



Service Description

Cystic Fibrosis (CF)

1 Background

Cystic fibrosis (CF) is an autosomal recessive disease, caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The incidence of cystic fibrosis is approximately 1 in 1,461 in Ireland and approximately 1 in 19 Irish people carry a CF mutation. If partners each carry a CF mutation, they have a 1 in 4 chance for each pregnancy of having a child with CF.

Mutations result in a wide phenotypic spectrum, from severe classical CF, characterised by pancreatic insufficiency and chronic endobronchial infection, through to milder forms. Other pathologies linked to mutations in the CFTR gene include Congenital Bilateral Absence of Vas Deferens (CBAVD), liver disease, recurrent pancreatitis and disseminated bronchiectasis. More than 1500 CF mutations have been identified to date.

2 Standard service

A Essential referral information

In addition to supplying standard patient identification and referral information (see Section I below), the following should be clearly indicated:

- Patient's symptoms – so we can determine whether it is a diagnostic or a carrier test referral
- Sweat test levels, if performed, and the test centre location
- Any family history, including names, date of birth, relationship, genetic test results or the test centre location
- If testing is required as a pre-requisite to assisted reproduction.
- Ethnic origin of patient, if not of Irish decent

Cystic Fibrosis PIR forms to help service users to give us the information we require are available: please see details in section I below.

It is the responsibility of the referring clinician to ensure consent has been obtained for testing and storage.

B Samples required

Generally 5-10ml of EDTA blood (FBC bottle) is required. Sample identification policy is detailed at (see Section I below).

Blood specimens must be appropriately packaged (see Section I), and preferably sent by courier to arrive as soon as possible. Do not freeze prior or during postage.

Please note that extracted DNA is stored from patient's samples at the National Centre for Medical Genetics, and kept indefinitely unless a written request for its disposal is received from the patient or their parent/guardian.

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C Restrictions on testing

Carrier testing is limited to adults over the age of 16 where there is a family history of CF, or where a family member has been found to be a carrier of a CF mutation (i.e NOT a population screen).

Predictive testing for newborns is available only when both CF mutations in the family have been identified by NCMG, or if a copy of the report on the index case (or parents of the index) from another test centre is provided.

Prenatal testing must be arranged in advance with the laboratory, through our clinical genetics department if possible.

Self-referrals are not accepted.

D Tests offered

Diagnostic Test

Diagnostic tests for patients with a clinical diagnosis of CF, or clinical symptoms strongly suggestive of CF.

For patients (especially newborns) where there is a strong family history of CF, and the likelihood of being an (unaffected) carrier is a strong possibility, we will ask to test the parents first to assess the likelihood of the couple having a child with CF. This avoids unintentionally revealing carrier status in a minor and increasing parental anxiety.

Carrier Test

Carrier detection for individuals over the age of 16 with a family history of CF and/or a partner with the same.

Carrier detection is also offered where it is a pre-requisite for a couple awaiting/undergoing assisted reproduction.

Prenatal Diagnosis

Prenatal diagnosis – in cases where the mutations in both parents have been characterised. Prenatal testing must be arranged in advance with the laboratory, through a Clinical Genetics department if possible.

Predictive Test

Predictive testing for newborn babies when both CF mutations have been identified in the parents and/or full siblings with CF. Predictive testing for half siblings is not carried out. Testing of the new partner is recommended instead to assess the likelihood of the new couple having a child with CF.

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Tests available include:

- Screen of the 11 'common' Irish mutations by Amplification Refractory Mutation System (ARMS) analysis, detects 92.5% of Irish mutations.
- Mutations analysed: p.Phe508del ($\Delta F508$), p.Ile507del ($\Delta I507$), p.Arg117His (R117H), p.Gly542X (G542X), p.Gly551Asp (G551D), p.Arg560Thr/Lys (R560T/K), c.489+1G>T (621+1G>T), p.Arg352Gln (R352Q), p.Asn1303Lys (N1303K), c.1585-1G>A (1717-1G>A), p.Arg553X (R553X).
- Intron 8 poly T tract variant – Screened in CBAVD cases, and when the R117H mutation has been identified in association with another CF mutation in query affected cases/diagnostic cases.

E Diagnostic Sensitivity of tests

Estimated sensitivity of the routine 11 CF mutation screen is 92.5% in the Irish population. Please note: coverage may be reduced or unknown for other populations. Please always provide information on the ethnic origin of your patient.

F Interpretation:

Results are given in the form of a written interpretative report to the referring clinician.

