

## Protocol 2 BRCA1 and BRCA2 mutation testing Frequently asked questions

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### **Q: Who is eligible for BRCA1 and BRCA2 mutation (termed BRCA) testing?**

BRCA testing (i.e. to look in blood for mutations in the BRCA1 and BRCA2 genes) can be conducted in breast cancer (BC) or ovarian cancer (OC) patients that meet one or more of the eligibility criteria as follows:

- 1) Epithelial ovarian cancer
- 2) Breast cancer ≤45 years
- 3) Bilateral breast cancer, both ≤60 yrs
- 4) Triple-negative breast cancer\*
- 5) Male breast cancer
- 6) Breast cancer and a parent, sibling or child meeting any of 1-5

### **Q: How were the eligibility criteria for BRCA testing decided?**

The eligibility criteria for BRCA testing are in line with NICE recommendations [www.nice.org.uk/guidance/cg164](http://www.nice.org.uk/guidance/cg164) which state that any patient with ≥10% chance of having a BRCA mutation should be tested. Extensive evaluation and data audit has shown that patients meeting the above eligibility criteria are at ≥10% risk of a BRCA mutation.

### **Q: Are the eligibility criteria the same in Oncology and Genetics?**

Yes. The same eligibility criteria are used for patients tested through Oncology and Genetics Units.

### **Q: What is epithelial ovarian cancer?**

Epithelial ovarian cancer is cancer which started in the surface layer covering the ovary. It is the most common type of ovarian cancer accounting for 85-95% cases.

### **Q: What is triple-negative breast cancer?**

Triple-negative breast cancer is a breast cancer negative for oestrogen receptor (ER), progesterone receptor (PR) and HER2 expression. For the purpose of genetic testing this means an Allred score of 0, 1 or 2 for ER and PR receptors and HER2 Score of 0 or 1+ by immunohistochemistry, or a score of 2+ by immunohistochemistry and DDISH negative

### **Q: Who can perform BRCA testing in patients?**

Geneticists and non-geneticists that have completed the online training can perform BRCA testing. Instructions for completing the training process are available at [www.mcqprogramme.com/brcatesting](http://www.mcqprogramme.com/brcatesting). Contact [mcq@icr.ac.uk](mailto:mcq@icr.ac.uk) if you have any queries.

### **Q: When should discussion of BRCA testing be undertaken?**

This should be at the discretion of the clinician. BRCA testing can be discussed and undertaken at the time of diagnosis, during active cancer management or during follow up. However, please be aware that the result takes ~3 weeks from receipt of sample, so if the result is required for management decisions, timing of testing must be planned accordingly.

**Q: What information should I give to the patient prior to obtaining consent?**

The information sheet 'BRCA1 and BRCA2 gene testing - Information sheet for patients with cancer' (MCG IS1) should be given to the patient. Patients should be informed that BRCA mutations are a cause of cancer and knowing whether or not a BRCA mutation is involved in causing their cancer can be helpful for their current and future management. The clinician may like to describe the specific relevance of the test for the specific patient. The patient should also be aware that the result can provide information of relevance to the wider family. However, it is important to remember that most tests are normal and therefore detailed discussions regarding risk management for patient and relatives, prior to testing, are not required. If a patient has questions that require either more time or more expertise than you are able to provide, the patient should be referred to Genetics. E-learning modules 1 (MCG ELM1) and 2 (MCG ELM2) provide further information about BRCA testing.

**Q: What should I do if a patient has additional queries before BRCA testing?**

Patients with additional queries can be referred to Genetics for an appointment and further discussion. Please contact the Genetics unit on [cancergenetics@rmh.nhs.uk](mailto:cancergenetics@rmh.nhs.uk)

**Q: Which consent form should I use?**

You should use the 'Consent for Genetic Testing' form (MCG F1) which is available on EPR. The form is also available online at [www.mcgprogramme.com/BRCAtesting](http://www.mcgprogramme.com/BRCAtesting). E-learning module 4 (MCG ELM4) explains how to take consent. Once completed, the form should be scanned onto EPR and a copy given to the patient. It should NOT be sent to the lab.

