes into a patient’s cells:
  - Viral delivery: the use of a modified virus that contains the desired gene yet does not cause an infection. As viruses work by inserting their genes into the host’s cells, viruses can be genetically manipulated to deliver therapeutic genes directly into a patient’s cells – sometimes being targeted at a particular organ or cell type.
  - Non-viral delivery: the creation of nanoparticles, containing the therapeutic gene, so small they can be transported by the bloodstream and absorbed by target cells.

Applications

- Conditions targeted in Australian gene therapy trials include cancer, cystic fibrosis, haemophilia and HIV/AIDS.
- One gene therapy that has been approved for routine treatment is for squamous cell carcinoma, which was approved in China in early 2004. In this treatment a tumour suppressor gene is introduced into patient’s cells using a modified viral vector.
- There have been growing concerns regarding the safety of gene therapy vectors. The high efficiency of random integration into the host’s DNA has always been perceived to have a hypothetical risk for mutagenesis.
- The use of gene therapy in the treatment of severe combined immune deficiency (SCID) by a French research group (Cavazzana-Calvo M et al) was hailed as the first example of a genetic condition being successfully treated by gene therapy.
- Seven out of ten infants treated to date have restored immune function. However two of the children treated initially developed leukaemia in 2002 and 2003, caused when the virus used to deliver the therapeutic gene activated a cancer-causing gene (oncogene).
- The clinical trials were halted but have now been resumed only for patients with no other treatment options.
- This experience illustrates the need for this therapy to be conducted as part of clinical trials.

Ethical issues

- Beyond its medical applications, concerns have been raised that gene therapy could be used for superficial reasons, such as enhancing athletic ability.
- The potential cost of gene therapy is also a matter of concern if it places too great a burden on health care systems or is only available to those who can afford it.
- Additionally, the possible genetic manipulation of the egg or sperm cells (*germ line gene therapy*) remains the subject of intense ethical and philosophical discussion.
Stem cells

- Stem cells are those that are not differentiated to function in a specific manner in a particular part of the body.
- They can multiply indefinitely, and as they do, can be directed to differentiate and thus specialise as certain cell types.
- A potential use for stem cells is the generation of new pancreatic cells for the treatment of diabetes and nerve cells for Parkinson disease and paralysis.
- Stem cells can be sourced from adult and embryonic tissue.

Adult stem cells (somatic stem cells)

- An adult stem cell is an undifferentiated cell - found among the differentiated cells in a tissue or organ - that can renew itself and differentiate to yield the major specialised cell types of the tissue or organ.
- The primary role of these stem cells in a living organism is to maintain and repair the tissue in which they are found.
- Certain kinds of adult stem cells seem to have the ability to differentiate into a number of different cell types, given the right conditions.
- If this differentiation of adult stem cells can be controlled in the laboratory, these cells may become the basis of therapies for many serious common conditions. Although adult stem cells have been identified in many organs and tissues, there are often only a very small number of them in each tissue.
- Adult stem cells are thought to reside in a specific area of each tissue where they may remain quiescent for many years until they are activated by disease or tissue injury.
- The adult tissues reported to contain stem cells include:
  - Brain
  - Bone marrow
  - Peripheral blood
  - Blood vessels
  - Skeletal muscle
  - Skin
  - Liver.
- Stem cells isolated from bone marrow have been used in transplants for 30 years and those isolated from the peripheral blood are being used increasingly for both autologous and allogeneic transplants.
- Transplantation of skin cells for patients with severe burns has already been accomplished.
Embryonic stem cells

- Embryonic stem cells isolated from the inner cell mass of human embryos, have the potential to develop into all, or nearly all, of the tissues in the body.
- This is unlike adult stem cells whose multiplying and differentiating capabilities are limited.
- Because of these traits, embryonic stem cells have great potential to be used in medicine to create cells that are needed for treatments that replace disease and damaged cells.
- With consent from donors, embryonic stem cell lines are currently derived from excess IVF embryos that are about 1 week old and consist of a mass of about 100 cells.
- When the desired number of cells is reached, the cells can be directed to form particular types of specialised cells such as heart, muscle, nerve, and blood cells. This creates the opportunity for discovery of new regenerative medicines and potential cell therapies.
- However, embryonic stem cells are likely to be allogeneic and if so will require immunosuppression.
- It is important to note that embryonic stem cells do not have the capacity to develop into a functional human embryo.
- Embryonic stem cells are ‘immortal’ in the sense that they can multiply in the laboratory for years. However, the immortal nature of embryonic stem cells means that they are associated with tumour formation.
- Whilst it is possible in the future that research on embryonic stem cells may no longer offer any advantages over non-embryonic stem cells, significant research is required before this can be demonstrated.
- In December 2002, the Australian Government passed legislation to provide for a nationally consistent regulatory scheme for human embryo research. The framework is embodied in two pieces of Commonwealth legislation:
  > The Prohibition of Human Cloning Act 2002, which bans practices, including human cloning, deemed to be unacceptable. That act has recently been amended to permit ‘therapeutic cloning’ (somatic cell nuclear transfer) if a licence is obtained. ‘Reproductive cloning’, breeding duplicate people by implanting a cloned human embryo into a woman, remains a criminal offence punishable by up to 15 years imprisonment.
  > The Research Involving Human Embryos Act 2002, which established a licensing system for the use of excess embryos from ART (assisted reproductive technology). Licenses to carry out work on embryos, including research, is administered by the Embryo Research Licensing Committee, a Principal Committee of the NHMRC.
Genetically modified (GM) foods

- Genetically modified (GM) foods have ingredients in them that have been modified by gene technology.
- This technology allows food producers to alter certain characteristics of a food crop by adding, removing or altering genetic material.
- In Australia, no fresh vegetables, fruit, meat, fish or agricultural products, other than those listed below, are sold as GM.

Applications

- Foods on sale in Australia that potentially use genetically modified (GM) ingredients come from the six GM commodity crops:
  > Soybeans – can be found in soy-based products and as an ingredient in processed foods such as bread, pastries, snack foods and edible oil products
  > Corn products – can be found in corn oil, corn flour, corn syrup, used in snack foods, fried foods and confectionery. This does not include corn cobs
  > Potatoes – can be used in processed products such as snack foods. This does not include fresh potatoes
  > Sugar beet – can be used as sugar in some imported processed foods
  > Canola oil – can be found in cooking oils, and a variety of tinned foods, and snack foods
  > Cottonseed oil 1- can be found in edible vegetable oils and margarines

- In addition to the above-listed GM crops, enzymes derived from GM sources (although the enzymes themselves are not genetically modified) are also used in the creation of some foods, such as sugar and cheese, although there are no GM ingredients in the end product.

1 Cottonseed oil is produced from GM cotton. GM cotton is the only GM food product approved to be grown commercially in Australia. The other GM foods are imported from other countries.

