# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Guideline

## Ovarian cancer: identifying and managing familial and genetic risk

## Draft for consultation, September 2023

This guideline is for adults with a genetic risk of having a pathogenic variant associated with ovarian cancer (familial ovarian cancer).

Familial ovarian cancer affects people with female reproductive organs (ovaries, fallopian tubes and/or a uterus). This includes women, trans men and non-binary people with female reproductive organs. Men, trans women and non-binary people with male reproductive organs can also carry a pathogenic variant associated with ovarian cancer. This means that they are at risk of developing other cancers, and they can pass the pathogenic variant to their children.

Risk management and decision-making support for people with male reproductive organs who have, or are at risk of having, a pathogenic variant associated with ovarian cancer is not included in the guideline. This is because they are not at risk of developing ovarian cancer, and the decisions that they would have to make are different and outside the scope of this guideline.

### Who is it for?

- Healthcare professionals working in primary, secondary and tertiary care
- Cancer alliances
- Commissioners (including clinical commissioning groups and NHS England specialised commissioning)
- Voluntary sector organisations

- Adults (18 years and older) with a genetic risk of having a pathogenic variant associated with ovarian cancer, and their families and carers (where appropriate)

### What does it include?

- the recommendations
- recommendations for research
- rationale and impact sections that explain why the committee made the recommendations and how they might affect practice or services
- the guideline context.

Information about how the guideline was developed is on the guideline's webpage. This includes the evidence reviews, the scope, details of the committee and any declarations of interest.

NICE has also produced a guideline on the recognition and initial management of ovarian cancer.

1

# Contents

# Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

## 1.1 Organisation of services

### Commissioners and service providers in all settings (primary care, genetics services and specialist multidisciplinary services)

1.1.1 Commissioners and service providers should ensure that there are referral pathways to genetics services for people at risk of having a pathogenic variant associated with ovarian cancer. Such pathways can be facilitated by providing, for example:

- clear referral criteria (see the sections on assessing the risk of having a pathogenic variant and criteria for genetic testing)
- an online referral form (to be completed by the referring clinician)
- a family history questionnaire (to be completed by the person) that accompanies the referral form
- information and support (see the section on information and support).

1.1.2 Commissioners and service providers should ensure that there is training and information available for healthcare professionals on equality and inclusiveness issues that could improve access to services, for example, for people who:

- are from under-represented or underserved communities who may need more support to access services (for example, people who are

physically disabled, people with neurodevelopmental conditions or a learning disability, people from Black, Asian and minority ethnic backgrounds, and people who are LGBTQ+)

- may not come forward for testing because they do not realise that they may be at risk of having a pathogenic variant associated with ovarian cancer (for example, men, trans women and non-binary people with male reproductive organs).

### Primary care services

1.1.3 Primary care professionals should be responsible for:

- providing information and support (see the section on information and support)
- referral to genetics services and/or other specialist services (see recommendation 1.1.1 and the sections on assessing the risk of having a pathogenic variant and criteria for genetic testing).

### Genetics services

1.1.4 Genetics services should be responsible for:

- providing information and support (see the section on information and support)
- assessing the risk of having a pathogenic variant
- assessing the risk of developing ovarian cancer
- genetic counselling and genetic testing
- arranging cascade testing of relatives, if appropriate
- discussing potential management options
- referral (if needed) to the familial ovarian cancer multidisciplinary team and/or other specialist services.

### Gynaecology oncology multidisciplinary team

1.1.5 The gynaecology oncology multidisciplinary team should be responsible for genetic counselling and testing for anyone with invasive epithelial ovarian cancer or the ovarian cancer histotypes in recommendation 1.4.5.

## Familial ovarian cancer multidisciplinary team

1.1.6 The familial ovarian cancer multidisciplinary team should be responsible for:

- clinical care pathways and management protocols
- the 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 criteria for genetic testing)
- providing information and support (see the section on information and support)
- assessing the risk of developing ovarian cancer
- discussing potential management options
- carrying out monitoring and reviews
- liaising with other services and healthcare professionals, including primary care and specialist services (see recommendation 1.1.8)
- contributing to local and network audits
- facilitating access to clinical trials.

1.1.7 The familial ovarian cancer multidisciplinary team should have a designated lead clinician, and include healthcare professionals with expertise in areas including:

- clinical genetics
- gynaecology
- gynaecological oncology.

1.1.8 The familial ovarian cancer multidisciplinary team should have established relationships with, and agreed referral pathways to, other specialist services such as:

- psychological services
- menopause services
- fertility services
- breast cancer risk management services
- ovarian cancer services

- colorectal cancer services.

For a short explanation of why the committee made these recommendations and how they might affect services, see the rationale and impact section on organisation of services.

Full details of the evidence and the committee's discussion are in evidence review C: service configuration.

## 1.2 Information and support

These recommendations are for anyone who has a risk of having a pathogenic variant associated with ovarian cancer. This includes women, men, trans people and non-binary people, and their family or carers (as appropriate).

### Information and support about familial ovarian cancer in all settings

1.2.1 Healthcare professionals in all settings (primary care, genetics services and specialist multidisciplinary services) should provide ongoing information and support in line with:

- table 1 on information and support about familial ovarian cancer in all settings
- NICE's guideline on patient experience in adult NHS services
- NICE's guideline on people's experience in adult social care services
- NICE's guideline on shared decision making.

**Table 1 Information and support about familial ovarian cancer in all settings**

| |
|---|
| • Information about the risk of having a pathogenic variant associated with ovarian cancer from a person's family history.<br>• Information about the risk of having a pathogenic variant associated with ovarian cancer for people from Ashkenazi Jewish, Sephardi Jewish and Greenlander family backgrounds.<br>• Information for men, trans women and non-binary people with male reproductive organs who may have a genetic risk of having a pathogenic variant associated with ovarian cancer and other cancers.<br>• 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 – BEAT (Bloating, feeling full on Eating, Abdominal pain, Toilet changes); also see also the section on awareness of symptoms and signs in the NICE guideline on ovarian cancer.
- Advice about ovarian cancer risk, including information about:
  - level of ovarian cancer risk
  - hormone replacement therapy (HRT) and oral contraceptives
  - lifestyle factors
  - family size and timing.
- Information about referral for genetic counselling and 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.
- Details of any trials or studies that may be appropriate.

1.2.2 Healthcare professionals should ensure that information and support:

- supports shared decision making
- is balanced and accurate
- is available on an ongoing basis
- is available when needed
- is relevant to the person's circumstances
- is tailored to the person's needs, for example, is in an accessible format or available in a different language.

1.2.3 Provide opportunities for people to review decisions, and share any additional information on how they can access services for further discussions, for example, at:

- re-referral to specialist services
- patient initiated follow-up appointments directly with specialist services
- self-referral to genetics services.

