Item: BMJ-UK; Article ID: slae040424;
Article Type: Standard article; TOC Heading: Practice; DOI: 10.1136/bmj.q807

1566

*Guidelines*

# Ovarian cancer: identifying and managing familial and genetic risk—summary of new NICE guidance

Eric Slade, health economics adviser,[1] Laura Berg, systematic reviewer,[1] Katharina Dworzynski, guideline lead,[1] Ranjit Manchanda, professor of gynaecological oncology and consultant gynaecological oncologist, guideline topic adviser[2 3 4] on behalf of the Guideline Committee

[1]National Institute for Health and Care Excellence, London

[2]Wolfson Institute of Population Health, Queen Mary University of London

[3]Barts Health NHS Trust, Royal London Hospital

[4]Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine

Victoria Barber, Rebecca Bowen, Adam Brentnall, Alison L Cameron (chair), D Mark Davies (co-opted member), Melanie C Davies, D Gareth Evans, Judith Hayward, R Manchanda (topic adviser), W Glenn McCluggage, Tracie Miles, Kevin Monahan (co-opted member), Davina Moses, Fiona Robb (lay member), Adam N Rosenthal, Lucy Side, Joanne Stanford (lay member), Britta Stordal (co-opted member), Vishakha Tripathi

Correspondence to E Slade eric.slade@nice.org.uk; R Manchanda r.manchanda@qmul.ac.uk

**Box start**

**What you need to know**

- Men and people born with male reproductive organs have a genetic risk of carrying a pathogenic variant associated with ovarian cancer and other cancers
- Refer for genetic counselling and testing people who have a first or second degree relative diagnosed with ovarian cancer, those from high risk groups, anyone identified through cascade testing, or those diagnosed with ovarian cancer linked to pathogenic variants
- For women, trans men, and non-binary people born with female reproductive organs who are at increased risk of ovarian cancer, risk reducing surgery that is age appropriate for their pathogenic variant or family history is the most effective way to reduce the risk of ovarian cancer

**Box end**

In the UK, around 7500 women are diagnosed with ovarian cancer annually. Approximately 340 000 to 440 000 UK women carry a pathogenic variant in a high risk gene that increases their risk of developing the disease.[1] However, only around 3% of people with a high risk gene know that they carry it.[2] Most ovarian cancers associated with high risk genes are diagnosed at advanced stage, leading to poor clinical outcomes. Genetic testing can identify at-risk carriers, who can opt for preventive measures such as risk reducing surgery, which significantly lowers the risk of developing ovarian cancer.[3]

This article summarises new guidance by the National Institute for Health and Care Excellence (NICE) on identifying and managing familial and genetic risk of ovarian cancer.[4] It covers select recommendations of relevance to those working in primary care and providers who refer to specialist services. Recommendations from this guideline are for anyone who has an increased probability of carrying a pathogenic variant in one of the cancer susceptibility genes associated with ovarian cancer, as well as those at increased familial or genetic risk of having ovarian cancer. This includes women, men, trans people, and non-binary people, and their family or carers.

## Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the guideline committee (GC)'s experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

**box start**

**GRADE Working Group grades of evidence**

- High certainty—we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**box end**

## Multidisciplinary care

People with pathogenic variants require comprehensive care that considers their lifetime risk of ovarian cancer, fertility, body image, and menopause status. Access to different care teams across primary and secondary services, and intensity of support, varies according to need throughout a person's life. Therefore, coordinated multidisciplinary care is important for all patients with pathogenic variants and at increased risk of ovarian cancer. Although multidisciplinary care for patients at high risk of familial ovarian cancer is established in some centres, there is lack of evidence regarding impact on patient outcomes. However,

similar teams exist for care of people with familial breast cancer, and these have led to improvement in clinical outcomes.

