Cystic Fibrosis and Genetic Testing, Patient Information Leaflet

What is cystic fibrosis and the *CFTR* gene?

Cystic fibrosis (CF) is a complex condition, which can affect many parts of the body. The most common associated complications are recurring lung infections and chronic lung disease, pancreatic insufficiency (e.g. diabetes mellitus), difficulty gaining weight, chronic gastrointestinal symptoms and male infertility.

Almost every cell in our body contains DNA. DNA provides the instructions for how our cells should work. A gene is a length of DNA which codes for the production of a particular protein. If this code is disrupted by a genetic variant ("spelling mistake") this can affect the function of the protein, and cause health problems.

CF is caused by having a genetic variant ("spelling mistake") in both copies of your *CFTR* gene. We inherit one copy of the *CFTR* gene from our mother, and one from our father.

There are lots of different genetic variants which can occur in the *CFTR* gene. Some of these are well recognised and described, and are so are called "common" or "recurrent" variants. It is also known that some variants tend to be more severe (i.e. they have a large impact on the *CFTR* gene), and some are considered milder (i.e. they have a smaller impact on the *CFTR* gene). Generally, more severe variants are associated with more severe disease, and vice versa.

It is estimated that ~ 1 in 20 of us are carriers of CF (i.e. having a variant in only one copy of the *CFTR* gene). Being a carrier of CF is not expected to have any implications for your health, but it may have reproductive implications.

What are "*CFTR*-related disorders"?

CFTR-related disorders are other health conditions that are caused by disruption of the *CFTR* gene. Generally, they are considered less severe than CF.

CFTR-related disorders include chronic sinusitis, chronic cough or wheeze, pancreatitis and male infertility, due to congenital absence of the vas deferens (CAVD).

CFTR-related disorders are typically caused by having a genetic variant in one copy of your *CFTR* gene, and a "milder" variant in the other copy and/or the poly 5T variant. *CFTR*-related disorders can be very variable. Two individuals with the same variants may be affected differently, or have no associated health problems at all.

What is the poly 5T variant?

The 'Poly5T variant' describes a very common sequence in the *CFTR* gene. In isolation, it is not typically associated with health problems. However, if the 'Poly5T variant' occurs with another *CFTR* variant, on opposite copies of the *CFTR* gene ("in trans"), this can sometimes cause health problems (See *CFTR*-related disorders).

What do my results mean for me?

The information below aims to support you in understanding your genetic test report. However, please be aware that more personalised or specific information may be available on your report.

If you have more than one genetic variant detected in your *CFTR* gene, the laboratory may request further testing of your family members (e.g. parents or siblings) to determine if those variants are on the same copy of the *CFTR* gene ("is cis"), or on opposite copies ("in trans"). This information can be helpful in working out the significance of genetic results for your own health, and reproductive implications.

***CFTR* result**	**Possible implications**
A pathogenic[1] variant in both copies of my *CFTR* gene (affected)	• Typically associated with having CF or a *CFTR*-related disorder. • Increased risk of having a child with CF, depending on partner's carrier status.
A pathogenic variant in only one copy of my *CFTR* gene (a carrier)	• Typically associated with being a carrier of CF. • Being a carrier of CF is not typically associated with any health problems. • Increased risk of having a child with CF, depending on partner's carrier status.
A pathogenic variant in one copy of my *CFTR* gene AND the poly 5T variant.	• If the *CFTR* variant and the poly 5T variant are on the same copy of the *CFTR* gene, this is typically associated with being a "carrier" of CF. • If the *CFTR* variant and the poly 5T variant are on opposite copies of the *CFTR* gene, this is typically associated with being a carrier of CF +/- having a *CFTR*-related disorder. • Increased risk of having a child with CF, depending on partner's carrier status.
The poly 5T variant in one, or both, copies of my *CFTR* gene.	• Having the poly 5T variant on both copies of the *CFTR* gene is associated with an increased risk of having a *CFTR*-related disorder. • Having the poly 5T variant on one copy your *CFTR* gene is not typically associated with health problems. • Both scenarios are associated with an increased risk of having a child with *CFTR*-related disorder, depending on partner's carrier status.

[1]A pathogenic variant is a variant that is believed to affect the function of the gene.

Does my partner need genetic testing?

If you are planning to have children, you may want to know whether or not your partner is also a carrier of CF. As above, it is estimated that 1 in 20 of us are carriers of a variant in one copy of the *CFTR* gene.

If your partner is also a carrier of a variant in their *CFTR* gene, your chance of having a child with CF or a *CFTR*-related disorders is high. Couples at risk of having an affected child may be eligible for reproductive therapies (e.g. preimplantation genetic testing (PGT) or genetic testing during pregnancy).

Your partner can request testing for the most common *CFTR* variants via their own GP, or another relevant health professiona. **On the genetic test request, the doctor should state your details so that the laboratory can link the two results.** This will help the laboratory to provide you with a more accurate report. Requests for genetic testing which do not link to a relevant individual may be rejected.