1.2.4 At each appointment:

- ask the person about their emotional health
- ask about any psychological or emotional issues that could affect decision making, such as anxiety
- provide information and support (see table 1 on information and support about familial ovarian cancer in all settings)
- offer referral to genetic counselling or psychological services, if needed.

1.2.5 Raise awareness that men and people with male reproductive organs can have a genetic risk of having a pathogenic variant associated with ovarian cancer and other cancers.

1.2.6 Ensure that services are easy to access (for example, by offering online appointments) and welcoming for everyone, particularly for people who may have additional support needs (also see recommendation 1.1.2).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on information and support about familial ovarian cancer in all settings.

Full details of the evidence and the committee's discussion are in:

- evidence review A: information and support
- evidence review B: support interventions
- evidence review D: optimal methods of assessing probability
- evidence review F: carrier probability – any person
- evidence review H: population with high probability.

## Information and support about risk assessment and genetic testing in genetics services

1.2.7 Healthcare professionals in genetics services should provide ongoing information and support in line with:

- table 2 on information and support about risk assessment and genetic testing in genetics services **and**
- table 1 on information and support about familial ovarian cancer in all settings.

**Table 2 Information and support about risk assessment and genetic testing in genetics services**

**At referral for risk assessment and genetic testing**

- Information about how the risk of having a pathogenic variant is assessed, and how to obtain a comprehensive family history if needed.
- Clarification about which family members could be at risk, and advice about appropriate ages for testing.
- Information about genetic testing (both predictive testing and mutation finding), including details of what genetic testing involves, what the tests mean and how informative they are likely to be, and the likely timescale of getting the results.
- Information and support on the importance of, and how to discuss, the results of assessment and testing with relatives, including different methods of contacting relatives about cascade testing.
- Information about potential next steps depending on the risk assessment (including referral back to primary care, management within secondary care and/or a specialist genetics service, risk-reducing surgery and surveillance).
- Information and support to aid decision making about topics such as genetic testing, risk-reducing surgery, fertility and whether the person wants to have children, and menopause and managing symptoms.

**At referral back to primary care**

- Information about why genetic testing is not advised (as applicable).
- Advice to return to primary care to discuss any implications if there is a change in family history or symptoms develop.

1.2.8 In genetics services, a healthcare professional with skills and experience in information provision and shared decision making specifically related to genetics and cancer risk should offer genetic counselling to people who meet the referral criteria for genetic testing. See the sections on assessing the risk of having a pathogenic variant and criteria for genetic testing.

1.2.9 Take into account the following factors when deciding whether to offer face-to-face or remote (for example, video call, telephone) genetic counselling:

- the person's preference

- the decision that needs to be made (for example, genetic testing or risk-reducing surgery)
- accessibility needs (for example, geographic location, digital access, language or communication impairment, participation of family members in other locations)
- the need for an interpreter.

1.2.10 Consider giving information in a group session before an individual genetic counselling session.

1.2.11 Consider using a patient decision aid (for example, an app) alongside genetic counselling to support shared decision making. See the recommendations on patient decision aids in the NICE guideline on shared decision making.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on information and support about risk assessment and genetic testing in genetics services.

Full details of the evidence and the committee's discussion are in:

- evidence review A: information and support
- evidence review B: support interventions
- evidence review D: optimal methods of assessing probability
- evidence review F: carrier probability – any person.

### Information and support in specialist services if a person has a pathogenic variant or likely pathogenic variant

1.2.12 Healthcare professionals in specialist services (genetic services, gynaecology oncology multidisciplinary teams and familial ovarian cancer multidisciplinary teams) should provide ongoing information and support in line with:

- table 3 on information and support in specialist services if a person has a pathogenic variant or likely pathogenic variant **and**

- table 1 on information and support about familial ovarian cancer in all settings.

**Table 3 Information and support in specialist services if a person has a pathogenic variant or likely pathogenic variant**

**Risk of developing ovarian cancer**

- Information about the person's risk of developing familial ovarian cancer, how the risk is assessed, what their personal risk estimate means, and other factors that could increase or decrease the risk.
- Information and support to aid shared decision making.

**Reproductive choices**

- Information about the likelihood of passing down the pathogenic variant to their children.
- Information about the impact of risk-reducing surgery on fertility.
- Information about the availability of fertility preservation by storing eggs or embryos.
- Information about the availability of pre-implantation genetic testing of embryos to avoid passing down the genetic risk to their children.

**Risk-reducing surgery**

- Information about risk-reducing surgery and what it involves.
- Advice that risk-reducing bilateral salpingo-oophorectomy is the most reliable way to substantially reduce the likelihood of developing ovarian cancer and therefore improve life expectancy, but that there will still be a small residual risk.
- Information that if risk-reducing bilateral salpingo-oophorectomy is appropriate, it is because of a pathogenic variant associated with ovarian cancer, or a family history that has been shown to increase risk.
- Information about the timing of risk-reducing surgery and different surgical procedures (also see the recommendations on risk-reducing mastectomy in the NICE guideline on familial breast cancer).
- The possible biopsychosocial and sexual consequences of risk-reducing surgery.
- Information about the possible impact of risk-reducing surgery on other areas of the person's life, for example, that risk-reducing surgery will lead to early menopause (if premenopausal) and the symptoms they may experience, hormone replacement therapy (HRT), impact on sex life and body image, and fertility (see also the section on people with cancer who wish to preserve fertility the NICE guideline on fertility problems).
- The need for monitoring (ovarian cancer surveillance) if they choose to delay or not have risk-reducing surgery.
- Information about the risk of other cancers (for example, primary peritoneal, breast, pancreas, prostate, bowel).

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on information and

support in specialist services if a person has a pathogenic variant or likely pathogenic variant.

Full details of the evidence and the committee's discussion are in

- evidence review E: optimal methods to assess absolute risk
- evidence review K: benefits and risks of surveillance
- evidence review N: risk-reducing surgery.

## 1.3 Assessing the risk of having a pathogenic variant

These recommendations are for anyone who has a risk of having a pathogenic variant associated with ovarian cancer. This includes women, men, trans people and non-binary people.

1.3.1 Healthcare professionals should refer anyone to genetics services who meets the criteria for genetic testing as set out in the section on criteria for genetic testing, including anyone identified through cascade testing.

1.3.2 If a person had a direct-to-consumer genomic 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 genetic service to discuss whether referral is appropriate.

1.3.3 Genetics services should assess the probability of having a pathogenic variant using a calculation method with demonstrated accuracy, such as the Manchester scoring system, CanRisk (BOADICEA), BRCAPRO, or criteria based on family history that are designed for the threshold used for testing.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on assessing the risk of having a pathogenic variant.

Full details of the evidence and the committee's discussion are in:

- evidence review B: support interventions

- evidence review D: optimal methods of assessing probability.

## 1.4 Criteria for genetic testing

### Family history of ovarian cancer

These recommendations are for anyone who has a risk of having a pathogenic variant associated with ovarian cancer. This includes women, men, trans people and non-binary people.

