# BRCA1 and BRCA2 – genetic testing

**ID: 620** v.12 **Under review**

eviQ cancer genetics consensus statement: scope of genetic testing protocols

**Related pages:**

- Guide for health professionals ordering genetic testing
- Cancer predisposition genes: population carrier frequency
- Breast cancer – panel testing
- Ovarian cancer (epithelial) – panel testing
- Pancreatic cancer – panel testing
- Prostate cancer – panel testing
- BRCA1 or BRCA2 – risk management (female)
- BRCA1 or BRCA2 – risk management (male)
- PALB2 – risk management
- Considerations for germline testing for variants identified in solid tumours

## Target population

**Germline BRCA1 and BRCA2 pathogenic variant search should be considered in the following situations:**

a. individuals with a combined BRCA1 and BRCA2 pathogenic variant probability of ≥10% using the Manchester score[1] (a validated pathogenic variant prediction tool).

b. individuals with a combined BRCA1, BRCA2 and PALB2 pathogenic variant probability of ≥10% using CanRisk[2] (a validated pathogenic variant prediction tool). This may include unaffected individuals and obligate carriers with ≥10% pathogenic variant probability as well as individuals from a population where a common founder pathogenic variant exists.

c. individuals affected with breast cancer:
   i. with triple negative pathology diagnosed ≤50 years
   ii. with triple negative breast cancer diagnosed at any age where there is a close relative* with breast or ovarian# cancer
   iii. diagnosed ≤40 years
   iv. male breast cancer diagnosed at any age.

d. individuals with high grade ovarian# cancer diagnosed at any age.

e. males affected with prostate cancer who meet prostate cancer panel testing criteria.

f. individuals affected with pancreatic cancer who meet pancreatic cancer panel testing criteria.

**Pathogenic variant specific BRCA1 or BRCA2 testing should be considered when there is:**

a. a pathogenic somatic variant detected on tumour testing for this individual.

b. an individual with a personal and/or family history of breast, ovarian#, prostate or pancreatic cancer from a population where a common founder pathogenic variant exists who does not fulfil any of the criteria listed above.

c. a familial BRCA1 or BRCA2 pathogenic variant has been identified.

**close relative = first or second degree relative*
*#includes invasive, non-mucinous ovarian, fallopian tube and primary peritoneal cancer*

Genetic testing is important for good clinical care of individuals who are suspected of having a heritable pathogenic variant in these genes. Where feasible genetic testing should first be offered to individuals in the family with the highest probability of a pathogenic variant. The above criteria may include some individuals with lower than 10% likelihood of a pathogenic variant calculated by a structured algorithm, and the cost of genetic testing in such circumstances may not be covered by Medicare or the genetic service provider.

## Investigations before genetic testing

The results of the following investigations may significantly influence the likelihood of detecting a heritable pathogenic variant in the BRCA1 or BRCA2 genes:

- Verification of pathology for the affected individual offered genetic testing.
- Verification of pathology for any suspected ovarian cancer (any reported gynaecological or abdominal cancer). BRCA1 and BRCA2 are strongly associated with high grade serous epithelial pathology.
- Consideration of limited family structure or no knowledge of the family cancer history.
- Calculation of likelihood of a BRCA1 or BRCA2 +/- PALB2 pathogenic variant using a validated risk model (e.g. Manchester score, CanRisk).
- Previous genetic testing within the family.
- Consideration of immunohistochemistry for MMR proteins MLH1, MSH2, MSH6 and PMS2 in ovarian tumours with endometrioid or clear cell histopathology and/or family history of colorectal, endometrial (Lynch syndrome-associated) cancers.

