

## Genetic testing for women diagnosed with ovarian cancer

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### Purpose

Cancer Australia Position Statements address significant clinical issues, emerging issues in cancer control and issues of ongoing interest, using the best available evidence.

The purpose of this Position Statement is to provide information and recommendations on genetic testing for women diagnosed with invasive epithelial ovarian cancer, based on available evidence and on consensus. The scope of this Position Statement encompasses genetic testing for heritable, or germline, gene mutations, with a focus on genetic testing of BRCA1 and BRCA2. The intended audiences are health professionals, medical colleges, consumers, media and policy makers.

This Position Statement has been endorsed by the Australian Society of Gynaecologic Oncologists, the Human Genetics Society of Australasia, the Medical Oncology Group of Australia, Ovarian Cancer Australia, and the Royal College of Pathologists of Australasia.





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## Recommendations

Cancer Australia recommends that women newly diagnosed with invasive epithelial ovarian, fallopian tube or primary peritoneal cancer<sup>a</sup>, regardless of their age or family history should be offered assessment of their genetic risk. It is recommended that women with a previous diagnosis of invasive epithelial ovarian cancer be offered assessment of genetic risk at their next follow-up visit.

Based on this assessment of risk, genetic testing for a heritable mutation<sup>b</sup> should be considered.

### BRCA1 and BRCA2 heritable mutations

A woman with invasive epithelial ovarian cancer should be offered genetic testing for a heritable mutation in BRCA1 or BRCA2, if she meets any of the following criteria:

- has high grade (Grade 2 or 3) invasive non-mucinous ovarian cancer, diagnosed at 70 years or younger.
- has invasive non-mucinous ovarian cancer at any age, with a personal history of breast cancer, or a family history of breast or ovarian cancer.
- is from a population where a common founder mutation exists, such as the Ashkenazi Jewish population.
- is assessed as >10% chance of having a BRCA1/2 mutation, using a prediction tool (such as BOADICEA, BRCAPRO or Manchester score).
- has relapsed platinum- sensitive ovarian cancer, is a candidate for treatment with PARP inhibitors and meets [MBS](#) criteria.

### Lynch syndrome

- For a woman with invasive epithelial ovarian cancer who has a personal or family history of endometrial, colorectal or other cancer suggestive of Lynch syndrome, tumour tissue should be tested for Lynch syndrome abnormalities.
- If an abnormality associated with Lynch syndrome is identified in the tumour, genetic testing for a heritable mutation in a DNA mismatch repair gene should be offered.

### Genetic counselling for women with ovarian cancer

- Before genetic testing for a heritable mutation, information should be provided on the possible outcomes and implications of genetic testing, including opportunities for personalised treatment decisions.
- After genetic testing for a heritable mutation, referral to a specialised genetic service should be offered:
  - if a heritable mutation or a variant of uncertain significance is identified, for post-test genetic counselling.
  - if a woman has a significant family history regardless of genetic test results, for further familial cancer risk assessment.

### Implications for family members



- If a heritable mutation is identified in a woman with ovarian cancer, relevant family members can be offered referral for genetic counselling and genetic testing for the known mutation.
- If a family member is found to carry the mutation, they should be offered cancer-specific risk management options.

## Key Practice Points

It is best practice that genetic testing is ordered by a clinician experienced in interpreting the results, and written informed consent be obtained before testing is undertaken for a heritable mutation. Mainstreaming<sup>c</sup> genetic testing for BRCA1/2 heritable mutations can be considered in the setting of specialist gynaecological cancer services with access to appropriately trained health professionals. Pre-test information may be provided by a range of health professionals.

Genetic testing for BRCA1/2 heritable mutations and Lynch syndrome should be undertaken in a National Association of Testing Authorities (NATA) and Royal College of Pathologists of Australasia (RCPA) accredited laboratory.

## Footnotes

- a. The term 'epithelial ovarian cancer' is used in this Position Statement to include epithelial ovarian, fallopian tube and primary peritoneal cancer.
- b. The term 'heritable mutation' refers to a germline mutation, namely a mutation that is inherited or passed on to children through the germline (eggs or sperm).
- c. Mainstreaming is integration of genetic testing into routine cancer services. In mainstreaming, genetic testing is frequently undertaken by a member of the cancer team other than a genetic specialist.





## Methodology and Scope

This Position Statement was developed by Cancer Australia, based on a high level review of recent evidence, and national and international guidelines to March 2017 to provide the evidence base.

