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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):

![Newborn screening](image)


- 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 1st 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 (e.g. 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>
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<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>
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* 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.
http://www.cysticfibrosis.org.au

Cystic Fibrosis Medicine.
http://www.cysticfibrosismedicine.com/index.html


The Australian Lung Foundation.

Bibliography


Cystic Fibrosis Mutation Database.


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 Australia at http://www.cysticfibrosis.org.au
- Cystic Fibrosis Medicine at http://www.cysticfibrosismedicine.com
- The Lung Foundation at http://www.lungnet.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