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

- has not had breast cancer or ovarian cancer **and**
- has a raised probability of having a pathogenic variant (see table 4 on genetic testing criteria) **and**
- has a relative who has had breast cancer or ovarian cancer but the relative (or their tissue) is not available for genetic testing.

**Table 4 Genetic testing criteria**

| **Age of the person** | **Female:**<br>**Offer genetic counselling and testing if the probability percentage of having a pathogenic variant is:** | **Male:**<br>**Offer genetic counselling and 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 |

1.4.2 If a person has not had breast cancer or ovarian cancer, genetics services should offer genetic counselling and testing if they are a first-degree relative of a person with a known pathogenic variant (cascade testing).

1.4.3 If a person has not had breast cancer or ovarian cancer, genetics services should offer genetic counselling and testing if:

- they are a blood relative of a person with a known pathogenic variant **and**
- no intervening blood relative (or their tissue) is available for genetic testing.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on family history of ovarian cancer.

Full details of the evidence and the committee's discussion are in:

- evidence review F: carrier probability – any person
- evidence review G: carrier probability – family history of syndrome.

## At-risk populations

This recommendation is for anyone who has a risk of having a pathogenic variant associated with ovarian cancer. This includes women, men, trans people and non-binary people.

1.4.4 If a person is from one of the following populations, genetics services should offer genetic counselling and testing, even if the person has no family or personal history of ovarian cancer. This is because people from the following populations have a higher risk of having a founder pathogenic variant associated with familial ovarian cancer, and should be offered genetic testing for this variant:

- Ashkenazi Jewish
- Sephardi Jewish
- Greenlander.

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on at-risk populations.

Full details of the evidence and the committee's discussion are in evidence review H: populations with high probability.

### People with ovarian cancer

This recommendation is for women, trans men and non-binary people with some or all of the following female reproductive organs: ovaries, fallopian tubes and/or a uterus.

1.4.5 Offer genetic counselling and testing to anyone diagnosed with:

- invasive epithelial ovarian cancer
- ovarian Sertoli–Leydig cell tumour
- small cell carcinoma of the ovary hypercalcaemic type
- ovarian sex cord tumour with annular tubules
- embryonal rhabdomyosarcoma of the ovary
- ovarian gynandroblastoma.

Also see the NICE guideline on ovarian cancer: recognition and initial management.

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on people with ovarian cancer.

Full details of the evidence and the committee's discussion are in evidence review I: carrier probability – women with ovarian cancer.

## 1.5 Gene panel testing

1.5.1 Select a gene panel from the UK national genomic test directory (see the sections on assessing the risk of having a pathogenic variant and criteria for genetic testing), to test for pathogenic variants.

1.5.2 Decide which gene panel from the UK national genomic test directory to use in relation to each person's family or personal history (ovarian cancer alone, breast and ovarian cancer, or Lynch syndrome).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on gene panel testing.

Full details of the evidence and the committee's discussion are in evidence review J: which genes to include in panel testing.

## 1.6 Assessing the risk of developing ovarian cancer

These recommendations are for women, trans men and non-binary people with some or all of the following female reproductive organs: ovaries, fallopian tubes and/or a uterus.

1.6.1 If a person is under the care of genetics services or a familial ovarian cancer multidisciplinary team and has not had genetic testing, the service or team should offer to assess their risk of developing ovarian cancer.

1.6.2 If a person has a pathogenic variant associated with an increased risk of ovarian cancer, the familial ovarian cancer multidisciplinary team should offer to assess their risk of developing ovarian cancer.

1.6.3 When assessing a person's risk of developing ovarian cancer, use a tool with demonstrated accuracy that includes their age and family history of ovarian and other cancers (such as CanRisk).

1.6.4 When assessing a person's risk of developing ovarian cancer using a tool or method that includes only their age and family history, or their age and pathogenic variant, inform the person that there are other factors that could also increase or decrease their risk.

1.6.5 When assessing a person's risk of developing ovarian cancer, take into account factors that may not be accurately assessed by tools, for example, parity, use of the combined oral contraceptive pill, endometriosis, and whether relatives have only ovarian cancer.

1.6.6 When discussing a person's risk of developing ovarian cancer:

- provide a summary in the person's preferred format that includes their personal risk estimate **and**
- follow the recommendations in the sections on communicating risks, benefits and consequences and putting shared decision making into practice in the NICE guideline on shared decision making.

1.6.7 For information on familial and other risk factors for breast cancer that also increase ovarian cancer risk, see the NICE guideline on familial breast cancer.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on assessing the risk of developing ovarian cancer.

Full details of the evidence and the committee's discussion are in:

- evidence review D: optimal methods of assessing probability
- evidence review E: optimal methods of assessing absolute risks.

## 1.7 Primary preventive medicines

These recommendations are for women, trans men and non-binary people with some or all of the following female reproductive organs: ovaries, fallopian tubes and/or a uterus.

### Aspirin

1.7.1 For recommendations on the use of aspirin for people with Lynch syndrome, see the section on reduction in risk of colorectal cancer in people with Lynch syndrome in the NICE guideline on colorectal cancer.

In September 2023, this was an off-label use of aspirin. See NICE's information on prescribing medicines.

### Combined oral contraceptives

1.7.2 When thinking about using a combined oral contraceptive solely to reduce the risk ovarian cancer, take into account:

- the reduction in the risk of developing ovarian cancer and the increased risk of developing breast cancer **and**
- the timing of any risk-reducing surgery (mastectomy or salpingo-oophorectomy; see the section on risk-reducing surgery).

In September 2023, this was an off-label use of combined oral contraceptives. See NICE's information on prescribing medicines.

1.7.3 Discuss the reduced risk of developing ovarian cancer and the increased risk of developing breast cancer when offering a combined oral contraceptive for purposes other than prevention of ovarian cancer (see also the section on hormonal contraceptives in the NICE guideline on familial breast cancer).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on primary preventive medicines.

Full details of the evidence and the committee's discussion are in evidence review M: preventive medicine.

## 1.8 Risk-reducing surgery

These recommendations are for women, trans men and non-binary people with some or all of the following female reproductive organs: ovaries, fallopian tubes and/or a uterus.

### Factors to take into account when considering risk-reducing surgery

1.8.1 Only offer risk-reducing surgery to people who have:

- completed their family or are not planning to conceive naturally (that is, they would only conceive using assisted reproduction) **and**
- a total lifetime risk of ovarian cancer of 4% or over (if premenopausal) or 5% or over (if postmenopausal) because they have:
  - a pathogenic variant associated with familial ovarian cancer **or**
  - a strong family history of ovarian cancer.

1.8.2 When discussing risk-reducing surgery, provide information and support in line with:

- table 3 on information and support in specialist services if a person has a pathogenic variant or likely pathogenic variant **and**
- table 1 on information and support about familial ovarian cancer in all settings.