## Probability of a heritable pathogenic variant

The frequency of heritable pathogenic variants in the BRCA1 and BRCA2 genes in unselected individuals with breast cancer is around 2%[3] and with invasive ovarian cancer >14%[4] in many ethnic groups.

| Factors | Probability of detecting a heritable pathogenic variant |
|---|---|
| Outside of the pathogenic variant prediction scores, specific tumour features can inform the decision to offer testing: | |
| Age ≤40 with invasive breast cancer | 12%[5]<br>9.3% in non-TNBC[5]<br>24% in TNBC[5] |
| Triple negative breast cancer | 11.2% (any age)[6]<br>16.5% (diagnosed <50 years)[6] |
| High grade (grades 2 & 3) invasive non-mucinous ovarian, fallopian tube or primary peritoneal cancer | 15.3%[4]<br>9% (age ≤70 years with no family history)[4] |
| Ashkenazi Jewish ancestry | 2.5%[7]<br>10% (any age and affected with breast cancer)[7] |
| Patient has a first or second degree relative with documented pathogenic variant | Up to 50% |

*Abbreviation: TNBC = triple-negative breast cancer*

## Circumstances in which testing is not indicated

Genetic testing is not generally indicated outside these guidelines although needs to be considered on an individual basis.

Where the most appropriate person in the family has been tested and no pathogenic variant found, further BRCA testing is usually not required in the family.

A variant-specific test (rather than sequencing a single gene or gene panel) may be more cost effective and appropriate where:

- a known pathogenic variant has been identified in a relative
- a specific pathogenic variant has been identified on somatic tumour testing.

Predictive testing should never be ordered when only a variant of uncertain significance or benign/likely benign variant has been identified in a family.

## Testing methods

A range of testing methodologies are needed to identify pathogenic changes in the BRCA 1 or BRCA 2 genes including:

- sequencing
- copy number analysis (e.g. MLPA).

Information about DNA tests and testing laboratories is available from:

- RCPA catalogue of genetic tests and laboratories
- GeneReviews®
- European Directory of DNA Diagnostic Laboratories
- Genetic Testing Registry
- NHS National Genomic Test Directory

Where possible, BRCA1 and BRCA2 testing should be done as part of a panel test (refer to Breast cancer panel testing, Ovarian cancer (epithelial) panel testing, Pancreatic cancer panel testing or Prostate cancer panel testing). Clinical features and/or additional family history may guide choice of additional genes (CDH1, TP53, PTEN, MMR).

If a decision is made to test these genes as part of a cancer gene panel, care should be taken to select a panel where the individual genes tested have both clinical validity and clinical utility.

If these genes are tested using genomic sequencing ("next generation sequencing" or NGS), and testing has not identified a pathogenic variant , the value of testing using another methodology (e.g. MLPA, Sanger sequencing) should be considered in high risk families.

If genetic testing in DNA from peripheral blood is uninformative, testing of two or more different tumour samples may be indicated to assess for mosaicism.

## Result interpretation

| Result | Reference database | Considerations and advice |
|---|---|---|
| **Pathogenic variant search** | | |
| Pathogenic variant | BRCA Exchange<br>Leiden Open Variation Database (LOVD)<br>Insight<br>Human Gene Mutation Database (HGMD)<br>National Genetics Reference Laboratory-Manchester (DMuDB) | • BRCA1 or BRCA2 – risk management (female)<br>• BRCA1 or BRCA2 – risk management (male) |
| Variant of uncertain significance | | Review pathogenicity of variants periodically<br>Identify other genes for which a pathogenic variant search could be considered |
| No reportable variant | | Identify other genes for which a pathogenic variant search could be considered |
| **Predictive testing** | | |
| Family pathogenic variant identified | | • BRCA1 or BRCA2 – risk management (female)<br>• BRCA1 or BRCA2 – risk management (male) |
| Family pathogenic variant not found | | Screening based on revised estimate |

If a pathogenic variant is identified, refer to a clinical genetics service or familial cancer centre for review, family risk notification and predictive testing.

If a variant of uncertain significance is identified, consider referral to a clinical genetics service or familial cancer centre for review and guidance.