The research questions were informed by the Medical Services Advisory Committee (MSAC) Clinical Utility Card for heritable mutations which increase risk in breast and/or ovarian cancer.<sup>1</sup> Searches were undertaken in PubMed, including an updated literature search using the eviQ protocol search strategy for: 'Genetic testing for heritable mutations in the BRCA1 and BRCA2 genes'.<sup>2</sup> Recent Australian and international guidelines and position statements were sourced.

A Working Group provided expert input into the development of the Position Statement. The Working Group comprised members with clinical, academic and community knowledge and experience, including: specialist and primary care health professionals who provide care for women with ovarian cancer; consumers, including ovarian cancer survivors and/or carers; researchers, practicing geneticists and genetic counsellors.

The scope of this Position Statement encompasses genetic testing for women diagnosed with ovarian cancer (affected women) and genetic testing for heritable, or germline, gene mutations, with a focus on genetic testing of BRCA1 and BRCA2.

For further information refer to [Technical Report: Genetic testing for women diagnosed with ovarian cancer](#).





## Genetic testing for women diagnosed with ovarian cancer

### Background

In 2017 in Australia, it is estimated that 1,580 new cases of ovarian cancer will be diagnosed and that there will be 1,047 deaths from ovarian cancer.<sup>3</sup> Ovarian cancer is the eighth most common cancer in women and the sixth most common cause of death from cancer in women in Australia.<sup>3</sup>

Most ovarian cancers start in the epithelial cells of the ovary or fallopian tube. Epithelial ovarian cancer is the most common type of ovarian cancer, comprising around 90% of ovarian cancers. Epithelial ovarian cancers may be mucinous or non-mucinous, and non-mucinous epithelial ovarian cancers include serous, endometrioid, clear cell, mixed and undifferentiated tumours.<sup>4</sup>

Epithelial ovarian cancer is often diagnosed at an advanced stage and survival outcomes are poor. Women diagnosed with invasive epithelial ovarian cancer in Australia have a 44% chance of surviving for 5 years compared to the general population.<sup>3</sup>

Epithelial ovarian cancer may be associated with heritable, or germline, mutations in genes including: BRCA1 and BRCA2 (BRCA 1/2), and DNA mismatch repair (MMR) genes associated with Lynch syndrome.<sup>5</sup> Heritable mutations may be carried by both male and female blood relatives. There can also be gene mutations that are only in the tumour itself called somatic mutations, which are not inherited.<sup>6</sup>

### BRCA1/2 heritable mutations in women with invasive epithelial ovarian cancer

Heritable BRCA1/2 mutations are found in approximately 14% of women in Australia with non-mucinous invasive epithelial ovarian cancer unselected for family history, and in approximately 17% of women with high grade serous (non-mucinous) epithelial ovarian cancer unselected for family history.<sup>7</sup>

Heritable mutations in BRCA1/2 are not associated with low malignant potential, or borderline, ovarian tumours,<sup>8</sup> and are rarely detected in mucinous ovarian cancer (less than 1%).<sup>9, 10</sup>

For women with a personal history of both breast and ovarian cancer, heritable BRCA1/2 mutations are found in approximately 50%.<sup>7, 9</sup>

Heritable BRCA1/2 mutations are found in approximately 38% of women in Australia with non-mucinous invasive ovarian cancer who have a family history of breast or ovarian cancer.<sup>7</sup> However there is no known family history of breast or ovarian cancer in over one-third of women with invasive epithelial ovarian cancer in whom a heritable BRCA1/2 mutation is identified.<sup>7, 9, 11</sup>

The prevalence of BRCA1/2 mutations in women with ovarian cancer varies with age and is greatest for women in their 40s and 50s.<sup>9</sup> Over one-quarter of women with invasive epithelial ovarian cancer in whom a heritable BRCA1/2 mutation is identified, are over 60 years at diagnosis.<sup>7, 9</sup> Based on a limited number of studies, prevalence of BRCA1/2 mutations for women with ovarian cancer aged 70 years or older at diagnosis, is less than 10%.<sup>10, 12-15</sup>

In some ethnic populations such as the Ashkenazi Jewish population, prevalence of heritable BRCA1/2 mutations





in women with ovarian cancer is high due to common founder mutations. The frequency of BRCA1/2 mutations for the Ashkenazi Jewish population has been estimated at approximately 2.5% in Australia compared to less than 1% in the general population.<sup>16, 17</sup> Heritable BRCA1/2 mutations are found in approximately 30% of Ashkenazi Jewish women with ovarian cancer.<sup>17, 18</sup>

There are tools such as BOADICEA, BRCAPRO and the Manchester score that predict the likelihood of a BRCA1/2 mutation based on family and personal history, and breast cancer histopathology.<sup>19-21</sup> Sufficient information to guide genetic risk assessment is usually provided by age, histology and family history for women with ovarian cancer.