**Q: Which lab form should I use?**

There is a specific lab form 'BRCA test request form' (MCG F2). The form will be available in clinics and online at [www.mcgprogramme.com/BRCAtesting](http://www.mcgprogramme.com/BRCAtesting). Please send the form to the TGL clinical lab in BLB in ICR, together with the sample (1x9ml EDTA). Genetics can use the comprehensive Genetics test form if preferred

**Q: How long does it take to get a BRCA result?**

The results of full analysis of the BRCA1 and BRCA2 genes typically take about ~3 weeks, but may take up to 4 weeks. If there is a known mutation in the family the result takes ~2 weeks.

**Q: Should *in situ* breast cancer be included when assessing eligibility?**

Yes. *In situ* cancer, such as DCIS (ductal carcinoma in situ) and LCIS (lobular carcinoma in situ), should be included in the same way as invasive breast cancer in assessing eligibility for BRCA testing.

**Q: How should multiple metachronous ipsilateral breast cancers be assessed?**

Two (or more) separate, ipsilateral breast cancers which have occurred 5 or more years apart should be considered as separate cancers in the assessment of eligibility for BRCA testing (i.e. they should be counted as a bilateral breast cancer), unless it is clear the second cancer is a recurrence. This is a pragmatic approach as it is currently not possible to robustly identify which are separate primaries and which recurrence, but most are likely to be separate cancers.

**Q: How should multiple synchronous ipsilateral breast cancers be assessed?**

These should be counted as a single breast cancer for assessing eligibility for genetic testing. Simultaneous ipsilateral breast cancers are sometimes termed multifocal or multicentric.

**Q: How strict are the age cut-offs for testing?**

Age cut-offs are strictly applied. For example, a woman with bilateral breast cancer diagnosed at 58 years and 61 years would not be eligible for testing, but if she were diagnosed at 58 years and 60 years she would be eligible. It is recognised, and inevitable, that individuals close to a threshold may have similar likelihoods of carrying a mutation but different eligibility. We are working hard to make eligibility generally more permissive, but in the meantime it is important for clinicians and patients to have confidence that criteria are being consistently applied.

**Q: Can BRCA testing be undertaken in individuals who do not meet eligibility criteria?**

Yes. Patients who do not meet any of the NHS eligibility criteria can have a self-funded test. It should be made fully clear to these patients that the chance of detecting a mutation is <10%. Self-funding patients should be consented in the normal way. When submitting the Test Request Form, the “self-funded” option should be ticked and patients should be directed to [www.tglclinical.com/self-funded](http://www.tglclinical.com/self-funded) so that payment can be collected.

**Q. What is the cost of a self-funded test?**

The cost to a patient for a self-funded test is the same as the cost for the NHS. Patients should be directed to [www.tglclinical.com/self-funded](http://www.tglclinical.com/self-funded) for details of costs and payment.

**Q. Should I wait for patients to complete payment before doing a self-funded test?**

No. Patients can be consented for testing and the blood sample taken following the standard NHS process. Self-funding patients should complete the form at [www.tglclinical.com/self-funded](http://www.tglclinical.com/self-funded) so that payment can be arranged once the test is completed.

**Q: What is the testing eligibility for private patients?**

Any Royal Marsden private patient with breast or ovarian cancer can have BRCA testing. A specific process for this has been set-up and is available in Private Care, or from [rahmanRMPC@icr.ac.uk](mailto:rahmanRMPC@icr.ac.uk).

**Q: Are patients referred for clinical trials eligible for BRCA testing?**

Yes, as long as they meet the eligibility criteria.

**Q: Can Ashkenazi individuals have founder mutation testing if they are not eligible for full BRCA gene testing?**

No. We no longer do Ashkenazi Jewish (AJ) founder mutation testing instead of full BRCA gene testing. Such patients can have self-funded full BRCA testing.