Safety

- It is the role of Food Standards Australia New Zealand (FSANZ), which is part of the Australian Government Health Portfolio, to ensure that all food, including GM food, is safe and that safety guidelines are based on strict standards.
- All GM foods intended for sale in Australia and New Zealand are subjected to a pre-market safety assessment by FSANZ. No GM food will be allowed onto the supermarket shelves unless it has gone through the safety assessment process and been approved for sale and consumption by FSANZ.
- GM food products on sale in Australia and New Zealand, either as a whole food or as in ingredient in a processed food, must have their GM status identified if introduced genetic material or protein is present in the final food. This identification will appear on the packaging label or near the food if it is unpackaged.
- Products that do not have to be labeled include:
  > Highly refined food, such as sugar or cottonseed oil, where the refining process removes any GM material
  > Processing aids and food additives, where there is no GM material present in the final food product
  > Flavours which are present in an amount less than 0.1% (1 in 1000 parts) in the final food product
  > Food prepared in restaurants or takeaway shops.
• Genetic modification has the potential to provide foods that have specific consumer benefits, such as being healthier, safer, cheaper, or can be grown more efficiently.
• GM crops may also have some environmental benefits; for example, the use of fewer chemicals (e.g., pesticides) during their production.
• Researchers are planning to develop foods that directly benefit consumers by:
  > Increasing concentrations of vitamins and improving ratios of fats and other constituents
  > Removing the allergy-causing substances and potential toxins that occur naturally in many plants
  > Inserting substances known to help prevent chronic diseases such as cancer and heart disease
• However, GM crops may also pose risks to the environment, which is why proper procedures that are set out by the Office of the Gene Technology Regulator (OGTR) must be followed.

**Regulation**

• The standard for GM foods is enforced by the States’ and Territories’ food or health agency.
• A national survey in 2004 found that foods complied with the GM labeling laws.
• When the jurisdictions test foods for compliance, the food may contain up to 1% of unintended GM product, however the manufacturer would have to prove that they ordered non-GM ingredients.
• Key government regulators include:
  > The Office of the Gene Technology Regulator (OGTR), which regulates the testing and release of all genetically modified organisms (GMOs) in Australia, under the Gene Technology Act 2000, in order to protect the health and safety of people and the environment from potential risks posed by gene technology
  > Australian Quarantine and Inspection Service (AQIS), which oversees imports and exports
  > Australian Competition and Consumer Commission (ACCC), which administers the Trade Practices Act 1974 to protect consumers from unfair trading practices and from false, misleading and deceptive conduct, which could include misleading labeling of foods.
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Gene Therapy Research Unit, The Children’s Hospital, Westmead, Australia.
http://www.chw.edu.au/prof/services/genetherapy/

National Center for Biotechnology Information. The promise of pharmacogenomics.

National Health and Medical Research Council (NHMRC). Australian Health Ethics Committee Issues for Health Ethics Committees – Stem Cell Research.

National Health and Medical Research Council (NHMRC). Gene and related Therapies Research Advisory Panel

Therapeutic Goods Administration.
www.tga.gov.au/

http://www.otgr.gov.au


Accessed March 2006
Genetic technology is a rapidly changing field. What is unknown today may be known tomorrow and some of what is known today may be proved wrong tomorrow.

Genetics is involved in a number of complex and sometimes controversial fields, such as:

- Designer drugs (pharmacogenomics)
- Gene therapy
- Stem cells
- Genetically modified foods.

In all these areas, research has shown that there are benefits to people. There is controversy over how beneficial the technologies are, the risks involved with using them and, in some cases, the ethics of using them.

All technologies are likely to develop further as people get more used to them and as their use is refined.

**Designer drugs**

These are drugs which are designed to work mostly with people who have a particular gene functioning in a particular way.

Pharmacogenomics is the study how a person’s genetic makeup affects their body’s response to drugs.

It is very early days for designer drugs, but one example is the use of the drug herceptin (to block the effects of the growth factor protein HER2, which transmits growth signals to breast cancer cells) to treat women with advanced breast cancer.

**Gene therapy**

Gene therapy involves changing or replacing faulty genes by inserting a normal gene into the body of a person with a serious illness.

We all carry about half a dozen faulty genes. Most of us do not suffer any harmful effects from our faulty genes because we carry two copies of nearly all genes. Scientists are looking at replacing the missing or faulty gene with a working gene as a treatment for genetic disorders.

This treatment is highly experimental, but has the potential to treat conditions that are currently incurable.
**Stem cells**

Most cells in the body do a particular job. There are many different cell types including: brain cells, skin cells, liver cells, kidney cells, red and white blood cells and heart cells. None of these types of cell can change into a different type of cell.

Stem cells are different. They have the ability to develop into many different types of cell.

Stem cells taken from bone marrow have been used for many years to treat people whose bone marrow is damaged by cancer treatment. Bone marrow stem cells can develop into red blood cells and several different types of white blood cell – these are also called adult stem cells. Based on current research, adult stem cells appear to have a more restricted ability to produce different types of cells and to self-regenerate. Many scientists are working with embryonic stem cells because they do not have this problem.

Embryonic stem cells are derived from embryos that are 5 to 6 days old. At this stage of development the embryo is a hollow ball of about 200 to 250 cells, no bigger than a pinhead, and is called a blastocyst.

It is illegal in Australia to conduct any type of research on embryos that are conceived naturally. Embryonic stem cells are taken from embryos that come from eggs fertilised in an IVF (in vitro fertilisation) clinic. Only embryos not required for implantation in IVF procedures are used. They are donated for research purposes only with informed consent from the donors. They are not derived from eggs fertilised within a woman’s body and embryos are not created specifically for research purposes.

Stem cells are controversial at the moment because of discussion over whether or not they should be taken from early embryos. They could help in the treatment of illness if the ethical issues are resolved.

Stem cells could potentially replace damaged tissue and cells in the body to treat a range of conditions including: heart failure, spinal injuries, diabetes and Parkinson disease. Stem cells could also be used to study early events in human development and why some cells become cancerous, and how some genetic diseases develop, which may lead to clues as to how they may be prevented.

**Genetically modified foods**

Genetically modified (GM) foods are foods grown from plants which have had one or a few of their genes altered.

Genetically modified foods are grown in some parts of the world, but in Australia GM cotton is currently the only GM crop that is commercially grown. The food product that comes from the cotton plant is cotton seed oil. This oil is a highly refined product. In the process of making this oil, all the cotton plant’s genes, including the inserted gene that makes it genetically modified, is removed. So the makeup of cotton seed oil from a regular cotton seed plant and a GM cotton plant is no different.
Safety approval

All foods that are sold in Australia, including GM foods, must pass a comprehensive and demanding safety assessment by our food authority, Food Standards Australia New Zealand (FSANZ), to gain approval for consumption.

FSANZ’s safety assessment process for genetically modified foods is based on concepts and principles developed by the World Health Organization (WHO), the Food and Agriculture Organization (FAO) of the United Nations and the Organisation for Economic Co-operation and Development (OECD).

Eating genetically modified foods will not change our genes. There are a lot of myths and inaccurate information about GM foods, including that eating GM foods will insert the gene which has been inserted into the GM food into our genes. We eat millions of genes everyday. So when we eat an apple, we eat all the genes in that apple, but it will not change us in any way into an apple.