The familial ovarian cancer multidisciplinary team should be responsible for:

- Clinical care pathways and management protocols
- Lifelong care of people at risk of familial ovarian cancer (those with a pathogenic variant or those above a risk threshold; see the section on referral for genetic counselling and criteria for testing)
- Providing information and support (box 1, in all settings including primary care)
- Assessing the risk of developing ovarian cancer
- Discussing potential management options (eg, risk reducing surgery)
- Carrying out surveillance and reviews
- Liaising with other services and healthcare professionals, including primary care and specialist services (eg, psychological services, menopause services, fertility services, breast cancer risk management services, ovarian cancer services, colorectal cancer services)
- Contributing to local and network audits
- Facilitating access to clinical trials.

[*Limited evidence was identified and therefore recommendations were based largely on the experience and opinion of the GC*]

**Box start**

**Box 1 Information and support to be provided about familial ovarian cancer in all settings, including primary care, genetics services, and specialist multidisciplinary services**

- Information about the risk of ovarian cancer from a person's family history
- Information about the risk of ovarian cancer for people from Ashkenazi Jewish, Sephardi Jewish, and Greenlander backgrounds
- Information for men, trans women, and non-binary people born with male reproductive organs who may have a genetic risk of having a pathogenic variant associated with ovarian cancer and other cancers
- The message that if the person's family history alters (for example, if someone in their family develops ovarian cancer), their risk may alter
- Advice to return to discuss any implications if there is a change in family history or symptoms develop
- Ovarian cancer symptom awareness information (bloating, feeling full on eating, pelvic or abdominal pain, increased urinary urgency and/or frequency). Also see the section on awareness of symptoms and signs in the NICE guideline on ovarian cancer[5]
- Advice about ovarian cancer risk, including information about:
  - Level of ovarian cancer risk in relation to the general population
  - Hormone replacement therapy and oral contraceptives
  - Lifestyle factors
  - Family size and timing
- Information about referral for genetic counselling and genetic testing
- Information about the pathway for risk assessment and management

- Information and support about referral to a different service, what the service does, and why the person is being referred
- Information and support about psychological factors such as anxiety, and psychological support services
- Information about sources of support and information—for example, local and national support groups and networks, patient organisations, and specialist services
- Reassurance about bringing a family member, friend, or carer to appointments

**Box end**

## Overlooked groups eligible for referral for genetic counselling

Healthcare professionals and service providers should raise awareness about overlooked groups who are eligible for genetic counselling and testing. Qualitative evidence showed that many people believe that genetic risk mainly affects women.[6]

- Raise awareness that men, trans women, and non-binary people born with male reproductive organs can have a genetic risk of having a pathogenic variant associated with ovarian cancer and other cancers.

  [*Recommendations based on the experience and opinion of the GC*]

The prevalence of pathogenic variants that increase the risk of familial ovarian cancer varies across different ethnic groups. For example, people of Ashkenazi Jewish descent are five times more likely than the general population to carry pathogenic variants in BRCA genes.[7 8] A systematic review of clinical evidence, including cost effectiveness evidence, supports genetic counselling and testing for at-risk populations, even if they do not have a personal or family history of cancer.[4 9]

- Recognise and raise awareness that people from the following populations (with at least one grandparent from the respective population) have a higher risk of having a founder pathogenic variant associated with familial ovarian cancer, so should be offered referral for genetic counselling and testing for this variant, even if the person has no family or personal history of cancer:
  - Ashkenazi Jewish
  - Sephardi Jewish
  - Greenlander.

  [*Recommendations based on very low to high certainty evidence, and cost effectiveness evidence*]

## Referral for genetic counselling and criteria for testing

Based on evidence from multiple systematic reviews of effectiveness and cost effectiveness, along with bespoke modelling conducted for the guideline, recommendations for when to refer people to a genetic service for counselling and testing were established (fig 1).

