



External Service Description

Familial Breast/Ovarian Cancer

1 Background

Pathogenic mutations in the tumour suppressor breast cancer genes *BRCA1** and *BRCA2*** account for approximately 3-5% of all female breast and ovarian cancers. Inheritance follows an autosomal dominant pattern. Females who inherit a pathogenic mutation, in either of these genes, have a 60-85% lifetime risk of developing breast cancer and a lifetime risk of ovarian cancer of between 15 and 40%. Males who carry a mutation in the *BRCA2* gene have a 6.3% risk of developing breast cancer by the age of 70. The risk conferred to males by mutations in the *BRCA1* gene is not well characterised. Female relatives of male carriers of a *BRCA1* or *BRCA2* mutation are at risk of inheriting the *BRCA1* or *BRCA2* mutation and of therefore having a high risk of breast/ovarian cancer. For first degree female relatives, this risk is 50%.

Clinical indicators for hereditary breast cancer/ovarian in a family include the presence of a family history of breast/ovarian cancer, especially in a first degree relative and may also include any of the following: Presence of early onset disease (<40y at diagnosis), bilateral breast cancer, breast and ovarian cancer in the same individual, ovarian cancer before 60yrs of age, male breast cancer.

At the NCMG, testing of hereditary breast/ovarian cancer genes *BRCA1* and *BRCA2* is available as follows:

- Individuals with breast/ovarian cancer and a family history of breast/ovarian cancer may be offered full mutation screening of the *BRCA1* & *BRCA2* genes as appropriate, following assessment by a Clinical Genetics service.
- Where a pathogenic mutation in *BRCA1* or *BRCA2* has been identified in a family, adult family members may be tested for the presence or absence of the mutation as appropriate, following a Clinical Genetics referral.

* OMIM ID-113705

**OMIN ID-600185

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:

1. Full mutation screening of *BRCA1* and *BRCA2*: Detailed family history (ideally, in the form of a pedigree), type of cancer (breast/ovarian/prostate), age of diagnosis.

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Document Number: DOC453

Date Printed: 19.01.2010

Authorised by: MGM

Revision Number: 6

Page 1 of 5



National Centre for Medical Genetics
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Division of Molecular Genetics

2. Testing for a known family mutation: Whether the patient is affected or unaffected (with any cancer); details of the family mutation, details of the index case (name and date of birth), relationship of the patient to the index case, and family history details (ideally, in the form of a pedigree diagram).

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

B Samples required:

1. Full mutation screening of BRCA1 and BRCA2: Screening involves bi-directional sequencing of both of these large genes, therefore 10ml of blood in EDTA anticoagulant is required
2. Testing for a known family mutation (predictive and diagnostic testing): Approximately 3-5ml of blood in EDTA anticoagulant

Important note: Samples and associated paperwork must be clearly labelled with at least 2 identifiers (full name AND date of birth/Hospital number) for the individual to be tested. Please refer to NCMG Sample identification policy (see Section I below) for further details.

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

Please note that DNA extracted from samples received are stored at the National Centre of Medical Genetics, and are kept indefinitely unless a written request for disposal is received from the patient.

C Restrictions on testing

Molecular genetics analysis of *BRCA1* and *BRCA2* genes is only performed in conjunction with a counselling programme run by the National Centre for Medical Genetics. Patients should be referred to Professor Andrew Green, Consultant Clinical Geneticist, National Centre for Medical Genetics.

Predictive testing is only offered to adults (over the age of 16yrs).

D Tests offered:

Following DNA extraction by our Centre, *BRCA1* and *BRCA2* testing is generally carried out externally by the West Midlands Regional Genetics Centre in Birmingham (See section H below for exceptions).

1. Full mutation screening of *BRCA1* and *BRCA2*: All coding exons of *BRCA1* & *BRCA2* are screened using Multi-Plex Ligation dependent Probe Amplification (MLPA) & Bi-directional sequencing. This type of testing is provided for affected individuals with

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Document Number: DOC453	Date Printed: 19.01.2010	Authorised by: MGM
Revision Number: 6	Page 2 of 5	



National Centre for Medical Genetics
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clinical indicators of familial breast/ovarian cancer after assessment by the Clinical Genetics team at the NCMG.