Food labelling laws

As part of our general food labelling laws, GM foods/ingredients are labelled to allow people to choose whether or not to buy GM foods or foods with GM food ingredients. This labelling law applies to both Australian and overseas produced foods that are sold in Australia and New Zealand.

Contacts and further information

- Your local genetic service, which you can contact through your nearest community health centre, public hospital or health department.
- Australian Stem Cell Centre at [www.stemcellcentre.edu.au](http://www.stemcellcentre.edu.au)
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gtis-australia@unimelb.edu.au or visit Biotechnology Australia's website at [http://www.biotechnology.gov.au](http://www.biotechnology.gov.au)
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**Acrocentric:**
Acrocentric chromosomes are those with the centromere very close to one end. The acrocentric chromosomes are numbers 13, 14, 15, 21 and 22. The short ‘p’ arms are very short and usually contain DNA with no functional genetic material.

**Adult stem cell:**
A type of precursor cell in a specific tissue that is undifferentiated and is capable of self-renewal and differentiating into cells found in that tissue. An adult stem cell cannot repopulate all the tissues of the embryo.

**Allele:**
Alternative forms of a gene at a given locus.

**Allelic variants:**
Two or more alternative forms of a gene or DNA sequence.

**Alpha-fetoprotein (AFP):**
A protein which is made by the fetus but which can be found in the mother’s blood serum. The amount of the protein, both in the maternal serum and in the amniotic fluid, at particular periods during the pregnancy, may be associated with the presence of neural tube defects or chromosomal problems in the baby.

**Amino acids:**
Small chemical building blocks that join together to form proteins; there are 20 common amino acids which join in different combinations to make up proteins.

**Amniocentesis:**
A procedure for obtaining amniotic fluid for prenatal diagnosis. Using a sterile needle, a sample of amniotic fluid is removed from the uterus; the amniotic fluid contains cells from the fetus which can be analysed to determine if the fetus has a specific condition. The test is usually carried out between the 14th – 20th week of pregnancy, and ideally between the 15th to 17th week.

**Amniocyte:**
Fetal cell found in the amniotic fluid surrounding a fetus in the uterus.

**Analyte:**
Any chemical to be analysed.

**Aneuploidy:**
A condition where the number of chromosomes is not an exact multiple of the haploid number (23 in humans). Usually refers to an extra copy of a chromosome (trisomy) or the absence of a copy of a chromosome (monosomy).

**Anticipation:**
The situation where a genetic condition appears to become more severe and/or arise at an earlier age as it is passed through subsequent generations (seen in many trinucleotide repeat mutations).

**Autosomal dominant mutation:**
A dominant mutation in a gene which is carried on an autosomal chromosome.

**Autosomal dominant condition:**
A condition or characteristic encoded by a gene carried on an autosomal chromosome. That manifests both in carriers (one copy of the mutation; heterozygotes) and where the person has two copies of the mutation (homozygotes). Requires only one parent with the mutation to pass it on to offspring.

**Autosomal gene:**
Any gene which is located on an autosomal chromosome.

**Autosomal recessive mutation:**
A recessive mutation in a gene which is carried on an autosomal chromosome.

**Autosomal recessive condition:**
A condition or characteristic encoded by a gene on an autosomal chromosome that does not manifest in the heterozygote but manifests in the homozygote.