Query Affected/Genotype Report

- The presence of two mutations confirms a diagnosis of CF.
- Less than 1% of patients with classical CF in the Irish population would not have their mutations detected by the above 11 mutation screen. In these cases (and in cases where only one mutation has been identified), where CF is clinically indicated (eg positive sweat test; Cl^- & Na^+ > 60 mmol/L, or combined $NaCl$ > 90 mmol/L. However, published guidelines recommend that a sweat test that measures sodium and chloride separately should be performed), samples will be screened for the presence of rare mutations (see H Further Tests)

Carrier Status Reports

- The presence of one mutation confirms that the individual is a carrier of a CF mutation.
- The absence of all 11 Irish mutations in referrals for carrier status determination (in the absence of a family history of CF) reduces the risk of being a carrier from ~1/19 (Irish population risk) to approximately 1 in 241.
- Where there is a family history of CF, and the familial mutations are known and excluded for the sibs of a CF patient, the risk of being a carrier is negligible.
- Carrier results for a couple are reported as a joint report where they have both been tested at this Centre, and their risk of having a child with CF for each pregnancy is stated. Where a member of the couple has been tested at another test centre, this is referred to in the interpretation of the report and their risk of having a child with CF is stated, based on the information provided.

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Couples risk of having a child with CF

Father Mother	Affected	Carrier	11 Irish mutations absent
Affected	1	1/2	~ 1/500
Carrier	1/2	1/4	~ 1/1000
11 Irish mutations absent	~ 1/500	~ 1/1000	~ 1/250,000

CBAVD Reports

- All 11 Irish mutations absent: Presence of rare CF mutations is assumed in cases where CBAVD has been diagnosed by a consultant urologist.
- One mutation identified: As above
- 5T/5T (interpretation is difficult, as this allele is present in 5% of the normal population). The 5T variant has been shown to be associated with CBAVD. Some studies suggest that the 5T variant may be a CF mutation in its own right, causing disease with partial penetrance.

R117H/5T

- R117H is a mild mutation when inherited alongside a classical CF mutation, disease severity may be increased when 5T is also present.

G Target reporting times:

As reporting times are constantly evolving, please refer to www.genetics.ie/molecular, or contact the molecular genetics laboratory, to receive up-to-date information on anticipated reporting times for your referral.

The following are current target reporting times for each category of test offered (information correct as of 18/12/2009).

Urgent Diagnostic and Carrier Tests

Reports on babies < 6months of age, CVS samples and pregnant couples are reported within 2 weeks.

Prenatal diagnosis on amniocentesis samples (which require 2 weeks of culture) are reported within 4 weeks.

Routine Reports

Currently dispatched in 4-6 weeks from receipt of sample and relevant clinical details/family history information (as of 07/01/2008).

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- Request for copies of reports on the day that your patient is in clinic cannot normally be accommodated. We usually require 24 hours notice in which to fax a copy of a report.
- All requests for copies of reports, when not from the original referring clinician or referring centre, must be made in writing via email (to duty.scientist@olchc.ie), fax (01 409 6971) or by letter.
- Please contact the laboratory if you have not received a report within a week of your patient being due back in clinic.
- Please note that it our policy not to issue verbal results.

H Further tests

In cases where there is a diagnosis of CF, or strong clinical suspicion of CF or a positive sweat test, and where both CF mutations have not been identified by the 11-mutation screen; samples can be added to a panel for analysis by full sequencing of the CFTR gene & MLPA analysis for the detection of large deletions/rearrangements.

Further CFTR gene screening is now routinely sent to the Manchester Genetics Laboratory and are reported within 10 weeks. Previously further screening was carried out as a research collaboration with Professor Claude Ferec's Laboratory, in Brest, France and the results took many months.

I Web Links to Related Documents

Standard referral information/NCMG request form	http://www.genetics.ie/pir/2006_NCMG_Referral_Form.pdf
Sample/Patient identification policy	http://www.genetics.ie/pir/SampleIdentificationPolicyWeb.pdf
Packaging of specimens for transport	http://www.genetics.ie/pir/sending_samples.pdf
Cystic Fibrosis PIR form	http://www.genetics.ie/pir/CF_pir.pdf

Please note that hard copies of the above documents may be requested from:

Division of Molecular Genetics, National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin 12. Tel: 01 4096733; Fax: 01 4096971

The NCMG Molecular Genetics laboratory participates in external QA schemes run by the UK NEQAS for Molecular Genetics, the European Molecular Genetics Quality Network (EMQN), and the Cystic Fibrosis European Network. Results of assessments are available for inspection upon request.

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