**Q: What if a patient meets the criteria but chooses not to have a test?**

The test is optional. A patient may decline to be tested, ask to have longer to think about testing or be referred to Genetics if they want, or need, more detailed discussions.

**Q: What if a family member has already had BRCA testing?**

If a member of the family has already had a BRCA test, please contact the Genetics unit on [cancergenetics@rmh.nhs.uk](mailto:cancergenetics@rmh.nhs.uk) and note this on the lab form. It may influence the testing that is performed.

**Q: What if a relative has already been tested and does not carry a BRCA mutation?**

A BRCA test can still be performed on a second individual within the family if they meet the above eligibility criteria.

**Q: Can I undertake a BRCA test in an unaffected individual?**

Unaffected individuals with a family history of cancer are not eligible for NHS-funded BRCA testing. Recent data has shown that the mutation rate is well below the 10% NICE threshold for testing. Testing in an eligible affected relative is recommended. Or the individual can have a self-funded test.

**Q: How is the BRCA testing being done?**

We are using a next-generation sequencing panel called the TruSight Cancer panel, which has undergone extensive validation. All mutations are further confirmed by Sanger sequencing and/or MLPA as appropriate. Further details of the panel are available at [www.mcgprogramme.com](http://www.mcgprogramme.com) and [www.tglclinical.com](http://www.tglclinical.com).

**Q: Will we receive results of only the BRCA genes?**

Yes. At the current time we are reporting just the results of the BRCA1 and BRCA2 genes. We will be extending to additional genes that cause breast and/or ovarian cancer in the near future.

**Q: Who will give the patient the result of the BRCA test?**

The Genetics team will write to the patient with the result and will send an information sheet with additional information. The referring clinician and GP will also be notified. The result will be uploaded to the Germline Genetics tab on EPR together with an EPR annotation of the result.

**Q: What happens if no mutation is identified?**

The Genetics team will inform the patient of the result in writing and will send the patient a copy of the report and the information sheet 'Receiving a normal BRCA1 and BRCA2 test result' (MCG IS2). The Cancer team should use the information as appropriate for their cancer management. Usually no further input is required from Genetics. If the patient has an unusual cancer history, or extensive family history of cancer or has questions about the result please ask the Genetics team to send an appointment.

**Q: What happens if a mutation is identified?**

The Genetics team will inform the patient in writing and will send the patient a copy of the report and the information sheet 'Receiving a BRCA1 and BRCA2 test result that identifies a mutation' (MCG IS3) and an appointment for the Genetics clinic. The Cancer team should use the information as appropriate for their cancer management. The Genetics team will discuss with the patient the implications for their future cancer risk and will also evaluate which relatives may be impacted. The processes for cascading the information to relatives will be explained.

**Q: What if there is a variant requiring evaluation (VRE) identified?**

Very occasionally (<1%), we identify a variant that does not fulfil the criteria for pathogenic mutations, but requires further evaluation. In such cases, an information sheet (MCG IS4) and an appointment with Genetics is sent to the patient. The result and further analyses required are discussed with the patient. Once the additional evaluation has been completed (typically 2-6 months) the patient and clinician are informed of the final management class. Variants are only classified as VREs if there is suggestive evidence of pathogenicity that can potentially be confirmed by additional analyses (e.g. a splicing assay).

**Q: What if new evidence in the future shows a variant is pathogenic?**

We keep all variants identified under review and if any are reclassified Genetics will automatically re-issue reports and clear, revised recommendations. It is important to remember that rare variants in these genes are collectively common in the general population (present in about 10%), and the great majority are not pathogenic.

**Q: If a mutation is identified who will follow-up the patient's relatives?**

The Genetics team will give the patient a "To whom it may concern letter" to give to relatives. The letter will explain that a cancer predisposition gene mutation has been identified in the family and that relatives can ask their GP to refer them to the Royal Marsden Genetics team or their local genetics service to discuss the implications. This is standard practice in Genetics.