**Autosome:**
Any chromosome that is not a sex chromosome (that is not an X or Y chromosome). In humans, the autosomes are numbered 1 to 22 in decreasing size.
<table>
<thead>
<tr>
<th>Glossary Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Balanced translocation:</strong></td>
<td>A rearrangement of the chromosomes with no apparent loss or gain of chromosomal material. A person with this rearrangement is not affected in any way. When a translocation chromosome results in the gain or loss of genetic material, it is said to be unbalanced and may cause a problem in health, growth or development.</td>
</tr>
<tr>
<td><strong>Carrier of a chromosomal rearrangement:</strong></td>
<td>This definition applies to an individual who has a rearrangement of his/her chromosomes so that the normal genetic information is present (that is, it is 'balanced') but it is not in the usual 46 chromosome pattern.</td>
</tr>
<tr>
<td><strong>Carrier screening:</strong></td>
<td>Testing populations to determine if individuals are at increased risk of being carriers of a mutated gene for a particular condition.</td>
</tr>
<tr>
<td><strong>Carrier testing:</strong></td>
<td>Testing an individual who is at risk due to a family history to determine if he or she is a carrier of a mutated gene for a particular condition.</td>
</tr>
<tr>
<td><strong>Cascade testing:</strong></td>
<td>Identification within a family of carriers of a particular mutation following the finding of the first affected family member.</td>
</tr>
<tr>
<td><strong>Centromere:</strong></td>
<td>The constricted part of the chromosomes which separates it into its two arms. The short arm is called the 'p' arm (for 'petite'); the long arm is called the 'q' arm.</td>
</tr>
<tr>
<td><strong>Chelation:</strong></td>
<td>The binding of a metal ion to an organic molecule to form a complex, eg chelation of iron by desferrioxamine in β-thalassaemia patients allows the removal of excess iron from the blood after prolonged blood transfusion.</td>
</tr>
<tr>
<td><strong>Chimera:</strong></td>
<td>A special kind of mosaicism in which an individual or tissue contains a mix of cells derived from two genetically different individuals. The blood of a patient who had a transfusion from another individual would be chimeric for example.</td>
</tr>
<tr>
<td><strong>Chorion:</strong></td>
<td>The chorion develops into the placenta. Chorionic cells have the same genetic composition as cells of the fetus. Cells of the chorion are sampled during a prenatal diagnostic test called CVS (chorionic villus sampling).</td>
</tr>
<tr>
<td><strong>Chorionic villi:</strong></td>
<td>Folds of the membrane surrounding an embryo that will form the fetal part of the placenta.</td>
</tr>
<tr>
<td><strong>Chorionic villus sampling (CVS):</strong></td>
<td>A procedure for obtaining cells of the chorionic villi to enable testing of the fetus for specific abnormalities. Samples of the cells may be taken through the vagina but more commonly through the abdomen of the pregnant mother: it is usually carried out from the 11th week of pregnancy.</td>
</tr>
<tr>
<td><strong>Chromatid:</strong></td>
<td>One of the two identical strands of a chromosome, connected at the centromere after replication of the chromosome.</td>
</tr>
<tr>
<td><strong>Chromosome:</strong></td>
<td>A threadlike structure found in the nucleus of all the body cells (except red blood cells) consisting of DNA and proteins.</td>
</tr>
<tr>
<td><strong>Clinical heterogeneity:</strong></td>
<td>Refers to the occurrence of clinically different types of genetic conditions due to mutations in the same gene.</td>
</tr>
<tr>
<td><strong>Clonal:</strong></td>
<td>Genetically identical cells with a single common ancestor.</td>
</tr>
<tr>
<td><strong>Clone:</strong></td>
<td>An identical copy of a gene/s or a group of identical cells.</td>
</tr>
<tr>
<td><strong>Co-dominance:</strong></td>
<td>The equal expression of both copies of a gene in an individual, eg presence of both haemoglobin A and S on electrophoresis in an individual heterozygous for sickle-cell disease.</td>
</tr>
<tr>
<td><strong>Codon:</strong></td>
<td>A sequence of three bases in DNA or RNA that specifies a particular amino acid.</td>
</tr>
<tr>
<td><strong>Compound heterozygote:</strong></td>
<td>An individual who has two different mutations in homologous alleles of a gene or DNA sequence.</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
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</tr>
<tr>
<td><strong>Concordance:</strong></td>
<td>Presence of the same characteristic in both members of a pair of twins (or set of individuals). The opposite to discordant.</td>
</tr>
<tr>
<td><strong>Confinned placental mosaicism:</strong></td>
<td>Mosaicism that is seen only in the placenta but not in the fetus.</td>
</tr>
<tr>
<td><strong>Congenital bilateral absence of the vas deferens (CBAVD):</strong></td>
<td>The absence at birth of both of the pair of ducts in males that conduct spermatozoa from the epididymis to the urethra.</td>
</tr>
<tr>
<td><strong>Consanguinity:</strong></td>
<td>Relationship between two individuals with a common ancestor, for example, cousins</td>
</tr>
<tr>
<td><strong>Consultand:</strong></td>
<td>The person seeking, or referred for, genetic counselling.</td>
</tr>
<tr>
<td><strong>Crossing over:</strong></td>
<td>When chromosome pairs join together during meiosis, the two chromosomes may exchange material: part of one chromosome ‘crosses over’ and exchanges places with the corresponding part on its homologous chromosome.</td>
</tr>
<tr>
<td><strong>CVS:</strong></td>
<td>See chorionic villus sampling.</td>
</tr>
<tr>
<td><strong>Cytogenetics:</strong></td>
<td>The microscopic study of chromosomes and how changes in chromosome structure and number affect individuals.</td>
</tr>
<tr>
<td><strong>De novo mutation:</strong></td>
<td>A new mutation arising in a fetus that was not present in the parents.</td>
</tr>
<tr>
<td><strong>Deletion:</strong></td>
<td>The loss of some genetic material from a chromosome. If the deletion is large, it may be observed as missing chromosomal material; if it is small, it may only be detected by analysing the composition of the DNA.</td>
</tr>
<tr>
<td><strong>Deoxyribonucleic acid:</strong></td>
<td>See DNA.</td>
</tr>
<tr>
<td><strong>Derivative chromosome:</strong></td>
<td>Chromosome that has been altered as a result of a translocation.</td>
</tr>
<tr>
<td><strong>Desferrioxamine:</strong></td>
<td>A chelating agent that combines with iron in body tissues and fluids and is used to remove excess iron in patients with β-thalassaemia who receive regular blood transfusions.</td>
</tr>
<tr>
<td><strong>Dinucleotide:</strong></td>
<td>Two nucleotides.</td>
</tr>
<tr>
<td><strong>Diploid number:</strong></td>
<td>This is the number of chromosomes in the somatic (body) cells. There are two copies of each chromosome. In humans, the diploid number is 46.</td>
</tr>
<tr>
<td><strong>Discordant:</strong></td>
<td>The situation where both members of a pair of twins do not exhibit the same characteristics. Opposite to concordant.</td>
</tr>
<tr>
<td><strong>Disomy:</strong></td>
<td>The normal chromosome complement, i.e., having two copies of each chromosome, as seen in somatic cells.</td>
</tr>
<tr>
<td><strong>Dizygotic twins:</strong></td>
<td>Nonidentical twins, arising from two different eggs fertilised by two different sperm; such twins are also referred to as fraternal twins.</td>
</tr>
<tr>
<td><strong>DNA (deoxyribonucleic acid):</strong></td>
<td>The chemical compound which makes up genes within chromosomes and is the basic material of heredity. It is made up of chemicals called nucleotide bases, linked together in a chain. Two chains of nucleotides twist around each other to form a double helix.</td>
</tr>
<tr>
<td><strong>DNA sequencing:</strong></td>
<td>Determining the pattern or order in which the nucleotide bases occur in a piece of DNA. This sequence is the genetic code.</td>
</tr>
<tr>
<td><strong>Dominant:</strong></td>
<td>A trait or characteristic is dominant if it is phenotypically expressed in the heterozygote.</td>
</tr>
</tbody>
</table>
**Duplication:**
A part of the chromosome is present in two or more copies. If the duplication is large it may be observed under the microscope as a change in a chromosome; a small duplication may only be observed by examining the DNA structure of the chromosome or a gene.

**Dynamic mutation:**
A triplet repeat expansion mutation that readily changes repeat number from one generation to the next.

**Embryonic stem cells:**
A cell derived from the inner cell mass that is self-renewing in culture and, when re-introduced into the inner cell mass of a blastocyst, can repopulate all the tissues of the embryo. Adult stem cells, on the other hand, have limited capability of multiplying and differentiating.

**Empiric risk:**
A risk estimate that is given for the chance of occurrence or recurrence of a particular condition in an individual based on the observation of other families with that condition.

**Environmental factors:**
Factors in the environment which may have an effect on our development or growth, eg diet, atmospheric pollutants, cigarette smoke, preservatives, X-rays etc.

**Enzyme replacement therapy:**
A method of treating genetic conditions which are due to a deficiency of a particular enzyme. Overcoming the deficiency by providing the body with the enzyme enables the cells to function correctly and the symptoms of the condition may be corrected.

**Euchromatin:**
Chromatin that is light-staining during interphase, and is believed to contain genes that are actively transcribed.

**Exon:**
The part of the DNA sequence of a gene that is translated into a protein.

**Expressed gene:**
When the coded information contained in the gene is produced to form a polypeptide or RNA.

**Expressivity:**
The degree to which an inherited characteristic is expressed in a person. ‘Variable expressivity’ refers to the variation in expression and severity of particular characteristics or a condition.

**Fetal blood sampling:**
A prenatal diagnostic technique for obtaining a blood sample from the fetus.

**FISH:**
See fluorescence in situ hybridisation.

**Fluorescence in situ hybridisation:**
Identification of chromosomes and genes using specific probes that are tagged with a fluorescent dye. This technique can be used to study chromosomes in interphase cells, as well as cells arrested in metaphase.

**Founder effect:**
The high frequency of a gene in a population due to that population being derived from a small number of ancestors, one or a few of whom carried that gene.

**Fragile site:**
A small break or a constriction of a chromosome that can be visualised after special treatment of the chromosomes. In individuals affected with fragile X syndrome, a fragile site can be seen on their X chromosome under certain laboratory conditions.

**Fragile X premutation:**
A triplet repeat expansion in the FMR1 gene that is larger than the normal range but not sufficiently large to cause fragile X syndrome.

**Frameshift mutation:**
The addition (insertion) or deletion of a number of base pairs that is not a multiple of three, resulting in the transcription reading frame of the gene being changed.