2. Testing for a known family mutation (Predictive and diagnostic testing): Testing is provided both to individuals in the family who do not have cancer (predictive test) and to those who do have cancer (diagnostic test). Testing is offered as appropriate, following assessment by the Clinical Genetics team at the NCMG.

E Sensitivity of tests:

Full mutation screening of BRCA1 and BRCA2: This is performed by bi-directional sequencing which has an estimated sensitivity of > 99%

Testing for a known mutation in BRCA1 or BRCA2: Estimated sensitivity is 100%

F Interpretation:

Following analysis by the West Midlands Regional Genetics Centre in Birmingham, results are provided in the form of a written interpretive report based on whether or not a mutation has been identified and on the type of mutation found. Interpretation of results is based on current best practice guidelines for molecular genetics testing.

Confirmation of the presence of a pathogenic mutation:

- Diagnostic test (Females & males): The result is consistent with a diagnosis of familial breast/ovarian cancer. Predictive/Genotype testing can now be offered to family members.
- Predictive test (Females): The patient has a high lifetime risk of breast/ovarian cancer. Predictive/Genotype testing can now be offered to family members.
- Predictive test (BRCA2, Males): Risk of breast cancer is approximately 6%. Risk of other cancers is unknown. Risk to female relatives. Predictive/Genotype testing can now be offered to family members.
- Predictive test (BRCA1, Males): Risk of cancer in male carriers of BRCA1 mutations is unknown. Risk to female relatives. Predictive/Genotype testing can now be offered to family members.

For all of the above, female relatives are at risk of inheriting the *BRCA1* or *BRCA2* mutation and of therefore having a high risk of breast/ovarian cancer. For first degree female relatives, this risk is 50%.

Confirmation of the absence of a pathogenic mutation:

- Full screening of BRCA1 and BRCA2 – No mutation identified: A mutation in BRCA1 or BRCA2 is unlikely to be the cause of breast/ovarian cancer.
- Testing for a known familial mutation - Predictive test, family mutation is absent: The individual's lifetime risk of breast/ovarian/other cancer has been reduced to that of the general population.
- Testing for a known familial mutation – Diagnostic test, family mutation is absent: This mutation is highly unlikely to be the cause of this patient's cancer

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Document Number: DOC453	Date Printed: 19.01.2010	Authorised by: MGM
Revision Number: 6	Page 3 of 5	



National Centre for Medical Genetics
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Confirmation of the presence of an Unclassified variant:

Full mutation screening of BRCA1 and BRCA2 may result in the identification of a sequence variant of unknown clinical significance, with no pathogenic mutation having been identified. The report may state that the clinical significance of the mutation is unknown or that at present there is no evidence of any clinical significance.

In these cases, the West Midlands Regional Genetics Centre in Birmingham will present the current information available regarding the pathogenicity status of the sequence variant. It may be appropriate for further studies to be performed. Further tests might include analysis of other members in the family who have cancer in order to ascertain whether the variant is following the disease; or in the case of a putative splice-site mutation, RNA analysis may determine whether the variant has a detrimental affect on RNA. All arrangements for further testing will be made following assessment by the NCMG Clinical Genetics Service.

In accordance with current best practice guidelines for molecular genetics testing, predictive testing of family members without cancer is not appropriate for variants of unknown clinical significance.

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 (information correct as of January 2010):

- Full mutation screening of BRCA1 and BRCA2: Approx. 3 months
- Testing for a known family mutation (Predictive testing): Approx. 4-6 weeks
- Testing for a known family mutation in a patient with cancer (diagnostic test):
Approx 6 weeks

H Further tests

Where the family mutation has been identified by an external laboratory other than the West Midlands Regional Genetics Laboratory, and there is no mutation positive control stored at the NCMG; testing of family members will be performed by the original external laboratory, as appropriate.

I Web Links to Related Documents

Standard referral information/NCMG request form
Sample/Patient identification policy
Packaging of specimens for transport

http://www.genetics.ie/pir/2006_NCMG_Referral_Form.pdf
<http://www.genetics.ie/pir/SampleIdentificationPolicyWeb.pdf>
http://www.genetics.ie/pir/sending_samples.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

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Document Number: DOC453	Date Printed: 19.01.2010	Authorised by: MGM
Revision Number: 6	Page 4 of 5	



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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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Document Number: DOC453	Date Printed: 19.01.2010	Authorised by: MGM
Revision Number: 6	Page 5 of 5	