## Lynch syndrome

Lynch syndrome is associated with increased risk for endometrial, colorectal, ovarian and other cancers. Ovarian cancer associated with Lynch syndrome is commonly non-serous. Lynch syndrome has autosomal dominant inheritance and is due to a heritable mutation that causes dysfunction in a DNA mismatch repair gene.

Women with ovarian cancer who meet specific [criteria](#) based on personal or family history of cancer, have an increased likelihood of Lynch syndrome.<sup>22, 23</sup>

Analysis of the tumour tissue is undertaken as an initial step wherever possible, to screen tumours for abnormal mismatch repair.<sup>22</sup> Methods for screening tumours for abnormal mismatch repair include immunohistochemistry for the MLH1, MSH2, MSH6 and PMS2 proteins, microsatellite instability studies and MLH1 promoter methylation studies.<sup>22</sup>

If an abnormality associated with Lynch syndrome is identified in the tumour, genetic testing for a heritable mutation in a mismatch repair gene can be offered. A deficiency of mismatch repair protein identified in the tumour can indicate which mismatch repair gene to be tested.<sup>22</sup>

## Other heritable gene mutations and gene panel tests

Heritable mutations in other genes are also associated with ovarian cancer, though the ovarian cancer risk is uncertain.<sup>10, 24</sup>

Gene panel tests for heritable mutations in multiple genes are available. Depending on the genes selected for the panel and the clinical situation, the results may be complex and difficult to interpret and the clinical significance of the results may be uncertain.<sup>25, 26</sup>

## Genetic Counselling

Genetic counselling provides genetic risk assessment, and information about genetic tests, possible outcomes of tests and implications of test results, including for insurance.<sup>26</sup>

When genetic testing is offered to a patient with cancer, relevant pre-test information for informed consent includes possible outcomes and implications, including opportunities for personalised treatment decisions. Pre-test information may be provided by a range of appropriately trained health professionals.<sup>26-28</sup>

Post-test genetic counselling provides interpretation of the genetic testing results, including for variants of uncertain significance, and information on the implications for family members.<sup>26-28</sup>





## Implications of a heritable gene mutation for a woman with ovarian cancer

For a woman diagnosed with ovarian cancer, identification of a heritable mutation by genetic testing may inform her treatment decisions.

Response to platinum-based therapy is generally more favourable in women with heritable BRCA1/2 mutations.<sup>7</sup> Women with a BRCA1/2 mutation benefit most from the use of PARP inhibitors as maintenance therapy in platinum-sensitive relapsed ovarian cancer.<sup>29, 30, 31</sup>

Women with a heritable BRCA1/2 mutation are at increased risk for breast cancer.<sup>32</sup> Risk-reducing strategies for breast cancer which may be considered include bilateral prophylactic mastectomy and risk-reducing medications such as selective estrogen receptor modulators (e.g. tamoxifen, raloxifene) or aromatase inhibitors.<sup>33, 34</sup> Increased surveillance for breast cancer as appropriate, may include mammography, ultrasound or MRI.<sup>33, 34</sup>

## Implications for family members

Family members of a woman with an identified heritable mutation can be offered predictive genetic testing for the known mutation. Pre-test counselling by a genetic healthcare professional is needed for family members prior to predictive testing, and should include discussion on implications for insurance. Informed consent should be obtained prior to testing.

If the known mutation is not detected in the family member, they can usually be reassured and avoid unnecessary surveillance and intervention.

If the known mutation is identified in the family member, they can consider cancer-specific risk management options, including surveillance and risk-reducing strategies.<sup>33</sup> The most effective risk-reducing strategy for women at high risk of ovarian cancer is bilateral salpingo-oophorectomy. There is no effective screening for ovarian cancer.<sup>35, 36</sup>

## New models of genetic counselling and testing

New models for genetic counselling and testing are being introduced. These include mainstreaming genetic testing into routine cancer care, where pre-test information may be provided and consenting undertaken by a range of appropriately trained health professionals.<sup>12, 14, 37</sup>







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