**Fraternal twins:**
See dizygotic twins.
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<tr>
<td><strong>G-banding:</strong>&lt;br&gt;Banding patterns on chromosomes make it easier to examine the chromosomes under the microscope for abnormalities in structure and number. G-bands are one type of banding pattern, induced to appear on chromosomes by using Giemsa stain.</td>
</tr>
<tr>
<td><strong>Gamete:</strong>&lt;br&gt;Refers to the sperm cells in males and the egg cells in females.</td>
</tr>
<tr>
<td><strong>Gel electrophoresis:</strong>&lt;br&gt;The separation of chemicals in an agarose gel by virtue of their size and electric charge.</td>
</tr>
<tr>
<td><strong>Gene cloning:</strong>&lt;br&gt;Isolating a gene and then making multiple copies of it by inserting it into a bacterial cell or another organism.</td>
</tr>
<tr>
<td><strong>Gene mapping:</strong>&lt;br&gt;Determining the relative locations of different genes on chromosomes.</td>
</tr>
<tr>
<td><strong>Gene therapy:</strong>&lt;br&gt;Treating genetic conditions by inserting a correct copy of the gene in question, into the cells of individuals who have a condition due to a mutated gene.</td>
</tr>
<tr>
<td><strong>Gene:</strong>&lt;br&gt;The basic unit of heredity; a segment of DNA which contains all the information necessary for the production of a polypeptide or RNA molecule.</td>
</tr>
<tr>
<td><strong>Genetic code:</strong>&lt;br&gt;The information contained in the DNA which is ‘interpreted’ by the cells to produce proteins. The chemicals (nucleotides) which make up the DNA can be described by the letters A (adenine), T (thymine), C (cytosine) and G (guanine). Thus the genetic code can be written as a series of letters (for example AAA CGT TTC).</td>
</tr>
<tr>
<td><strong>Genetic counselling:</strong>&lt;br&gt;Diagnosis, information and support provided by health professionals with specialised training in genetics and counselling.</td>
</tr>
<tr>
<td><strong>Genetic counsellor:</strong>&lt;br&gt;A health professional with specialised training in genetics and counselling who can provide information and support for individuals or families with concerns about a genetic condition which may run in the family.</td>
</tr>
<tr>
<td><strong>Genetic engineering:</strong>&lt;br&gt;Laboratory techniques used to alter or manipulate the genetic makeup of cells or an organism by deliberately removing, changing or inserting individual genes.</td>
</tr>
<tr>
<td><strong>Genetic heterogeneity:</strong>&lt;br&gt;The same phenotype caused either by different mutations in the same gene or mutations in different genes.</td>
</tr>
<tr>
<td><strong>Genetic mapping:</strong>&lt;br&gt;Determination of the relative positions of genes on a chromosome and a measure of the distance between them.</td>
</tr>
<tr>
<td><strong>Genomic DNA:</strong>&lt;br&gt;The whole complement of an individual’s DNA.</td>
</tr>
<tr>
<td><strong>Genotype:</strong>&lt;br&gt;The genetic constitution of an individual, or more specifically the genetic information carried by a pair of alleles that determines a particular characteristic.</td>
</tr>
<tr>
<td><strong>Germline mosaicism:</strong>&lt;br&gt;The presence in the gonads of more than one genetically distinct line of germ cells.</td>
</tr>
<tr>
<td><strong>Germline:</strong>&lt;br&gt;The cells that give rise to gametes.</td>
</tr>
<tr>
<td><strong>Gonadal mosaicism:</strong>&lt;br&gt;The presence of two or more genetically distinct germ cell lines having arisen from one zygote, but differing due to a somatic mutation or non-disjunction.</td>
</tr>
<tr>
<td><strong>Guthrie card:</strong>&lt;br&gt;A piece of absorbent paper used in the examination of a drop of a newborn baby’s blood to exclude the presence of several congenital conditions, which may include phenylketonuria, cystic fibrosis and congenital hypothyroidism. Also called newborn screening card.</td>
</tr>
</tbody>
</table>
### H

**Haploid:**  
Having one copy of each chromosome. Gametes are haploid cells.

**Haplotype:**  
The genotype of a group of closely linked loci.

**Hemizygous:**  
The presence of a single copy of a gene. Usually refers to a gene on the X chromosome in males.

**Heterochromatin:**  
Dark-staining DNA that is usually not transcribed and consists of repetitive sequences.

**Heterozygote advantage:**  
The selective advantage of heterozygotes over homozygotes for a given locus. Acts to maintain the relatively high frequency of an allele in a population.

**Heterozygous:**  
Having the presence of two different alleles at a particular locus in an individual. Carrier state for a mutated gene.

**High performance liquid chromatography (HPLC):**  
A method of separating compounds based on properties such as size, charge and polarity.

**Homologous:**  
1. DNA or amino acid sequences that are very similar to each other.  
2. Chromosomes that pair during meiosis, one derived from the mother, one from the father. Partner chromosomes.

**Homologue:**  
One of two proteins of very similar structure.

**Homotetramer:**  
A protein complex made up of four identical subunits.

**Homozygote:**  
The presence of two identical alleles at a given locus on a pair of homologous chromosomes.

**HPLC:**  
See high performance liquid chromatography

**Human chorionic gonadotrophin:**  
A hormone produced by the placenta during pregnancy. Levels in the maternal serum are measured in screening for chromosomal conditions and neural tube defects.

### I

**Immunocytochemistry:**  
The use of specific antibodies to detect a protein in a biological specimen.

**In vitro fertilisation (IVF):**  
The process whereby an egg is fertilised with sperm in the test tube and then transplanted into a woman’s uterus.

**Inborn error of metabolism:**  
A congenital condition which results from a change in a gene which causes a deficiency in the presence or activity of particular enzymes important for the functioning of the body’s metabolism.

**Incidence:**  
The number of new cases of a condition, detected annually, per unit of the population. For genetic conditions, the incidence is quoted as the number of affected individuals per 1,000 births whether detected at birth or not.

**Inhibin A:**  
A protein hormone secreted by the corpus luteum and the placenta, present in maternal serum during pregnancy.

**Insertion:**  
1. The addition of a piece of chromosomal material into a chromosome in a place where it is not normally found. This may result in a condition, because the genetic code may then be read or translated incorrectly.  
2. The addition of bases in a DNA sequence which can change the reading frame of a gene (see frameshift mutation).

**Interphase:**  
The period of the cell cycle between cell divisions when DNA is replicated and repaired.

**Intracytoplasmic sperm injection (ICSI):**  
The injection with a fine needle of a single sperm into an egg. If it fertilises it may be implanted in a woman’s uterus with the intention of pregnancy.
### Intragenic:
Within a gene.

### Intron:
The part of the genetic sequence which is not translated into the final gene product or message.

### Inversion:
Where there are two breaks in a chromosome, the segment may flip over and rejoin, that is, become inverted. This results in the genes being in the reverse order along the chromosome causing the genetic code to be read or translated incorrectly.