- Healthcare professionals in primary care and secondary care should refer people for genetic counselling and genetic testing if any of the following apply:

- They have a first degree relative with a diagnosis of ovarian cancer
- They have a maternal or paternal second degree relative with a diagnosis of ovarian cancer (this includes people with an unaffected intervening blood relative)
- They meet the criteria for genetic testing (as set out below in the section on criteria for genetic counselling and genetic testing in genetic services, including table 1)
- They are from an at-risk population
- They have been identified through cascade testing
- They have a diagnosis of ovarian cancer and have not already had mainstream genetic testing.

[*Recommendations based on very low to high certainty evidence, the experience and opinion of the GC and cost effectiveness evidence*]

**Fig 1** Proposed algorithm for identifying and managing familial and genetic risk

Once referred to a genetic service, the probability of carrying a pathogenic variant should be calculated for people who are unaffected by ovarian cancer but who have an increased probability of carrying a pathogenic variant because of their family history (table 1).

These probabilities are calculated using validated tools, such as CanRisk.[10] If their probability of carrying a pathogenic variant is within the indicated level, the person being tested would be offered genetic counselling and testing.

• Genetics services should offer genetic counselling and genetic testing to anyone who:

- Has not had ovarian cancer and
- Has a raised probability of having a pathogenic variant (table 1) based on a verified family history and
- Has a relative who has had a confirmed diagnosis of breast cancer or ovarian cancer but genetic testing of the relative (or the tissue) is not possible or clinically appropriate ( eg, consent is declined).

[*Recommendations based on the experience and opinion of the GC and cost effectiveness evidence*]

Table 1 Criteria for carrying out genetic testing

| **Age of the person** | **Women, trans men, and non-binary people registered female at birth. Offer genetic counselling and genetic testing if the probability percentage of having a pathogenic variant is:** | **Men, trans women, and non-binary people registered male at birth. Offer genetic counselling and genetic testing if the probability percentage of having a pathogenic variant is:** |
|---|---|---|
| 30 to 39 years | 2% or higher | 6% or higher |
| 40 to 49 years | 2% or higher | 9% or higher |
| 50 to 59 years | 3% or higher | 10% or higher |
| 60 to 69 years | 6% or higher | 10% or higher |
| 70 years or over | 10% or higher | 10% or higher |

## Direct-to-consumer genetic testing

Genetic tests are now commercially available (known as "direct-to-consumer testing"). However, not all laboratories that produce these tests provide accurate results or prepare individuals for their outcomes, and many of these tests are unnecessary. As a result, confirming or refuting these test results can lead to significant NHS costs. Liaise with NHS genetic services to ensure that only people at increased risk of pathogenic variants associated with ovarian cancer are referred for genetic counselling and testing.

- If a person had a direct-to-consumer genetic test and is reported to have a pathogenic variant for which NHS testing is offered (for example, BRCA), healthcare professionals should liaise with the regional NHS genetics service to discuss whether referral is appropriate.
  [*Recommendations based on the experience and opinion of the GC*]

## Risk reducing surgery

For women, trans men, and non-binary people born with female reproductive organs with a total lifetime risk of ovarian cancer of ≥5% because of a pathogenic variant or a strong family history that increases the risk of ovarian cancer, the guideline recommends offering risk reducing surgery (bilateral salpingo-oophorectomy and peritoneal cytology) (table 2). The decision to initiate this surgery will depend on a personalised risk assessment and it may be indicated for people younger than the recommended ages in table 2. Discussion should consider the need for specialist menopause counselling (including that hormone replacement therapy is advised until the usual age of menopause unless there is a prior history of breast cancer or other contraindications) and psychological support.