1.8.3 When discussing risk-reducing surgery, take into account psychological factors (such as anxiety) that could influence decision making. Discuss psychological support services available and, if needed, refer the person for psychological support before surgery.

1.8.4 When discussing risk-reducing bilateral salpingo-oophorectomy surgery with people who are premenopausal:

- offer specialist menopause counselling before and after surgery **and**
- provide information and support to aid shared decision making (also see the section on information and support, in particular table 3 on information and support in specialist services if a person has a pathogenic variant or likely pathogenic variant).

1.8.5 Refer people who have bi-allelic pathogenic variants in mismatch repair genes, for example, homozygous PMS2, to a specialist tertiary team for discussions about risk-reducing surgery.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on factors to take into account when considering risk-reducing surgery.

Full details of the evidence and the committee's discussion are in evidence review N: risk-reducing surgery.

## Monitoring for people who choose to delay or not have risk-reducing surgery (ovarian cancer surveillance)

These recommendations are for women, trans men, non-binary people with some or all of the following female reproductive organs: ovaries, fallopian tubes and/or a uterus.

1.8.6 If a person is at risk of developing ovarian cancer and chooses to delay or not have having 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 only be seen as a short-term option
- regular monitoring (ovarian cancer surveillance) does not reduce their risk of developing ovarian cancer
- although regular monitoring means that ovarian cancer may be detected earlier, they should not view monitoring as an alternative to risk-reducing surgery (because there is little evidence on whether this leads to improved outcomes and saves lives)
- monitoring will involve them having a blood test every 4 months to check their level of the protein CA125 (cancer antigen 125), and a review at least once a year to discuss having risk-reducing surgery
- there is a possibility of getting a false-positive or false-negative test result.

1.8.7 The familial ovarian cancer multidisciplinary team (see the section on familial ovarian cancer multidisciplinary teams) should only consider monitoring (ovarian cancer surveillance) for people in the following groups who are at risk of developing ovarian cancer but who choose to delay or not have risk-reducing surgery:

- over 35 and have a BRCA1 pathogenic variant **or**
- over 40 and have a BRCA2 pathogenic variant **or**

- over 45 and have RAD51C, RAD51D, BRIP1 and PALB2 pathogenic variants.

1.8.8 If a person is at risk of developing ovarian cancer and chooses to delay or not have risk-reducing surgery, the familial ovarian cancer multidisciplinary team should:

- carry out serial 4-monthly CA125 longitudinal testing using an algorithm (for example, the Risk of Ovarian Cancer Algorithm [ROCA]); this should be centrally coordinated and reviewed with a call and recall mechanism
- have a review appointment with the person at least once a year to discuss having risk-reducing surgery (see the section on risk-reducing surgery).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on monitoring for people who choose to delay or not have risk-reducing surgery (ovarian cancer surveillance).

Full details of the evidence and the committee's discussion are in:

- evidence review K: benefits and risks of surveillance
- evidence review L: methods of surveillance.

## Types of risk-reducing surgery and timing in relation to the person's specific pathogenic variant

The recommendations are for risk-reducing surgery related to ovarian cancer. For people who have a pathogenic variant that also increases their risk of breast cancer and are considering risk-reducing mastectomy, also see the NICE guideline on familial breast cancer.

1.8.9 Offer risk-reducing surgery that is age appropriate to the person's 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. See table 5 on timing and types of risk-reducing surgery for people with a pathogenic variant that increases the risk of ovarian cancer.

**Table 5 Timing and types of risk-reducing surgery for people with a pathogenic variant that increases the risk of ovarian cancer**

| Pathogenic variant | Procedure | Age (also see recommendation 1.8.11) |
|---|---|---|
| BRCA1 | Bilateral salpingo-oophorectomy | No earlier than 35 years |
| BRCA2 | Bilateral salpingo-oophorectomy | No earlier than 40 years |
| RAD51C, RAD51D, BRIP1 or PALB2 pathogenic variant with a 4% (premenopausal) or 5% (postmenopausal) or more total lifetime risk of ovarian cancer | Bilateral salpingo-oophorectomy | No earlier than 45 years |
| MLH1, MSH2 or MSH6 | Hysterectomy with bilateral salpingo-oophorectomy (to reduce the risk of endometrial cancer as well as ovarian cancer) | No earlier than 35 years |

1.8.10 Consider risk-reducing total hysterectomy alone to prevent endometrial cancer for people (no earlier than 45 years) who have:

- a heterozygous PMS2 pathogenic variant **and**
- no family history of ovarian cancer.

1.8.11 If a person with a heterozygous PMS2 pathogenic variant has been offered total hysterectomy to prevent endometrial cancer, consider additional bilateral salpingo-oophorectomy depending on confirmed family history of ovarian cancer, age and menopausal status.

1.8.12 Consider risk-reducing surgery in people younger than the ages in recommendation 1.8.9 after carrying out an individualised risk assessment (including an assessment of menopausal symptoms) and providing

information and support to aid shared decision making (also see the section on information and support).

1.8.13 Only offer risk-reducing bilateral salpingectomy with delayed oophorectomy as part of a clinical trial.

1.8.14 Do not carry out risk-reducing total hysterectomy in people with pathogenic variants other than MLH1, MSH2, MSH6 and PMS2 unless a personalised risk assessment shows a high risk of endometrial cancer that would necessitate hysterectomy or there is another gynaecological indication for hysterectomy.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on types of risk-reducing surgery and timing in relation to the person's specific pathogenic variant.

Full details of the evidence and the committee's discussion are in evidence review N: risk-reducing surgery.

### Tests before risk-reducing surgery

1.8.15 Before carrying out risk-reducing bilateral salpingo-oophorectomy, perform a transvaginal ultrasound and a serum CA125 test to minimise the risk of missing asymptomatic ovarian cancer.

1.8.16 Before carrying out a risk-reducing hysterectomy, perform an endometrial biopsy to minimise the risk of missing asymptomatic endometrial cancer.

### Referral to the gynaecology oncology multidisciplinary team

1.8.17 If asymptomatic cancer is identified by preoperative investigation or postoperative histopathological or cytopathological analysis, refer the person to the gynaecology oncology multidisciplinary team (see the section on gynaecology oncology multidisciplinary team).

### During risk-reducing surgery

1.8.18 Carry out risk-reducing minimal access surgery, unless a laparotomy is more clinically appropriate.

1.8.19 Take peritoneal washings during risk-reducing surgery for cytological examination to test for the presence of malignant cells.

1.8.20 If any suspicious lesions are found outside the organs being removed, take a biopsy if it is feasible and safe to do.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on tests before risk-reducing surgery, referral to the gynaecology oncology multidisciplinary team, and what to consider during surgery.

Full details of the evidence and the committee's discussion are in evidence review N: risk-reducing surgery.