If a mosaic pathogenic variant is identified, refer to a clinical genetics service or familial cancer centre for review and guidance about the penetrance of phenotypic features (including cancer risk).

For additional information about the management of genetic test results when ordered by a non-genetic healthcare professional refer to eviQ's Guide for health professionals ordering genetic testing.

## Website resources

Centre for Genetics Education - NSW Health

CanRisk

National Comprehensive Cancer Network (NCCN) Guidelines

National Human Genome Research Institute

## References


1 Evans, D. G., F. Lalloo, A. Cramer, et al. 2009. "Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing." J Med Genet 46(12):811-817.

2 Carver, T., S. Hartley, A. Lee, et al. 2021. "CanRisk Tool-A Web Interface for the Prediction of Breast and Ovarian Cancer Risk and the Likelihood of Carrying Genetic Pathogenic Variants." Cancer Epidemiol Biomarkers Prev 30(3): 469-473.

3 Anglian Breast Cancer Study Group. 2000. "Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases." Br J Cancer 83(10):1301-1308.

4 Alsop, K., S. Fereday, C. Meldrum, et al. 2012. "BRCA mutation frequency and patterns of treatment response in BRCA

mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group." J Clin Oncol 30(21):2654-2663.

5 Copson, E.R., T.C. Maishman, W.J. Tapper, et al. 2018. "Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study." Lancet Oncol 19(2):169-180.

6 Couch, F. J., S. N. Hart, P. Sharma, et al. 2015. "Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer." J Clin Oncol 33(4):304-311.

7 Rubinstein, W. S. 2004. "Hereditary breast cancer in Jews." Fam Cancer 3(3-4):249-257.

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Bansal, A., G. C. Critchfield, T. S. Frank, et al. 2000. "The predictive value of BRCA1 and BRCA2 mutation testing." Genet Test 4(1):45-48.

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Evans, D. G., A. Howell, D. Ward, et al. 2011. "Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer." J Med Genet 48(8):520-522.

Evans, D. G., F. Lalloo, A. Wallace, et al. 2005. "Update on the Manchester Scoring System for BRCA1 and BRCA2 testing." J Med Genet 42(7):e39.

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Young, S. R., R. T. Pilarski, T. Donenberg, et al. 2009. "The prevalence of BRCA1 mutations among young women with triple-negative breast cancer." BMC Cancer 9:86.

Zhang, S., R. Royer, S. Li, et al. 2011. "Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer." Gynecol Oncol 121(2):353-357.

## History

### Version 12

| Date | Summary of changes |
|---|---|
| **23/11/2021** | Target population discussed at the September 2021 reference committee meeting. Discussion continued via MS Teams. Approved for publication with the following changes made:<br>• Target population<br>◦ Germline BRCA1 and BRCA2 pathogenic variant search...<br>▪ b. 'as well as individuals from a population where a common founder pathogenic variant exists.' added to end of sentence<br>▪ c. added 'iv. male breast cancer diagnosed at any age'<br>◦ Pathogenic variant specific BRCA1 or BRCA2 testing...<br>▪ b. 'who does not fulfil any of the criteria listed above.' added to end of sentence<br><br>Version number increased to V.12. |

### Version 11

| Date | Summary of changes |
|---|---|
| **11/08/2021** | The following sections of the document were updated to align with a change made to the eviQ cancer genetics consensus statement: scope of genetic testing protocols document:<br>• Target population:<br>◦ a. 'individuals with a combined BRCA1 and BRCA2 pathogenic variant probability of ≥10% using a validated pathogenic variant prediction tool (e.g. CanRisk or Manchester score). This may include unaffected individuals and obligate carriers with ≥10% pathogenic variant probability (note: using the CanRisk algorithm only)' split into two criteria with minor wording changes as follows:<br>▪ 'a. individuals with a combined BRCA1 and BRCA2 pathogenic variant probability of ≥10% using the Manchester score (a validated pathogenic variant prediction tool)'<br>▪ 'b. individuals with a combined BRCA1, BRCA2 and PALB2 pathogenic variant probability of ≥10% using CanRisk (a validated pathogenic variant prediction tool). This may include unaffected individuals and obligate carriers with ≥10% pathogenic variant probability.'<br>• Investigations before genetic testing:<br>◦ Fourth bullet: +/- PALB2 added<br>• References: new reference added for CanRisk<br><br>Version number increased to V.11. |
| **10/11/2021** | Removed link to "European Directory of DNA Diagnostic Laboratories" |