- Offer risk reducing surgery that is appropriate for the person's age, specific pathogenic variant, and family history (including age of onset of any confirmed ovarian cancers in the family), after discussing the person's individual circumstances with the familial ovarian cancer multidisciplinary team.
  [*Recommendations based on very low to high certainty evidence, experience, and opinion of the GC, and cost effectiveness analysis*]

Table 2 Timing and types of risk reducing surgery for people with a pathogenic variant that increases the risk of ovarian cancer[11]

| Pathogenic variant | Procedure | Age |
|---|---|---|
| *BRCA1* | Bilateral salpingo-oophorectomy | No earlier than 35 years |
| *BRCA2* | Bilateral salpingo-oophorectomy | No earlier than 40 years |
| *$RAD_{51}C$, $RAD_{51}D$, $BRIP_1$*, or PALB2 pathogenic variant with a total lifetime risk of ovarian cancer of 5% or over | Bilateral salpingo-oophorectomy | No earlier than 45 years |
| *$MLH_1$, $MSH_2$, or $MSH_6$* | Hysterectomy with bilateral salpingo-oophorectomy (to reduce the risk of endometrial cancer as well as ovarian cancer)* | No earlier than 35 years |

*$MLH_1$*, *$MSH_2$*, or *$MSH_6$* pathogenic variants have also been included as they cause Lynch syndrome, which is associated with an increased risk of endometrial and ovarian cancer.
*Total hysterectomy, including the cervix, to ensure the removal of all at-risk tissue.

## Ovarian cancer surveillance

Risk reducing surgery is the most effective option for reducing the risk of ovarian cancer. Evidence from two UK-wide, prospective cohort studies showed that surveillance may lead to earlier cancer detection, but data for cancer mortality outcomes were unavailable.[12 13] Therefore, surveillance is only recommended as an interim risk management strategy for women, trans men, and people born with female reproductive organs who choose to delay or avoid risk reducing surgery. It should be carried out in a multidisciplinary familial ovarian cancer setting. Surveillance can also lead to false positive results, which may increase anxiety and lead to unnecessary surgery.

- If a person is at risk of developing ovarian cancer and chooses to delay or not have risk reducing surgery, discuss their reasons and explain that:
  - They have an increased risk of developing ovarian cancer and that the only way to reduce their risk is to have risk reducing surgery
  - Delaying risk reducing surgery should be seen only as a short term option
  - Regular surveillance does not reduce the person's risk of developing ovarian cancer
  - Although regular surveillance means that ovarian cancer may be detected earlier, they should not view surveillance as an alternative to risk reducing surgery (because little evidence is available on whether this leads to improved outcomes and saves lives)
  - Surveillance will involve the person having a blood test every four months to check their level of the protein CA125 (cancer antigen 125), with an algorithm to analyse results, and a review at least once a year to discuss the recommendation to have risk reducing surgery
  - There is a possibility of getting a false positive or false negative test result.

  [*Recommendations based on very low to moderate certainty evidence, experience, and opinion of the GC, and cost effectiveness evidence*]

## Implementation

Not all trusts have dedicated familial ovarian cancer multidisciplinary teams. Although setting up these teams may incur costs initially, they are anticipated to improve clinical outcomes, as has been seen with similar familial breast cancer teams.

Broadening eligibility criteria for genetic testing will make testing accessible to more people but may also result in increased pressure on primary care services through presentations and referrals. To mitigate this, clear referral criteria have been established, a recommendation for development of supporting online referral system, and people being screened should be asked to complete their own family history questionnaires.

Expanding the eligibility criteria will likely increase the demand for genetic services and support services, including menopause and psychological services. Identification of more

carriers may also lead to more people opting for risk management. However, it will reduce the number of cancers, making it a cost effective approach.

People who choose to delay or not undergo risk reducing surgery will now be eligible for ovarian cancer surveillance commencing from the eligible age for risk reducing surgery. The implementation of surveillance requires a call recall mechanism and appropriate infrastructure (screening invitations, appointments, tracking and testing). These fall under the remit of the familial ovarian cancer multidisciplinary teams, who should coordinate, audit, and interpret the results. It is expected that very few people would require surveillance since risk reducing surgery is the optimal way to reduce the risk of ovarian cancer.

## Future research

The guideline committee prioritised the following questions for future research:

- What are the performance characteristics of tools or models to assess the absolute risk of developing ovarian cancer?
- What are the long term benefits and risks of ovarian cancer surveillance for people at increased risk of ovarian cancer?
- What is the safety and efficacy of hormone replacement therapy after risk reducing salpingo-oophorectomy?