## 1.9 Pathology protocol for handling specimens from risk-reducing surgery

1.9.1 Submit all ovaries and fallopian tubes for histological examination using a SEE-FIM (Sectioning and Extensively Examining the FIMbriated End) protocol.

1.9.2 Carry out immunohistochemistry (p53 and Ki67/MIB1) only if a premalignant or malignant lesion is suspected on morphological examination.

1.9.3 Submit the adnexa in separate, appropriately labelled specimen containers so that the laterality is available to the pathologist. Include this information in the pathology report.

1.9.4 Always perform peritoneal cytology when carrying out risk-reducing surgery.

1.9.5 Submit the entire endometrium, including the lower uterine segment, for histological examination in risk-reducing hysterectomy specimens in people with Lynch syndrome.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on pathology protocol for handling specimens from risk-reducing surgery.

Full details of the evidence and the committee's discussion are in evidence review O: pathology protocol.

## 1.10 Hormone replacement therapy after risk-reducing surgery

These recommendations are for women, trans men and non-binary people who have had risk-reducing surgery on female reproductive organs.

1.10.1 Offer hormone replacement therapy (HRT) until the average age of menopause (usually around 51 years) for people who:

- have not had breast cancer **and**
- have had risk-reducing bilateral salpingo-oophorectomy before the average age of menopause.

1.10.2 Liaise with the person's breast cancer care team before offering HRT to people who:

- have had breast cancer **and**
- have had risk-reducing bilateral salpingo-oophorectomy.

1.10.3 When offering HRT to people in recommendation 1.10.1, offer:

- combined HRT to people who have a uterus **or**
- oestrogen-only HRT to people who do not have a uterus.

1.10.4 Offer vaginal oestrogen to people with genitourinary symptoms associated with menopause.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on hormone replacement therapy after risk-reducing surgery.

Full details of the evidence and the committee's discussion are in evidence review P: hormone replacement therapy after risk-reducing surgery.

## Terms used in this guideline

This section defines terms that have been used in a particular way for this guideline. For other definitions, see the NICE glossary and the Think Local, Act Personal Care and Support Jargon Buster.

### Bi-allelic

Of or relating to both alleles of a single gene (paternal and maternal).

### Bilateral salpingo-oophorectomy

A surgical procedure to remove both (bilateral) fallopian tubes (salpingectomy) and the ovaries (oophorectomy).

### Cascade testing

A systematic process to identify individuals within a family at risk of developing a hereditary condition. Cascade testing begins with finding a pathogenic or likely pathogenic variant through testing (such as multigene panel testing) in 1 family member, usually affected with the condition. Then, testing just for the specific family variant is extended to blood relatives. This process is repeated as more affected individuals or pathogenic variant carriers are identified.

### First-degree relative

Mother, father, daughter, son, sister, brother.

### Founder pathogenic variant

A genetic alteration observed with high frequency in a group that is or was geographically or culturally isolated, in which 1 or more of the ancestors was a carrier of the altered gene.

### Genetic testing

The study of a person's DNA in order to identify potentially disease-causing differences (pathogenic variants) or susceptibility to particular diseases or abnormalities.

### Intervening blood relative

A relative on the same side of the family who is more closely related to the family member with ovarian cancer than the person themselves.

### Mismatch repair genes

Cells that have variations (changes) in certain genes that are involved in correcting mistakes made when DNA is copied in a cell. Mismatch repair (MMR) deficient cells usually have many DNA alterations, which may lead to cancer.

### Pathogenic variant

A genetic alteration that increases a person’s susceptibility or predisposition to a certain disease or disorder. If someone has a pathogenic variant, they are sometimes known as a ‘carrier’. This is because they ‘carry’, and can pass on to their children, a pathogenic variant associated with a disease (or trait) that is inherited in an autosomal dominant, autosomal recessive manner, even though they do not show symptoms of that disease (or features of that trait). The likelihood of having the pathogenic variant is also known as their ‘carrier probability’.

# Recommendations for research

The guideline committee has made the following recommendations for research.

# Key recommendations for research

## 1 Interventions to support decision making

What is the effectiveness of psychological interventions to support decision making by people who meet the referral criteria for genetic testing?

For a short explanation of why the committee made this recommendation for research, see the rationale section on information and support about risk assessment and genetic testing in genetics services.

Full details of the evidence and the committee's discussion are in:

- evidence review A: information and support
- evidence review B: support interventions
- evidence review D: optimal methods of assessing probability
- evidence review F: carrier probability – any person.

## 2 Assessing a person's risk of having a pathogenic variant associated with familial ovarian cancer

What are the optimal tools to assess mutation carrier probability for a wider range of ovarian cancer susceptibility genes, not limited to BRCA1 and BRCA2?

For a short explanation of why the committee made this recommendation for research, see the rationale section on assessing the risk of having a pathogenic variant.

Full details of the evidence and the committee's discussion are in evidence review D: optimal methods of assessing probability.

## 3 Assessing the risk of developing ovarian cancer

What are the performance characteristics of tools or models to assess the absolute risk of developing ovarian cancer?

For a short explanation of why the committee made this recommendation for research, see the rationale section on assessing the risk of developing ovarian cancer.

Full details of the evidence and the committee's discussion are in evidence review E: optimal methods of assessing absolute risks.

## 4 Ovarian cancer surveillance

What are the long-term benefits and risks of ovarian cancer surveillance for people at increased risk of ovarian cancer?

For a short explanation of why the committee made this recommendation for research, see the rationale section on monitoring for people who choose to delay or not have risk-reducing surgery (ovarian cancer surveillance).

Full details of the evidence and the committee's discussion are in:

- evidence review K: benefits and risks of surveillance
- evidence review L: effectiveness of surveillance.

## 5 Hormone replacement therapy after risk-reducing surgery

What is the safety and efficacy of hormone replacement therapy (HRT) after risk-reducing salpingo-oophorectomy?

For a short explanation of why the committee made this recommendation for research, see the rationale section on HRT after risk-reducing surgery.

Full details of the evidence and the committee's discussion are in evidence review P: HRT after risk-reducing surgery.

# Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice or services.

## Organisation of services

Recommendations 1.1.1 to 1.1.8

### Why the committee made the recommendations

There was limited evidence, with a small number of studies and uncertainties about the effect size and the way the studies were conducted, so the committee based the recommendations on the evidence and their knowledge and experience.

#### Commissioners and service providers in all settings

The committee discussed their experience of variations in how people are referred from healthcare professionals, for example, whether people are referred first to specialist gynaecological services or directly to genetic specialist services. They decided to recommend direct referral to make services more efficient, together with ways of making the referral process smoother.