**Q: If the patient does not have a BRCA mutation, are there additional genetic tests that should be performed?**

Some patients may be eligible for further tests, particularly if they were diagnosed at a particularly young age, if they have multiple primary cancers or if there is an extensive family history of cancer. We recommend that such patients are referred to Genetics.

**Q: What are the insurance implications for cancer patients?**

If a cancer patient applies for life cover, critical illness or income protection cover after the gene test is performed then it will need to be disclosed, along with the other information about their cancer diagnosis. This is unlikely to have impact on the cover/terms they are offered over and above the impact of their cancer diagnosis. If the gene test was performed after an insurance policy was set-up the result does NOT need to be disclosed.

**Q: Are there insurance implications for the cancer patients relatives?**

Relatives would need to tell the insurance company about the cancer diagnosis and if a gene mutation has been found when asked about their family history (if they are aware of it). If the test is normal some insurance companies may take this into consideration to mitigate the unfavourable impact of the family history on the policy. Unaffected individuals do not have to disclose the results of predictive gene testing to insurance companies but may choose to do so, particularly if the test is negative.

**Q: What breast surveillance should be recommended in families with a negative BRCA test?**

The surveillance should be recommended according to Protocol 1.

- In breast-ovarian cancer families, a negative BRCA test may alter surveillance recommendation and the breast surveillance category should be calculated on the basis of breast cancers alone.
- In breast cancer only families a negative BRCA test does not alter surveillance recommendation.
- Individuals with breast cancer and residual breast tissue should be recommended the appropriate breast surveillance, if they are no longer in follow-up for their cancer.

**Q: Who should have discussions about risk-reducing bilateral mastectomy?**

Risk-reducing bilateral mastectomy should be discussed with BRCA1, BRCA2 and TP53 mutation carriers – see Protocol 3 and Protocol 5.

The lifetime risk of BRCA negative families will only very exceptionally reach those seen in BRCA mutation carriers.

BRCA negative families with the following structure should be discussed / evaluated to see if discussion of risk-reducing bilateral mastectomy is warranted for unaffected first-degree relatives of breast cancer cases:

- Five or more cases of breast cancer <60 years *or*
- Four cases of breast cancer <50yrs (all at least TDR)

For BRCA negative families with four or fewer breast cancer cases risk-reducing bilateral mastectomy should not be discussed unless raised by the individual. Women from such families may still wish to consider mastectomy due to personal reasons, but the risks in these families do not warrant recommendation based on genetic risk.

**Q: Who should have discussions about ovarian cancer risk?**

Ovarian cancer risk should be discussed:

- In women with BRCA1 or BRCA2 mutations – see Protocol 3.
- In BRCA negative families, if the consultee has two or more first or second-degree relatives with ovarian cancer. At least one should be a first-degree relative of the consultee. At least two of the ovarian cancer cases should be first-degree relatives of each other. Risk-reducing bilateral salpingo-oophorectomy can be considered after child-bearing is complete and can be offered from 50 years, or earlier if two or more ovarian cancers occurred before 50 years.
- Ovarian surveillance should not be recommended outside of a research study.

In BRCA negative families with breast cancer only, no discussion, surveillance or risk-reducing surgery for ovarian cancer is required. There is no evidence of a significant increase in ovarian cancer risk in such families.

**Q: How do I manage a family with a BRCA1 or BRCA2 mutation?**

Management should be in accordance with Protocol 3.

**Q: How do I manage a BRCA variant?**

Reports from TGLclinical should always provide clarity about the management recommendations of variants. External reports may not provide this. If you are unclear about the management of a variant email: [vus@icr.ac.uk](mailto:vus@icr.ac.uk). Ensure that the lab report and a summary of the clinical history are included in the email.

**Q: Who should I contact if I have any questions?**

Any additional questions or comments should be emailed to [cancergenetics@rmh.nhs.uk](mailto:cancergenetics@rmh.nhs.uk).