If your partner is also found to carry a *CFTR* variant, you may benefit from a referral to Clinical Genetics to discuss your results, and any reproductive options available to you.

Please be aware that carrier testing for cystic fibrosis usually only checks for the 50 most common *CFTR* variants in the local population. Consequently, while a normal test result is reassuring, it cannot totally rule out being a carrier. The laboratory take this into account when they provide adjusted risk figures on your genetic test report. In general, if your partner does **not** have one of the 50 most common *CFTR* variants, the chance of having a child with CF, will be less than a couple in the general population.

Do my family members need genetic testing?

It is likely that you inherited your variant(s) in *CFTR* from a parent. This means that your siblings, and aunts and uncles, may also have one or more variants in their *CFTR* gene. Your close relatives may wish to have genetic testing if they are planning to children, or if they have any symptoms consistent with CF, or a *CFTR*-related disorder. As above, this can be arranged via their own GP. **On the genetic test request, the doctor should state clearly your details, and their relationship to you, so that the laboratory can link the results**. Requests for genetic testing which do not link to a relevant individual may be rejected.

If you have children, it is possible that your variant(s) in *CFTR* has been passed on to your children. We do not recommend testing healthy children to check whether or not they are a carrier of a variant in their *CFTR* gene. Testing can be undertaken when the child is old enough to make their own decision about whether or not to have testing. However, if your child has symptoms which could be consistent with CF or a *CFTR*-related disorder, they may warrant a referral to Paediatrics to explore this further, and to consider genetic testing.

Sometimes the laboratory advise genetic testing of close relatives to help determine whether two *CFTR* genetic variants are on one copy of the *CFTR* gene ("in cis"), or if they are on opposite copies ("in trans"). This information can be helpful in working out the significance of genetic results for your own health, and reproductive implications.

Inheritance pattern of CF / risk of having a child with CF?

CF and *CFTR*-related disorders are inherited in an autosomal recessive manner. This means that couples where both parents are carrier for CF have a 1 in 4 (25%) chance of having a baby with the condition. See below for other potential reproductive scenarios.

Please be aware that more personalised or specific information may be available on your report.

Partner 1	**Partner 2**	**Typical reproductive outcomes**
Carrier of CF	Carrier of CF	• 1 in 4 (25%) chance of having a child with CF.

		• 2 in 3 (66%) of **un**affected children will be a carrier of CF.
Carrier of CF	Not known to be a carrier	• Very low. Risk is not zero as no genetic test can entirely rule out being a carrier of CF. • 1 in 2 (50%) chance that children will be a carrier of CF.
Affected by CF	Not known to be a carrier	• Very low. Risk is not zero as no genetic test can entirely rule out being a carrier of CF. • All **un**affected children will be carriers of CF.
Affected by CF	Carrier of CF	• 1 in 2 (50%) chance of having a child with CF. • All unaffected children will be carriers of CF.

Reproductive options for couples at risk of having a child with CF.

If your partner is also a carrier of a variant in their *CFTR* gene, your chance of having a child with CF or a *CFTR*-related disorders is high. Couples at risk of having an affected child may be eligible for reproductive therapies (e.g. preimplantation genetic testing (PGT) or genetic testing during pregnancy).

Do I need an appointment with Clinical Genetics?

We do not see patients in the Genetics Clinic for carrier testing. This can be requested via the GP, or another relevant health professional. See our website for more information on how this can be done.

Couples at risk of having a child with CF or a *CFTR*-related disorder can be referred to Clinical Genetics discuss reproductive options.

We do not follow-up or treat patients with CF or CFTR-related disorders in the Genetics Clinic. These patients are managed by relevant specialities (e.g. specialist CF clinics).

Screening for CF at birth and the sweat test.

All babies in the UK undergo screening for CF at birth, via the day 5 blood spot (Guthrie test). This measures immunoreactive trypsinogen (IRT). Samples with abnormally raised IRT levels will undergo genetic testing to check for the most common variants in *CFTR*.

Where genetic results, or clinical presentation, are unclear, a “sweat test” is sometimes undertaken. A sweat test measures the amount of salt in sweat, which will be abnormally high in someone with CF.

Further useful information.

NHS leaflet on cystic fibrosis (CF): https://www.nhs.uk/conditions/cystic-fibrosis/	Cystic Fibrosis Trust; Testing for cystic fibrosis carriers in families: https://www.cysticfibrosis.org.uk/sites/default/files/2022-02/Carrier%20testing%20factsheet.pdf
Leeds Genomic Laboratory; More detailed scientific information on *CFTR* testing and variants: https://www.leedsth.nhs.uk/a-z-of-services/the-leeds-genetics-laboratory/constitutional-genetics/molecular-genetics/by-disorder/cystic-fibrosis/	Genetic Alliance: https://geneticalliance.org.uk/information/living-with-a-genetic-condition/insurance-family-history-and-genetic-testing/
NI Regional Genetics Service website: https://belfasttrust.hscni.net/service/laboratory-services/clinical-genetics/	