The committee discussed their experience of why people who may be at risk of having a pathogenic variant associated with ovarian cancer do not access services. People from under-represented and underserved groups may know that the guideline applies to them but may need more support to access services. This could include people who are physically disabled, people with neurodevelopmental conditions or a learning disability, people from Black, Asian and minority ethnic backgrounds, and people who are LGBTQ+. In addition, people may not realise that they may be at risk of having a pathogenic variant associated with ovarian cancer, for example, men, trans women and non-binary people with male reproductive organs. The committee agreed that these groups need encouragement to discuss referral to genetics services. The committee further noted that healthcare professionals are not always aware of these potential barriers and agreed that training and information would help raise awareness.

### Primary care services

The committee discussed that primary care has limited capacity to seek out potential index cases. However, if a family history is known (including family history from a population with increased risk), a person is known to be from an at-risk population or a person has ovarian cancer, GPs can refer people directly to genetics services. The committee also noted that information and support should be provided in primary care to enable people to make informed decisions.

### Genetics services

In the committee's experience, there is little variation in the responsibilities of genetics services because their services are specified by NHS England commissioning guidance for medical genetics services. The committee agreed to list the main responsibilities so that people know what to expect when they are being referred.

### Gynaecology oncology multidisciplinary team

Based on the evidence about the mainstreaming testing and counselling, which showed a general trend for services to run more efficiently and faster, the committee agreed that genetic counselling and testing of anyone with a histopathological diagnosis of epithelial ovarian cancer should be carried out by their gynaecology oncology multidisciplinary team.

### Familial ovarian cancer multidisciplinary team

Having a pathogenic variant or being above a threshold for testing leads to many decisions having to be made during the person's life, for example, in relation to fertility and risk-reducing surgery. The committee acknowledged that services run more effectively when roles and responsibilities are defined so that staff and people using the services know what to expect. They noted that the person's care would need to be coordinated because different services may become relevant to them at different points in their life (including providing information and support, and carrying out reviews). The committee decided that a multidisciplinary approach would facilitate this and that this should continue throughout the person's life. They discussed that the person would usually see the appropriate person relevant to their circumstances and would not usually see the entire team.

Based on their experience, the committee specified which expertise is essential for the familial ovarian cancer multidisciplinary team (core expertise that is always required) and what other services this multidisciplinary team would also need to have access to, such as menopause services.

### How the recommendations might affect services

The committee discussed that some of these services already exist but that there is variation in practice in how referral between them takes place and how they are set up.

The committee noted that broader eligibility criteria for genetic testing may result in more pressure on existing services, such as primary care. However, people are generally responsible for the completion of their family history questionnaires and specialist service referrals can be completed quickly online, which may help to mitigate some of the pressure on primary care services.

Not all trusts have dedicated familial ovarian cancer multidisciplinary teams, and there is variation in practice. The committee noted that similar teams already exist for breast cancer and have improved outcomes. Although the recommendations may incur initial set-up costs, this will be offset by improved outcomes. The recommendations will standardise service organisation. The committee also noted that, although access to specialists is essential and the overall care is coordinated by them, specialists do not need to be located in a single clinic, potentially mitigating the resource impact on services.

Return to recommendations

## Information and support

### Information and support about familial ovarian cancer in all settings

Recommendations 1.2.1 to 1.2.6 and table 1

#### Why the committee made the recommendations

The committee based their recommendations on qualitative evidence.

There was evidence that although people want information tailored to their individual situation, preferences and needs, this does not always happen. In addition, people want information at the most appropriate time, as well as several opportunities for discussions. There was also evidence that information about risks can be difficult to digest for people and varies according to each person's circumstances. There was evidence highlighting that people can feel overwhelmed by the volume and complexity of information and feel that it is not always sufficiently individualised. There was also evidence about the importance of involving families. The committee agreed the importance of providing sufficient information on an ongoing basis, tailored to the person's needs so that people can make informed choices.

The evidence showed that rather than receiving all information at once, which can be overwhelming, people appreciate having opportunities to review their decisions at key stages in the pathway. The committee noted that people would need to know how they can access services to make these discussions possible, and recommended providing opportunities to address this.

There was evidence that the considerable psychological impact is not always sufficiently addressed, so the committee recommended that healthcare professionals ask people about their emotional health and wellbeing at each appointment. This means that onward referral to genetic counselling or psychological services can be made if needed, for example, in situations where there is anxiety around testing or severe emotional distress.

There was evidence that many people believe that genetic risk only affects women and people with female reproductive organs. The committee agreed that this perpetuates a lack of clarity around the risk for men and people with male reproductive organs, and discussed the need to raise awareness about the risks.

Based on their knowledge and experience, and the equality impact assessment for this guideline, the committee highlighted that some groups may need additional support to access services, for example, by having online rather than in-person appointments.

To emphasise the need for standard information in all settings and the content of this information, the committee highlighted key information that should be given to people.

#### How the recommendations might affect practice

The committee agreed that it is current practice to provide information and support but noted that there is variation in when, what and how often it is provided. The recommendations should lead to greater consistency. Although this may take up additional time, it will allow people to better understand their risk and make informed choices. For example, appropriate information and support at the right time may mean a person choosing to have risk-reducing surgery, which will substantially reduce their cancer risk and associated healthcare costs. Also, existing processes to provide similar information and support to those at risk of familial breast cancer should help lessen the resource impact.

Return to recommendations

### Information and support about risk assessment and genetic testing in genetics services

Recommendations 1.2.7 to 1.2.11 and table 2

#### Why the committee made the recommendations

The committee based the recommendations on the evidence and their knowledge and experience. The committee discussed that informed choices can only be made with good information provision and agreed that information and support is needed when people come to genetics services, so summarised the information that should be provided as a minimum.

Evidence showed that, compared with usual care, genetic counselling is associated with a higher uptake of the options being considered and higher scores on a knowledge questionnaire about ovarian cancer risk (it could be inferred that better knowledge would lead to a higher-quality decision). The committee acknowledged that genetic counselling would not be needed by everyone but recommended it for people who meet the referral criteria for genetic testing.

Evidence comparing telephone with face-to-face genetic counselling showed no differences in outcomes apart from a higher uptake of options with face-to-face counselling. Economic evidence also showed telephone counselling to be a cost-effective option. The committee noted that the evidence was from 2014 and that online genetic counselling has become a lot more common since the COVID-19 pandemic. They agreed that online or face-to-face counselling should be offered. They also noted that certain factors may influence which option is most preferable. For example, face-to-face counselling may be more appropriate if an interpreter is needed, whereas online counselling may be more appropriate if family members in a different geographical location are attending the session.

The committee considered clinical and economic evidence that compared a group session in which a video was shown before individual genetic counselling sessions, with individual sessions alone. The committee noted that there were not many clinical differences but that there were cost savings associated with group sessions. The committee agreed that a group session before the individual session could be an option. Despite the potential cost savings, the committee did not want to be prescriptive about this because circumstances can vary widely (for example, level of risk, level of distress or other factors such as communication or language difficulties), which may mean that an individual session may be preferable for some people.