**• Box start**

### Further information on the guidance

This guidance was developed by NICE in accordance with NICE guideline methodology (www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf). A guideline committee (GC) was established by NICE, which in addition to the topic adviser (consultant gynaecological oncologist) incorporated healthcare and allied healthcare professionals (two general practitioners, one genetic epidemiologist/statistician, one consultant oncologist, one consultant gynaecologist, one consultant gynaecologist with an interest in fertility/menopause, one consultant histopathologist, one clinical nurse specialist, one psychologist, two consultant clinical geneticists, and one specialist genetic counsellor), and two lay members. The guideline committee also included co-opted members: one consultant breast cancer specialist, one consultant colorectal cancer specialist, and one genetic scientist.

The guideline is available at https://www.nice.org.uk/guidance/ng181.

The GC identified relevant review questions and collected and appraised clinical and cost effectiveness evidence. Quality ratings of the evidence were based on GRADE methodology (www.gradeworkinggroup.org). These relate to the quality of the available evidence for assessed outcomes or themes rather than the quality of the study. The GC agreed recommendations for clinical practice based on the available evidence or, when evidence was not found, based on their experience and opinion using informal consensus methods.

The scope and the draft of the guideline went through a rigorous reviewing process, in which stakeholder organisations were invited to comment; the GC took all comments into consideration when producing the final version of the guideline.

NICE will conduct regular reviews after publication of the guidance, to determine whether the evidence base has progressed significantly enough to alter the current guideline recommendations and require an update.

**Box end**

**Box start**

## How patients were involved in the creation of this article

Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

**Box end**

**Box start**

## Guidelines into practice

- What information do you provide about genetic counselling and testing for people who are at increased risk of familial ovarian cancer?
- What are the criteria for referring people for familial ovarian cancer related genetic counselling and testing?
- What is the most effective way to reduce ovarian cancer risk in women, trans men, and non-binary people born with female reproductive organs with pathogenic variants or a strong family history that increases the risk of ovarian cancer?

**Box end**

The members of the Guideline Committee were (shown alphabetically):

Victoria Barber, Rebecca Bowen, Adam Brentnall, Alison L Cameron (chair), D Mark Davies (co-opted member), Melanie C Davies, D Gareth Evans, Judith Hayward, R Manchanda (topic adviser), W Glenn McCluggage, Tracie Miles, Kevin Monahan (co-opted member), Davina Moses, Fiona Robb (lay member), Adam N Rosenthal, Lucy Side, Joanne Stanford (lay member), Britta Stordal (co-opted member), Vishakha Tripathi.

The technical members of the Guideline Development Team: Laura Berg (systematic reviewer), Nathan Bromham (senior systematic reviewer between July 2021 and June 2023), Emma Clegg (information scientist), Esther Clifford (project manager from October 2023), Katharina Dworzynski (guideline lead), Hayley Shaw (project manager between July 2021 and October 23), Suhayl Kassam (systematic reviewer between September 2021 and September 2023), Neil Ryan (clinical fellow), Katriona O'Donoghue (systematic reviewer between August 2022 and December 2022), Tim Reeves (information scientist between July 2021 and March 2022), Mia Schmidt-Hansen (senior systematic reviewer from June 2023), Eric Slade (health economics adviser), Sarah Stockton (information scientist between July 2021 and April 2022).

We acknowledge the support of expert witnesses Rosa Legood, Alistair McGuire, and Xia Wei.

Competing interests: We declared the following interests based on NICE's policy on conflicts of interests (https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaration-of-interests-policy.pdf): none.

The guideline authors' full statements can be viewed at https://www.nice.org.uk/guidance/ng241/history.

