Protocol 2
BRCA1 and BRCA2 mutation testing guidelines
Frequently asked questions

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If you have any questions or comments please email cancergenetics@rmh.nhs.uk

Q: Who is eligible for BRCA1 and BRCA2 mutation (termed BRCA) testing?
Individuals at 10% risk of carrying a mutation are eligible for NHS testing as outlined in NICE guidance CG164 (http://www.nice.org.uk/guidance/cg164). We undertook extensive evaluation and audit to determine practical clinical criteria that allow identification of individuals that meet the threshold for full BRCA testing. These criteria are given in Protocol 2 (10% threshold). However, empirically the mutation detection rate has been >10% using these criteria. Moreover, the NICE cost evaluation noted that testing was cost effective at threshold of 5%. We are therefore currently evaluating more practical and permissive criteria as outlined in Protocol 2 v5.

Q: Are women with ovarian cancer eligible for BRCA testing?
All women with non-mucinous ovarian cancer diagnosed at any age, are eligible for testing. Women with mucinous ovarian cancer and another primary cancer are also eligible.

Q: Can I use clinical criteria alone to decide who is eligible for testing?
Clinical criteria alone are used apart from criteria A7 and C1 in which the Manchester Score needs to be calculated in order to decide if the individual is eligible for testing (see below).

Q: Should *in situ* breast cancer be included?
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: What if the age of breast cancers in some relatives is unknown?
An estimated decade of age of the cancer occurring should be used if possible. Otherwise assume the breast cancer occurred at age 60 years.

Q: What should I do if there is limited family history available?
Only the available history should be taken into account.

Q: What is the Manchester score?
The Manchester score is an empirical scoring system which estimates the chance of identifying a mutation in BRCA1 or BRCA2. A score is assigned depending on the age and type of cancer in an individual. As BRCA1 and BRCA2 are tested together in the diagnostic setting, we use a combined score for both genes together.

To calculate the Manchester score every individual in a direct lineage in a family affected with breast, ovarian, prostate or pancreatic cancer is given a score from the table on Protocol 2. These scores are summed to give the total Manchester score.

Q: Can I include individuals from both sides of the family to calculate the Manchester Score?
No. All the individuals used in the score should be on the same side of the family.

Q: Are intervening unaffected female relatives allowed in the Manchester Score?
One intervening unaffected female relative is allowed. A further intervening female relative is allowed if they have had risk-reducing mastectomy or oophorectomy prior to age of natural menopause (<50 years). Cancers through any additional female intervening individuals should not be included.

Q: How is the Manchester score calculated if there are intervening unaffected male relatives?
Affected female relatives through an intervening male are shifted up a single degree of relationship.

Q: How should half-siblings be considered?
Half-siblings related through their mother should be considered second-degree relatives. Half-siblings related through their father should be considered first-degree relatives.

Q: How does the Manchester scoring system deal with bilateral cancers?
Each cancer is scored separately, so an individual with bilateral breast cancer should be given a score for each cancer.

Q: Which individual in a family should be tested for mutations?
Efforts should be made to test the most informative individual for the family i.e. an individual affected with breast and ovarian cancer, male breast cancer, ovarian cancer, bilateral breast cancer or young-onset breast cancer should be preferentially tested.

Q: When should BRCA testing be undertaken in a male with prostate cancer?
A man with prostate cancer can be tested if the Manchester Score is ≥15 and no sample is available from a female affected with breast or ovarian cancer or male with breast cancer. A first degree relative must be affected with breast or ovarian cancer and cases of ovarian cancer must be confirmed.

Q: When is it appropriate to undertake a second BRCA test within a family?
A second test can be performed if:

- Another affected individual within the family meets testing criteria A1-5, or B1-2 *or*
- A SDR or TDR affected relative of the BRCA negative individual meets the eligibility criteria after “removing” the tested individual from the pedigree.

Q: When is it appropriate to undertake a BRCA test in an unaffected individual?
This is only appropriate to consider in families in which there are no living affected individuals available to test and all the following criteria are reached

- Manchester score of ≥17 for family
- Person to be tested must have at least one FDR affected with breast or ovarian cancer (this does not allow an intervening male relative)
- All cases of ovarian cancer and all breast cancers diagnosed under 40 years should be verified

Q: Can unaffected testing be undertaken in a family where affected relatives are unavailable but not deceased?
No. At present NHS unaffected testing is limited to those families in whom affected relatives are deceased. Affected relatives who live abroad should seek testing in their own country. Individuals can have testing if they wish to pay for it.

Q: Can Ashkenazi individuals have founder mutation testing if they are not eligible for full BRCA gene testing?
No. We are no longer doing Ashkenazi Jewish (AJ) founder mutation testing instead of full BRCA gene testing. This is because a) the full gene eligibility criteria are now more permissive; b) the AJ mutations identified through founder testing by TGLclinical were in patients eligible for full gene testing; c) the mutation detection rate, particularly in unaffected individuals, for founder mutation testing has been very low; d) it is no longer cost-effective to have a separate test for the three AJ mutations compared to full gene testing.

Q: Is research BRCA testing available to women that do not meet NHS criteria?
Some individuals may be eligible for testing through the Breast and Ovarian Cancer Study (BOCS). Please see www.icr.ac.uk/bocs for eligibility criteria.

Q: Can individuals that do not meet NHS criteria have BRCA testing?
Yes, this is available but must be paid for by the patient. It should be made fully clear that the chance of detecting a mutation is <10%.

Q: What breast surveillance should I recommend 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: Should MRI be recommended in BRCA negative families?
No. If an untested individual from a BRCA negative family meets the NICE recommended threshold for MRI, they will also meet the criteria for BRCA unaffected testing (see below). Thus a BRCA test should be performed in the individual and MRI only instituted if a mutation is identified.

Q: When should I discuss 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: When should I discuss ovarian risk?
Ovarian 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. Ensure that the lab report and a summary of the clinical history are included in the email.