### Isochromosome:
An abnormal chromosome in which the arms ('p' and 'q') are of equal length and the information in each of the two arms is genetically identical. This is formed by a rearrangement and duplication of a chromosome.

### Isoform:
An alternative form of a protein resulting from differential transcription of the relevant gene either from alternative promoter or alternate splicing.

### K

#### Karyotype:
The term used to describe an individual's chromosomes that have been photographed through the microscope and then arranged according to a standard classification based on their group and size.

### Kb:
A segment of DNA which is 1,000 base pairs in length.

### L

#### Linkage analysis:
The method of following the segregation of a condition within a family in relation to polymorphic markers to predict the likelihood of a person carrying the condition allele.

#### Linkage:
The tendency for genes or segments of DNA which are located close together on the same chromosome to be inherited together.

#### Locus:
The position on a chromosome of a gene.

### M

#### Manifesting carrier:
A person who is a heterozygote (carrier of a mutation) for a recessive condition and shows symptoms of that condition. Most often used to describe female carriers of X-linked recessive conditions who have the condition.

#### Marker chromosome:
A chromosome, or part of a chromosome, usually small, of unknown origin.

#### Marker DNA:
A polymorphic sequence of DNA linked to a gene causing a condition that can be used to track the inheritance of the gene within a family.

#### Maternal serum testing:
A test which assesses the risk of fetal abnormalities such as neural tube defects and Down syndrome by analysing a number of substances in the mother's blood during pregnancy.

#### Meconium:
The first stools of a newborn baby that are sticky and dark green, and composed of cellular debris, mucus and bile pigments.

#### Meiosis:
The cell division which only takes place in reproductive cells and results in egg and sperm cells which contain 23 chromosomes (the haploid number).

#### Meiosis I:
The first division of meiosis resulting in halving of the chromosome number.

#### Meiosis II:
The second division of meiosis in which the two chromatids of each chromosome separate, resulting in two gametes.

#### Mendelian inheritance:
This refers to the inheritance of single genes and follows specific patterns: autosomal dominant, autosomal recessive and X linked inheritance.
<table>
<thead>
<tr>
<th>Term</th>
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<tbody>
<tr>
<td>Metabolism</td>
<td>The physical and chemical processes by which energy is made available for essential body functioning, growth and development.</td>
</tr>
<tr>
<td>Metacentric</td>
<td>Refers to a chromosome which has its centromere in the middle and the short (p) and long (q) arms are of equal length.</td>
</tr>
<tr>
<td>Metaphase</td>
<td>The stage of meiosis and mitosis where homologous chromosomes are lined up with their pairs along the centre of the cell.</td>
</tr>
<tr>
<td>Microsatellite instability</td>
<td>Variations in the length of regions of repetitive DNA (microsatellites) present in somatic cells compared to the germline. Can be a marker of inherited bowel cancer.</td>
</tr>
<tr>
<td>Mismatch repair (MMR) genes</td>
<td>Genes encoding proteins involved in the repair of DNA. Mutations in these genes can cause hereditary non-polyposis colorectal cancer.</td>
</tr>
<tr>
<td>Missense mutation</td>
<td>A single-base substitution mutation that results in a codon that specifies a different amino acid.</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>These organelles in the cell are the main energy source: they are often called the powerhouse of the cell. The mitochondria also contain their own DNA and therefore genes; mitochondrial genes follow maternal inheritance.</td>
</tr>
<tr>
<td>Mitosis</td>
<td>The process of cell division in all cells except the reproductive cells. Mitosis results in ‘daughter’ cells which are genetically identical to the parent cells.</td>
</tr>
<tr>
<td>Monoclonal</td>
<td>A group of cells that are all identical copies of an original cell.</td>
</tr>
<tr>
<td>Monogenic</td>
<td>A characteristic which is due to the information contained in a single gene.</td>
</tr>
<tr>
<td>Monosomy</td>
<td>Where one chromosome is represented once only instead of twice; eg girls with Turner syndrome have only one X chromosome instead of the usual two copies (monosomy X). Monosomy of any of the autosomal chromosomes is usually a lethal condition.</td>
</tr>
<tr>
<td>Monozygotic twins</td>
<td>Twins that arise from a single egg fertilised by a single sperm. These twins are therefore genetically identical. They are also referred to as identical twins.</td>
</tr>
<tr>
<td>Mosaic</td>
<td>An individual who has some cells with an abnormal or unusual genetic or chromosomal makeup while the rest of the cells in the body have the usual genetic or chromosomal constitution. For example, a person who is mosaic for trisomy 21 would have some cells which have 47 chromosomes with an extra chromosome number 21 and other body cells which have the usual 46 chromosome complement. The number of cells with abnormal genetic or chromosomal content will determine the level of severity of the condition.</td>
</tr>
<tr>
<td>mRNA</td>
<td>An abbreviation for messenger RNA which is the molecule that transfers the genetic DNA message to the ribosomes where it is translated into proteins.</td>
</tr>
<tr>
<td>Multifactorial inheritance</td>
<td>A pattern of inheritance which results from the interaction of one or more genes with environmental factor(s).</td>
</tr>
<tr>
<td>Multiplex PCR</td>
<td>The use of several pairs of primers in one polymerase chain reaction, each of which initiates the amplification of a particular section of DNA.</td>
</tr>
<tr>
<td>Mutagen</td>
<td>A physical or chemical agent which causes a permanent change (mutation) in a gene. It may or may not be a carcinogen.</td>
</tr>
<tr>
<td>Mutation</td>
<td>A permanent change in a gene. If the mutation occurs in the germ line cells, it is then able to be inherited. Mutations in somatic cells cannot be inherited. Mutations can occur naturally and spontaneously or they may be due to exposure to mutagens.</td>
</tr>
</tbody>
</table>
**Neural tube defect (NTD):**
An abnormality which results when the neural tube in the fetus fails to close. Spina bifida and anencephaly are forms of NTD.

**Newborn screening:**
The screening of newborn babies for pre-symptomatic detection and early treatment of genetic conditions. Newborns are screened most commonly for congenital hypothyroidism, cystic fibrosis, phenylketonuria, galactosaemia and other rare metabolic conditions.

**Newborn screening card:**
A piece of absorbent paper used in the examination of a drop of a newborn baby's blood to exclude the presence of several congenital conditions, which may include phenylketonuria, cystic fibrosis and congenital hypothyroidism. Also called Guthrie card.

**Nondisjunction:**
Where the chromosome pairs fail to separate correctly in meiosis, resulting in sperm or egg cells which have missing or extra chromosomes, e.g. if chromosome number 21 fails to separate in the formation of an egg (or sperm), one egg (or sperm) will contain an extra copy of chromosome 21 (24 chromosomes) while the other egg (or sperm) will contain only 22 chromosomes.

**Nonsense mutation:**
A single-base substitution mutation resulting in the formation of a stop codon in a gene and therefore a shortened (truncated) protein.

**Nuchal translucency:**
The translucent area on the back of the fetal neck visualised by ultrasound scan. It is caused by the accumulation of fluid between the skin and soft tissue.