Using a decision aid alongside genetic counselling showed benefits compared with genetic counselling alone for some outcomes such as higher satisfaction with the support received and better decision quality. Adding a decision aid was also associated with a higher number of people taking up the option that was considered (which related to ovarian cancer screening). However, the evidence was not clear about the components used in the decision aid so the committee's recommendation reflected the uncertainty about whether a decision aid made up of different components would be equivalently effective. The committee noted general principles related to decision aids in the NICE guideline on shared decision making.

To emphasise the need for standard information about risk assessment and genetic testing in genetics services and the content of this information, the committee highlighted key information that should be given to people.

There was no evidence for any particular type of psychological intervention to support decision making and the committee therefore made a recommendation for research on the effectiveness of psychological interventions. However, the committee noted that making decisions related to cancer risk can be stressful and can cause some people considerable distress because it may impact their families' lives as well as their own, so psychological support could be beneficial.

**How the recommendations might affect practice**

Genetic counselling is current practice. However, the broader eligibility criteria for genetic testing may lead to an increased demand for these services, resulting in additional pressure on existing genetic services. Some of this pressure may be reduced by people choosing remote counselling or having group counselling sessions before individual genetic counselling.

The provision of group counselling varies in practice and there may be some implementation costs for services that do not already provide this. However, providing group counselling would result in shorter individual counselling sessions, thereby helping to alleviate some of the pressure on genetic services and potentially leading to cost savings over time. Remote counselling may be more efficient and it may, for example, enable more appointments to take place.

Patient decision aids (or aids that help the healthcare professional make decisions) are already used in some services but there is variation in practice. The recommendation would make decision aids more available in practice. Healthcare professionals already provide a range of approaches to support decision making so adapting this to the relevant decision context would not change current practice.

It is already current practice to refer someone who is distressed or has difficulties in reaching a decision, for psychological support. The recommendation may potentially increase referrals, but addressing such problems early on could result in significant benefits to patients and cost savings to the NHS. For example, a lack of psychological support may prevent engagement with care, delay genetic testing or risk-reducing surgery uptake.

The committee highlighted the limited availability of specialised psychological services in some regions, specifically those designed to deal with psychological issues arising due to genetic testing and risk management. They noted that all services should have referral pathways to psychological services so that people in psychological distress can receive the support they need. The committee also recognised that genetic counselling could help address certain psychological concerns and that some people may need only 1 consultation with a psychologist, thus mitigating the potential impact on psychological services.

Return to recommendations

## Information and support in specialist services if a person has a pathogenic variant or likely pathogenic variant

Recommendation 1.2.12 and table 3

### Why the committee made the recommendation

The committee based the recommendation on qualitative evidence and evidence about other specialist assessment or risk management services or strategies.

The evidence showed that people want information at the most appropriate time as well as several opportunities for discussions. An important time for this would be when the person knows that they have a pathogenic variant or likely pathogenic variant. The committee agreed the importance of providing sufficient information on an ongoing basis. They recommended that in specialist services, people should receive general as well as more specific information depending on their circumstances. They also agreed that people need to have information about their risk of cancer, surveillance and risk-reducing surgery. There was evidence that women are concerned about reproductive options and how having a pathogenic variant affects this. The committee therefore also agreed that people should have information about reproductive choices.

To emphasise the need for standard information in specialist services if a person has a pathogenic variant or likely pathogenic variant and the content of this information, the committee highlighted key information that should be given to people.

### How the recommendation might affect practice

The committee agreed that it is current practice to provide information and support, but noted that there is variation in when, what and how often it is provided. The recommendation should lead to greater consistency. Although this may take up additional time, it will allow people to better understand their risk and make informed choices. This will improve people's satisfaction with services and may reduce their risk of developing ovarian cancer and associated healthcare costs.

Return to recommendations

## Assessing the risk of having a pathogenic variant

Recommendations 1.3.1 to 1.3.3

### Why the committee made the recommendations

The committee based the recommendations on evidence as well as their knowledge and experience. The available evidence only focused on tools that identify people at risk of carrying a BRCA1 or BRCA2 pathogenic variant.

The committee agreed that healthcare professionals should refer all people to genetics services who meet the criteria for genetic testing to identify people at risk of having a pathogenic variant. They emphasised that this would not only include people coming forward for testing but also family members of people with a pathogenic variant who would be referred for cascade testing.

The committee noted that genetic tests are now commercially available (known as direct-to-consumer testing), and discussed what would happen if a person accesses NHS services and presents with a positive genetic test result. They agreed that not all laboratories produce accurate test results or prepare people for their test results. Therefore, positive test results for a pathogenic variant for which NHS testing is offered will need to be discussed with an NHS genetics service to decide if referral is needed. This is consistent with the joint guidance by the Royal College of GPs and the British Society for Genetic Medicine.

There was evidence that there are a number of tools with good performance statistics (sensitivity, specificity and area under the curve) to identify BRCA1 and

BRCA2 variants. The committee provided examples but did not want to be too prescriptive because further calculation methods could be developed.

Given the uncertainties about variants other than BRCA1 and BRCA2, and to address the gap in the evidence, the committee also made a recommendation for research on optimal tools to assess mutation carrier probability for a wider range of ovarian cancer susceptibility genes, not limited to BRCA1 and BRCA2.

### How the recommendations might affect practice and services

The committee noted that once criteria are met, it is current practice to arrange a referral to genetics services. The criteria have changed (see the rationale and impact sections for section 1.4) but the associated action in the current section would be standard practice.

Direct-to-consumer testing is becoming more popular. The recommendation will standardise practice and possibly reduce the burden on services having to manage unreliable test results. The committee agreed that there are significant NHS costs in confirming or refuting direct-to-consumer testing results and these are not warranted unless there are clinical indications for testing. By liaising with NHS genetic services, it can be ensured that only people at increased risk are referred. This is consistent with the joint guidance by the Royal College of GPs and the British Society for Genetic Medicine and should be current practice for most services.

Some tools are already being used but there is variation in practice. Where they are currently not used, introducing them will not incur a substantial cost and will lead to better identification and risk management.

Return to recommendations

## Criteria for genetic testing

### Family history of ovarian cancer

Recommendations 1.4.1 to 1.4.3 and table 4

### Why the committee made the recommendations

The committee based the thresholds for genetic testing on results from an economic model that had been specifically conducted, which showed variation in the cost effectiveness of panel genetic testing, where the thresholds differed according to the gender and age of the index cases.

The committee discussed that cascade testing of family members of people with a pathogenic variant is already current practice. It helps identify people who also have the same pathogenic variant so risks can be managed to help prevent cancer.

The committee discussed genetic testing for people with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer. They did not make any recommendations because people would be tested or cascade tested if they or a family member had any of the syndromes specified in the protocol.

They also decided not to make a research recommendation for this topic because these syndromes are very rare, so research would be unlikely or unfeasible to be carried out.