### Version 10

| Date | Summary of changes |
|---|---|
| **09/04/2021** | The following sections of the document were updated to align with the publishing of the Ovarian cancer (epithelial) panel testing and Pancreatic cancer panel testing protocols:<br>• Related pages: added links to "Ovarian cancer (epithelial) panel testing" and "Pancreatic cancer panel testing"<br>• Target population: added criterion e. "individuals affected with pancreatic cancer who meet pancreatic cancer panel testing criteria" under "Germline BRCA1 and BRCA2 pathogenic variant search should be considered in the following situations:"<br>• Testing methods: Ovarian cancer (epithelial) panel testing and Pancreatic cancer panel testing links added in the brackets of the following sentence: Where possible, BRCA1 and BRCA2 testing should be done as part of a panel test (refer to Breast cancer panel testing or Prostate cancer panel testing).<br><br>Version increased to V.10. |

### Version 9

| Date | Summary of changes |
|---|---|
| **09/12/2020** | The following sections of the document were updated to align with the new eviQ cancer genetics genetic testing template:<br>• Related pages: added links to "Guide for health professionals ordering genetic testing" and "Cancer predisposition genes: population carrier frequency". Removed link to "Pre-test counselling"<br>• Circumstances in which testing is not indicated: template wording updated<br>• Testing methods: template wording updated<br>• Result interpretation: template sentences added (including link to "Guide for health professionals ordering genetic testing")<br>• Counselling: section deleted<br>• Version number increased to V.9. |

### Version 8

| Date | Summary of changes |
|---|---|
| **02/07/2020** | Protocol reviewed at October 2019 eviQ cancer genetics reference committee meeting and discussions continued via email. Approved for publication with the following changes made:<br>• Target population: Criteria reviewed and refined. Separated into two subsections for clarity - "Germline BRCA1 and BRCA2 testing" and "Pathogenic variant specific BRCA1 and BRCA2 testing"<br>◦ Germline BRCA1 and BRCA2 pathogenic variant search should be considered in the following situations<br>▪ Part a: validated pathogenic variant prediction tool BOADICEA replaced by CanRisk. BRCAPRO removed as no longer used.<br>▪ Part b: "Individuals affected with breast cancer: diagnosed ≤40 years" added |