Funding: Eric Slade, Laura Berg, and Katharina Dworzynski are employees of NICE, which is funded by the Department of Health and Social Care to develop clinical guidelines. Ranjit Manchanda is an employee of Queen Mary University of London and Barts Health NHS Trust. No authors received specific funding from NICE, the Department of Health and Social Care, or the NHS to write this summary.

Contributorship and the guarantor: All four authors confirm that they meet all four authorship criteria in the ICMJE uniform requirements. Eric Slade is the guarantor for this article. The views expressed in this publication are those of the authors and not necessarily those of NICE.

Provenance and peer review: commissioned; not externally peer reviewed.

<eref>1 National Institute for Health and Care Excellence. Final guideline scope Ovarian cancer: identifying and managing familial and genetic risk 2023. https://www.nice.org.uk/guidance/ng241/history</eref>

<jrn>2 Manchanda R, Blyuss O, Gaba F, et al. Current detection rates and time-to-detection of all identifiable *BRCA* carriers in the Greater London population. *J Med Genet* 2018;55:538-45. PubMed doi:10.1136/jmedgenet-2017-105195</jrn>

<jrn>3 Crosbie EJ, Flaum N, Harkness EF, et al. Specialist oncological surgery for removal of the ovaries and fallopian tubes in BRCA1 and BRCA2 pathogenic variant carriers may reduce primary peritoneal cancer risk to very low levels. *Int J Cancer* 2021;148:1155-63. PubMed doi:10.1002/ijc.33378</jrn>

<eref>4 National Institute for Health and Care Excellence. Ovarian cancer: identifying and managing familial and genetic risk (NICE guideline NG10225). 2024. https://www.nice.org.uk/guidance/ng241</eref>

<eref>5 National Institute for Health and Care Excellence. Ovarian cancer: recognition and initial management (clinical guideline CG122). 2011. https://www.nice.org.uk/guidance/cg122</eref>

<jrn>6 Young AL, Butow PN, Rhodes P, et al. Talking across generations: Family communication about BRCA1 and BRCA2 genetic cancer risk. *J Genet Couns* 2019;28:516-32. PubMed doi:10.1002/jgc4.1055</jrn>

<jrn>7 Manchanda R, Burnell M, Gaba F, et al. Randomised trial of population-based BRCA testing in Ashkenazi Jews: long-term outcomes. *BJOG* 2020;127:364-75. PubMed doi:10.1111/1471-0528.15905</jrn>

<eref>8 Jewishbrca.org. The NHS Jewish BRCA Testing Programme. https://jewishbrca.org/</eref>

<unknown>9. Manchanda R, Legood R, Burnell M, et al. Cost-effectiveness of population screening for BRCA mutations in Ashkenazi Jewish women compared with family history–based testing. *J Nat Cancer Inst* 2015;107:dju380.</unknown>

<jrn>10 Archer S, Babb de Villiers C, Scheibl F, et al. Evaluating clinician acceptability of the prototype CanRisk tool for predicting risk of breast and ovarian cancer: A multi-methods study. *PLoS One* 2020;15:e0229999. PubMed doi:10.1371/journal.pone.0229999</jrn>

<jrn>11 Wei X, Sun L, Slade E, et al. Cost-effectiveness of gene-specific prevention strategies for ovarian and breast cancer. *JAMA Netw Open* 2024;7:e2355324. PubMed doi:10.1001/jamanetworkopen.2023.55324</jrn>

<jrn>12 Rosenthal AN, Fraser LSM, Philpott S, et al; United Kingdom Familial Ovarian Cancer Screening Study collaborators. Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom familial ovarian cancer screening study. *J Clin Oncol* 2017;35:1411-20. PubMed doi:10.1200/JCO.2016.69.9330</jrn>

<jrn>13 Philpott S, Raikou M, Manchanda R, et al. The avoiding late diagnosis of ovarian cancer (ALDO) project; a pilot national surveillance programme for women with pathogenic germline variants in *BRCA1* and *BRCA2*. *J Med Genet* 2023;60:440-9. PubMed doi:10.1136/jmg-2022-108741</jrn>