**Nucleotides:**
The basic components of DNA. The nucleotides are denoted by the letters A (adenine), G (guanine), C (cytosine) and T (thymine). The sequence of these nucleotides forms the genetic code.

**Nucleus:**
The structure in a cell which contains the genetic material.

**Obligate mutation carrier:**
A family member who is clinically unaffected with a genetic condition, but, on the basis of analysis of the family health tree, must carry a particular mutation.

**Oestriol:**
A female sex hormone produced by the ovaries, present in maternal serum during pregnancy. Levels tend to be raised when the fetus has aneuploidy, in particular trisomy 21.

**Oncogene:**
A gene which, when triggered, can lead to cancer (see proto-oncogene).

**Organelle:**
Structures within cells such as the nucleus, mitochondria and lysosomes which have special functions.

**'P' arm:**
Each chromosome is divided into two parts, joined by the centromere. The 'p' arm is the shorter of the two segments and is at the top of the chromosome. The longer segment is called the 'q' arm.

**PCR:**
See polymerase chain reaction

**Pedigree:**
A diagrammatic representation of a family health history.

**Penetrance:**
The probability of detecting the presence or clinical expression of a gene or combination of genes when they are present. If the penetrance of a particular allele with a mutation is less than 100%, not all individuals who carry that allele or alleles responsible for the condition will develop symptoms. Such a condition, or mutation, is said to have reduced or incomplete penetrance.

**Phenotype:**
The physical and/or biochemical characteristics of a person, an animal or other organism which are determined by their genetic makeup and/or environment.
### Glossary

<table>
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<th>Term</th>
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<tbody>
<tr>
<td><strong>Point mutation:</strong></td>
<td>A change in a single nucleotide in a DNA sequence of a gene.</td>
</tr>
<tr>
<td><strong>Polygenic:</strong></td>
<td>A condition or characteristic that is caused by many different genes acting together.</td>
</tr>
<tr>
<td><strong>Polymerase chain reaction (PCR):</strong></td>
<td>The repeated serial reaction involving the use of oligonucleotide primers and thermostable DNA polymerase that is used to amplify a particular DNA sequence of interest to enable genetic analysis.</td>
</tr>
<tr>
<td><strong>Polymerase:</strong></td>
<td>An enzyme that catalyses the creation of DNA or RNA from single nucleotides using an existing template.</td>
</tr>
<tr>
<td><strong>Polymorphisms:</strong></td>
<td>Strictly, the existence of two or more variants of a gene at significant frequencies in a population. Loose usages among molecular geneticists include: (1) an sequence variant present at a frequency &gt;1% in a population; (2) any non-pathogenic sequence variant, regardless of frequency.</td>
</tr>
<tr>
<td><strong>Positional cloning:</strong></td>
<td>The localisation of a gene to a particular region of a chromosome that then leads to its isolation.</td>
</tr>
<tr>
<td><strong>Post-zygotically:</strong></td>
<td>Occurring after fertilisation and the formation of a zygote.</td>
</tr>
<tr>
<td><strong>Predictive testing:</strong></td>
<td>A form of genetic testing which looks for the presence of a mutation in a gene prior to an individual developing any symptoms of the condition to determine if an individual is at increased risk for developing the condition in the future, e.g., testing for inherited susceptibility to breast and ovarian cancer. The detection of a specific mutation does not necessarily mean the individual will definitely develop the condition.</td>
</tr>
<tr>
<td><strong>Predisposition:</strong></td>
<td>A situation in which a person, due to their inherited genetic makeup, may have a particular susceptibility to a condition if exposed to the correct environmental triggers.</td>
</tr>
<tr>
<td><strong>Pre-implantation genetic diagnosis (PGD):</strong></td>
<td>The genetic testing of embryos prior to implantation in the uterus.</td>
</tr>
<tr>
<td><strong>Prenatal diagnosis:</strong></td>
<td>The detection of fetal abnormalities during pregnancy.</td>
</tr>
<tr>
<td><strong>Pre-symptomatic testing:</strong></td>
<td>A form of genetic testing which looks for the presence of a mutation in a gene prior to an individual developing any symptoms of the condition, e.g., testing for Huntington disease.</td>
</tr>
<tr>
<td><strong>Prevalence:</strong></td>
<td>Proportion of the whole population affected.</td>
</tr>
<tr>
<td><strong>Primers:</strong></td>
<td>The oligonucleotide sequences flanking the region of DNA to be amplified using the PCR technique.</td>
</tr>
<tr>
<td><strong>Proband:</strong></td>
<td>The first affected individual studied in a family.</td>
</tr>
<tr>
<td><strong>Probe:</strong></td>
<td>A small segment of DNA of known origin, manufactured in the laboratory, which is designed to recognise the DNA on specific parts of chromosomes. A coloured chemical can be attached to the probe and used to confirm the presence or absence of a particular gene or mutation.</td>
</tr>
<tr>
<td><strong>Promoter:</strong></td>
<td>The region of DNA prior to the start of a gene that RNA polymerase recognises to enable the initiation of transcription.</td>
</tr>
<tr>
<td><strong>Protease:</strong></td>
<td>A digestive enzyme that causes the breakdown of proteins.</td>
</tr>
<tr>
<td><strong>Proto-oncogene:</strong></td>
<td>Genes that are part of a person's usual genetic makeup. They have a role in various aspects of cell division. If these genes are changed in some way, they may give rise to oncogenes that can lead to cancer.</td>
</tr>
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### Q

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<td><code>'Q' arm:</code></td>
<td>Each chromosome has two segments joined by the centromere. The 'q' arm is the longer of these two segments. The shorter segment is called the 'p' arm.</td>
</tr>
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### R

**Reading frame:**
One of the potential ways of reading a nucleotide sequence as a series of triplets.

**Recessive:**
A trait or characteristic that is only present in homozygotes.

**Recombination:**
The exchange between homologous chromosomes of sections of chromosomes during meiosis.

**Recurrence risk:**
The risk that an inherited condition will occur again in a family.

**Regulatory gene:**
A gene containing information for the regulation (switching on or off) of other genes.

**Replication:**
The identical duplication of DNA or of a cell.

**Restriction enzyme:**
Enzymes that can cut DNA into strands at specific places along its length.

**RFLPs (restriction fragment length polymorphisms):**
The fragments of DNA which result when it is cut by special enzymes called restriction enzymes. The patterns of these fragment lengths are used to indicate the presence or absence of mutations in particular genes.

**Ribonucleic acid:**
See RNA.

**Ribosomes:**
Cytoplasmic organelles composed of ribosomal RNA and protein, on which polypeptide synthesis from mRNA occurs.

**Ring chromosome:**
This occurs as a result of the fusion of the two ends of the same chromosome; there is a consequent loss of genetic material.

**RNA:**
An abbreviation for ribonucleic acid, a chemical similar to DNA which has an important role in protein manufacture. There are several types of RNA (see mRNA).