| Date | Summary of changes |
|---|---|
| | ▪ Part c: ovarian cancer criteria changed to "Individuals with high grade ovarian cancer diagnosed at any age" with footnote "includes invasive, non-mucinous ovarian, fallopian tube and primary peritoneal cancer" (in previous version, criteria was age ≤70 years)<br>▪ Part d: added "Males affected with prostate cancer who meet Prostate cancer panel testing criteria"<br>◦ Pathogenic variant specific BRCA1 or BRCA2 testing should be considered when there is:<br>▪ Part b: "a personal and/or family history of breast and/or ovarian cancer, from a population where a common founder mutation exists" changed to "a personal and/or family history of breast, ovarian, prostate or pancreatic cancer from a population where a common founder mutation exists."<br>◦ The following criterion was removed from the target population due to lack of evidence: "Where there is limited family structure or no knowledge of family cancer history...". Consideration of limited family structure or no knowledge of family history added to "Investigations before genetic testing"<br>◦ Added sentence: "The above criteria may include some individuals with lower than 10% likelihood of a pathogenic variant calculated by a structured algorithm, and the cost of genetic testing in such circumstances may not be covered by Medicare or the genetic service provider."<br>• Investigations before genetic testing: 6 bullet points added<br>• Probability of a heritable pathogenic variant: Table updated. Factors and probabilities added with references, to align with some of the inclusion criteria in the target population<br>• Testing methods: Paragraph added: "Where possible, BRCA1 and BRCA2 testing should be done as part of a panel test (refer to Breast cancer panel testing protocol or Prostate cancer panel testing protocol). Clinical features and/or additional family history may guide choice of additional genes (CDH1, TP53, PTEN, MMR)."<br>• Result interpretation: reference databases reviewed. BRCA Exchange and Insight added to list<br>• Protocol template changes applied<br>• "Mutation" changed to "pathogenic variant" and "unclassified variant" changed to "variant of uncertain significance" throughout document for consistency among eviQ cancer genetics protocols per agreement among the cancer genetics reference committees' chairs. Definition of "pathogenic variant" added as a pop-up<br><br>Version number increased to V.8. Review again in 2 years. |
| **25/08/2020** | Minor wording change in Target population section:<br><br>b. Individuals affected with breast cancer:<br>i. with triple negative pathology diagnosed ≤50 years OR where there is a close relative* with breast or ovarian# cancer<br>ii. with breast cancer diagnosed ≤40 years<br><br>changed to<br><br>b. Individuals affected with breast cancer:<br>i. with triple negative pathology diagnosed ≤50 years<br>ii. with triple negative breast cancer diagnosed at any age where there is a close relative* with breast or ovarian# cancer<br>iii. diagnosed ≤40 years |

### Version 7

| Date | Summary of changes |
|---|---|
| **13/08/2010** | Published |
| **28/02/2011** | Target population and investigations which should be considered before germline testing updated as per consensus of reference committee. |
| **07/03/2011** | Combined Manchester Score changed from 15 to 16 as per reference committee feedback. |
| **05/09/2011** | Reviewed at RC meeting - Target population updated. Circumstances in which testing is not indicated amended to include considering testing outside these guidelines on an individual basis and where the most appropriate person in the family has been tested and no mutation found, further testing is not required.<br><br>Ages in target population changed to less than or equal to to align with the references. |
| **15/02/2012** | Discussed at national reference committee meeting October 2011 and following changes made under:<br><br>**Target Population** "high grade serous or endometroid ovarian" **changed to** "high grade invasive non-mucinous ovarian" |

| Date | Summary of changes |
|---|---|
| | **Added** "where a known pathogenic mutation has been identified in a relative"<br><br>**Factors which influence the pre-test probability of a germline mutation**<br>**Factor:**<br>Tumour features may be included in decision to test:<br>• young (< 41 yrs) triple negative breast cancer (+/- basal markers)<br>• invasive ovarian < 60 yrs<br><br>**changed to**<br>Tumour features can inform the decison to test:<br>• young (< 41 yrs) triple negative breast cancer (+/- basal markers) without family history<br>• invasive ovarian cancer <60 yrs (all subtypes)<br><br>Minor additions to clarify **Diagnostic and Predictive testing sections**<br><br>**Reference list updated**<br>Berry D.A. et al 2002 and Risch, H.A. et al 2006 moved to history tab<br>James, P.A. et al 2006 and Zhang, S. et al 2011 added to reference list |
| **04/07/2013** | Discussed at national reference committee meeting March 2013 and the following changes made:<br><br>All protocol headings updated according to new template.<br><br>**Target Population -** reformatted and updated<br>• with high grade invasive non-mucinous ovarian, fallopian tube or primary peritoneal cancer ≤ age 60 yrs **changed to**<br>• with an isolated high grade (Grades 2 & 3) invasive non-mucinous ovarian, fallopian tube or primary peritoneal cancer ≤ age 70 yrs.<br>• with invasive non-mucinous ovarian, fallopian tube or primary peritoneal cancer at any age and a family history* of breast or ovarian cancer - **added**<br><br>**Investigations which should be considered before germline genetic testing** - updated.<br><br>**Factors which influence the pre-test probablity of a heritable mutation** - updated.<br><br>**Diagnostic testing** - table updated.<br><br>**Interpretation of mutation testing results** - table updated.<br><br>**Website resources** - updated.<br><br>**Reference list** - updated<br>Zhang, S., R. Royer, S. Li, et al. 2011 and Evans, D. G., A. Howell, D. Ward, et al. 2011 moved to history tab.<br>Alsop, K et al 2012 and Hartman, A.R. et al 2012 added to reference list. |
| **26/03/2014** | Following discussion at March 5 2014 reference committee meeting the following change has been made:<br>• **Diagnostic testing** - Link to Human Genetics Society of Australasia removed. |
| **01/05/2014** | Following discussion of the NICE clinical guideline 164 - Familial breast cancer in relation to eviQ protocols at the October 30 2013 & 5 March 2014 reference committee meetings and further email discussion, the following recommendation has been added to the **Target population**:<br>• where local resources allow, if there is no affected relative available for testing, consider testing an unaffected individual with a calculated BRCA1/2 mutation probability of 20% or more using a BRCA1/2 mutation probability risk calculator e.g. BOADICEA.**<br><br>**This is a new recommendation for review in 12 months<br><br>Recommendation and protocol to be reviewed in 12 months |
| **30/09/2015** | Sentence added to Genetic Testing protocol template: if a decision is made to test this gene(s) as part of a cancer gene panel, care should be taken to select a panel where the individual genes tested have both clinical validity and clinical utility. |
| **02/03/2016** | Reviewed at May 2015 reference committee meeting and discussions continued via email. The following changes |

| Date | Summary of changes |
|---|---|
| | made:<br>• target population - updated, including addition of 'limited family structure' and age for individuals with triple negative breast cancer changed from ≤40 years to ≤50 years<br>• diagnostic testing - updated according to new template<br>• for yearly review. |
| **10/03/2017** | Based on changes to MBS criteria for BRCA1/2 testing (and it now having an MBS item number), protocol amended to reflect change:<br>• target population - 'based on ovarian cancer characteristics' updated<br><br>Protocol to undergo full review in May 2017 as planned. |
| **31/05/2017** | Transferred to new eviQ website. Version number changed to V.5. |
| **01/06/2018** | Removed four links to the Clinical molecular genetics society best practice guidelines (CMGS) in **Result Interpretation** section, as webpage no longer available. |
| **14/06/2018** | Protocol reviewed and presented at the November 2017 eviQ reference committee meeting. Discussion continued over email and document approved for publication with the following changes:<br>• **Target population:**<br>◦ 2. a. i – 'breast or ovarian' changed to 'breast and/or ovarian'<br>◦ 2. a. iii - 'where local resources allow, and' removed from beginning of sentence.<br>◦ 2. c. ii – 'relapsed' added after 'invasive'<br>◦ 2. c. iii - (i.e. relapsed ovarian cancer) added to end of bullet point.<br>◦ 3. 'limited family structure' changed to 'limited family structure or no knowledge of the family cancer history'<br>◦ Added '3. c. triple negative breast cancer under the age of 60'<br>• **Testing methods:**<br>◦ Gene Tests link renamed as GeneReviews<br>• **Website resources:**<br>◦ Further references section removed - references listed in History tab moved to front of protocol in the Bibliography section.<br>• Reference list updated to include Bibliography. |
| **28/08/2019** | Protocol title changed from 'Genetic testing for heritable mutations in the BRCA1 and BRCA2 genes' to 'BRCA1 and BRCA2 genetic testing' in accordance with Cancer Genetics Reference Committees' consensus. Version number increased to V.7 |



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