**Robertsonian translocation:**
A type of translocation exclusive to the acrocentric chromosomes (13, 14, 15, 21 and 22) in which two of these chromosomes join at or near their centromeres. This is effectively a fusion between two whole chromosomes.

### S

**Satellites:**
The region at the end of the short arm of acrocentric chromosomes separated from the rest of the chromosome by a thin stalk-like region. It contains DNA sequences that contain no functional genetic material.

**Sex chromosome:**
An X or a Y chromosome which are different from the 22 autosomes.

**Sex linked:**
A condition or characteristic which is determined by genes carried on the X chromosome.

**Short tandem repeats (STRs):**
Short sequences of DNA that are repeated many times in tandem. When the number of repeats is polymorphic within a population, this can be used as a marker. Used in identification genetic testing.

**Sibship:**
A group of individuals with at least one parent in common.

**Silent mutation:**
A single-base substitution where the altered nucleotide produces a codon that codes for the same amino acid, and therefore not changing the polypeptide sequence at all.

**Single base substitution:**
The substitution of one nucleotide for another. Can result in one of four types of mutation: missense mutation, nonsense mutation, splice-site mutation or silent mutation.

**Skewed X inactivation:**
The inactivation of one of X chromosome in disproportionately more cells than the other.

**Somatic cells:**
All the cells of the body except the reproductive cells (sex cells).
| **Somatic gene therapy:** |
| Correcting or transplanting genes that reside in somatic cells, not the germ cells or gametes. |

| **Somatic mutation:** |
| A change or mistake in a gene which is found in the cells of the body but not in the germ cells or gametes. Somatic mutations cannot therefore be passed on to future generations. |

| **Splice site mutation:** |
| A change in DNA sequence resulting in abnormal splicing of the mRNA transcript. Splicing is the removal of introns from mRNA. |

| **Splicing:** |
| The removal of introns from the mRNA transcript and the joining of exons. |

| **Sporadic:** |
| A mutation that results in a genetic condition and which appears for the first time in a family. The mutation takes place in either the egg or the sperm or at conception. |

| **Stem cells:** |
| A type of cell capable of both self-renewal and of proliferation and differentiation. They can be sourced from adult and embryonic tissue. |

| **Stop codon:** |
| A triplet of nucleotides that indicates where translation ceases. |

| **STR:** |
| See short tandem repeats |

| **Submetacentric:** |
| Describes a chromosome on which the centromere is somewhat distant from the middle of the chromosome so the two arms are of different lengths. |

| **Sweat electrolyte test:** |
| This is the most common diagnostic test for cystic fibrosis. Sweat production is stimulated by application of an electric current to a small area of skin, the sweat is collected and the salt (sodium chloride) content is determined. The test is inexpensive, sensitive and specific. |

| **Telomere:** |
| The terminal or end segment of each chromosome arm. |

| **Teratogen:** |
| An agent that produces or increases the incidence of birth defects or congenital abnormalities by interfering with development of the fetus during pregnancy. |

| **Tetramer:** |
| A molecule made up of four subunits. |

| **Tetraploidy:** |
| Four copies of every chromosome in a cell which results in 92 chromosomes in the cell, instead of the usual 46. |

| **Tetrasomy:** |
| Four copies of a particular chromosome present in a cell, resulting in 48 chromosomes in the cell instead of the usual 46. |

| **Transcription factor:** |
| A protein that binds to DNA and is involved in the regulation of transcription. |

| **Transcription:** |
| The process of making an RNA copy of a gene from the DNA template. |

| **Transgenic mouse:** |
| A mouse which has been genetically altered by injecting human or other foreign DNA from another animal into fertilised mouse eggs. This DNA becomes incorporated into the mouse DNA and the mouse will translate the information contained in the foreign gene. This has become a useful model for the study of various human conditions. |

| **Translation:** |
| The process whereby the genetic instructions in mRNA are read to form the corresponding polypeptide. |

<p>| <strong>Translocation:</strong> |
| This occurs when a piece of one chromosome breaks off and attaches to another, different chromosome. When no material is lost or gained the translocation is said to be ‘balanced’ and the individual is not affected. An ‘unbalanced’ translocation results in the loss or gain of genetic material which may result in a genetic condition. |</p>
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<td><strong>Trinucleotide repeat:</strong></td>
<td>See triplet repeat.</td>
</tr>
<tr>
<td><strong>Triple repeat (trinucleotide repeat):</strong></td>
<td>A form of genetic mutation which consists of a series of repeated identical sequences of DNA triplets which may be found either inside or outside a gene. An increase in the number of such repeats in a particular gene can lead to instability of the gene and manifestation of the corresponding condition. This form of genetic mutation has been associated with a number of genetic conditions to date, eg Huntington disease, fragile X syndrome, myotonic dystrophy etc.</td>
</tr>
<tr>
<td><strong>Triplet:</strong></td>
<td>A sequence of three nucleotides in the DNA sequence. Each triplet represents the code for a particular amino acid.</td>
</tr>
<tr>
<td><strong>Triploidy:</strong></td>
<td>Having three copies of every chromosome resulting in 69 chromosomes in a cell instead of the usual 46.</td>
</tr>
<tr>
<td><strong>Trisomy:</strong></td>
<td>Three copies of a particular chromosome are present in a cell resulting in 47 chromosomes instead of the usual 46.</td>
</tr>
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<td><strong>Tumour suppressor gene:</strong></td>
<td>A gene which contains the information for proteins whose role in cells is to suppress the formation of tumours by restraining cell growth. Loss of this control leads to development of malignancy. P53 and BRCA1 genes are examples of tumour suppressor genes.</td>
</tr>
<tr>
<td><strong>Unbalanced translocation:</strong></td>
<td>The exchange of genetic material between non-homologous chromosomes where the rearrangement results in a net loss or gain of genetic material.</td>
</tr>
<tr>
<td><strong>Uniparental disomy:</strong></td>
<td>Where both members of a chromosome pair are contributed by one parent rather than one from each parent. Uniparental disomy may be maternal or paternal.</td>
</tr>
<tr>
<td><strong>Variable expression:</strong></td>
<td>A range in the severity of a phenotype, presumably due to interactions with other genes and the environment.</td>
</tr>
<tr>
<td><strong>X chromosome inactivation:</strong></td>
<td>The random transcriptional inactivation of one X chromosome in every somatic cell in a female, occurring early in embryonic development.</td>
</tr>
<tr>
<td><strong>X linked dominant mutation:</strong></td>
<td>A dominant mutation in a gene carried on the X chromosome.</td>
</tr>
<tr>
<td><strong>X linked gene:</strong></td>
<td>Any gene which is located on the X chromosome.</td>
</tr>
<tr>
<td><strong>X linked recessive mutation:</strong></td>
<td>A recessive mutation in a gene carried on the X chromosome.</td>
</tr>
<tr>
<td><strong>Zygote:</strong></td>
<td>The single cell with 46 chromosomes resulting from the fertilisation of an egg (23) by a sperm (23). Through cell division (mitosis), the zygote develops into a multicellular embryo and then into a fetus.</td>
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