### How the recommendations might affect practice

Testing at a carrier risk below 10% is not current practice and the recommendations will make testing available to more people. This may require service providers to make arrangements for implementation. This could also increase the demand for support services such as psychological and menopause services. However, this will lead to more people being identified and taking up risk management, and is a cost-effective approach. Recommendations related to cascade testing are current practice.

Return to recommendations

## At-risk populations

Recommendation 1.4.4

### Why the committee made the recommendation

The committee considered clinical as well as economic evidence. The clinical evidence summarised the prevalence of pathogenic variants associated with ovarian cancer.

The evidence showed that the prevalence of BRCA1 and BRCA2 is higher in people from Ashkenazi Jewish family backgrounds (between 1.2% and 2.2%). The evidence also showed a higher prevalence of BRCA1 in Greenlandic people (between 1.1% and 11.64%).

Although the prevalence is lower in people from Sephardi Jewish family backgrounds compared with Ashkenazi Jewish backgrounds, there was economic evidence that population testing of Ashkenazi and Sephardi Jewish people was cost effective even if only 1 grandparent was from the family background.

The committee did not want to give a precise definition for the population, for example, by specifying a number of grandparents. They noted that the evidence did not always clearly define this, and that there could be variation in how much knowledge people have about their individual family history.

The committee agreed that the economic evidence supported population testing, even though the family background was the only criterion for genetic testing.

They also noted that this would not be full panel testing but only testing for the founder genetic variant, which would be cheaper.

### How the recommendation might affect practice

The committee discussed that population testing is not current practice, so there will be a resource impact. They noted that this may initially be difficult to implement because the whole of these populations will be invited for testing. This will become easier after the first wave because numbers would become naturally smaller. However, this could also increase the demand on existing services, including psychological and menopause support services. Implementing population testing will, however, identify more people who will participate in risk management, which is a cost-effective approach.

The committee noted that there are currently some pilot projects in the NHS (for example, the NHS Jewish BRCA testing programme as well as a published programme model: A collaborative genetic carrier screening model for the British Ashkenazi Jewish community), and linking up with these projects may make implementation easier because some of the pathways into the services would already be established.

Return to recommendations

## People with ovarian cancer

Recommendation 1.4.5

### Why the committee made the recommendation

The committee discussed the evidence that in people with ovarian cancer, the overall prevalence of BRCA1 and BRCA2 pathogenic variants is around 17%. When grouping by histological type of ovarian cancer, the highest prevalence of BRCA1 and BRCA2 pathogenic variants was around 22% in those with high-grade serous cancers. One study reported a prevalence of around 18% for pathogenic variants of BRCA1, BRCA2, RAD51C, RAD51D or BRIP1. There was also economic evidence that testing for pathogenic variants in people with ovarian cancer is cost effective. The committee agreed that this supports testing people with ovarian cancer to establish whether they carry a pathogenic variant. If a pathogenic variant is then identified, it will help not only manage the person's ongoing care but will also mean that family members can be tested for the pathogenic variant. Based on their expertise, the committee also recommended that people with other ovarian cancer histotypes associated with pathogenic variants should also be tested.

### How the recommendation might affect practice and services

The recommendation reflects current practice. There may be more people diagnosed with rarer non-epithelial ovarian cancers accessing genetic counselling and testing. However, these cancers are very rare and this recommendation is not expected to result in additional pressure on services.

Return to recommendations

## Gene panel testing

Recommendations 1.5.1 and 1.5.2

### Why the committee made the recommendations

Overall, the evidence showed that genes associated with an increased risk in ovarian cancer were consistent with the genes recommended by the UK national genomic test directory. Therefore, the committee agreed that BRCA1, BRCA2, MLH1, MSH2, MSH6, RAD51C, RAD51D, BRIP1 and PALB2 should be the genes tested for in panel testing. They noted that the national genomic test directory has different gene panels for different conditions that may increase the risk of ovarian cancer, such as Lynch syndrome, or a family history of breast as well as ovarian cancer. Because such panels would contain different pathogenic variants to test for, the committee recommended which gene panel to use in relation to each person's family or personal history.

### How the recommendations might affect practice and services

The committee noted that it is already standard practice to use the gene panels recommended by the UK national genomic test directory. However, the committee noted that the criteria for a gene test are quite different to those in this guideline and that this would lead to more people becoming eligible for gene testing. The committee agreed that although this would have a cost impact, it would improve outcomes because more people would be identified as having a pathogenic variant, and risk-reducing strategies as well as cascade testing can be planned.

Return to recommendations

## Assessing the risk of developing ovarian cancer

Recommendations 1.6.1 to 1.6.6

### Why the committee made the recommendations

There was only evidence identified for 1 tool to assess the absolute risk of ovarian cancer (CanRisk), so the committee used this evidence as well as their experience and knowledge. They noted that the methods for assessing both probability of having a pathogenic variant and the risk of developing ovarian cancer are related, and

stressed the need to take into account the recommendations in the section on assessing the risk of having a pathogenic variant (because someone with a high risk of having a pathogenic variant would therefore also have a higher likelihood of developing ovarian cancer).

The committee discussed the different services that may be involved in assessing someone's risk of developing ovarian cancer. Once an increased risk is established (see the section on criteria for genetic testing) and the person is under the care of genetics services or familial ovarian cancer multidisciplinary team, the service or team should offer to assess their risk of developing ovarian cancer. If it has already been established that the person has a pathogenic variant, the familial ovarian cancer multidisciplinary team would be responsible for the assessment.

The committee agreed that the evidence showed a reasonable level of accuracy for the CanRisk tool. It was also the only tool identified and they acknowledged that it would provide some framework for an assessment and so the committee decided to give this as an example of a tool to use. They acknowledged that CanRisk is used to assess the risk of developing breast and ovarian cancer, and that more specific tools to assess the risk of developing ovarian cancer may be developed.

To use tools such as CanRisk, it is important to have as much information as possible. However, with limited information, it should be explored with the person whether they know of any other potential risk factors that may increase their risk of ovarian cancer. Based on their experience, the committee discussed the factors that may not be accurately assessed by tools, so highlighted some of these for clinicians to take into account when assessing risk.

The committee agreed that communicating risk and numerical data can be a challenge, particularly in light of uncertainties around estimates. They also thought it would be helpful to present this information in a variety of ways to make it more understandable. The committee referred to the NICE guideline on shared decision making. They also referred to the NICE guideline on familial breast cancer for risk factors that increase both breast and ovarian cancer.

The committee also made a recommendation for research about tools or models to assess the absolute risk of developing ovarian cancer, to encourage further tools to be developed.

### How the recommendations might affect practice and services

It is standard practice to assess a person's risk of developing ovarian cancer. However, the way this is done varies, so the recommendations will improve efficiency and reduce variation.

Return to recommendations

## Primary preventive medicines

Recommendations 1.7.1 to 1.7.3

### Why the committee made the recommendations

#### Aspirin

The committee discussed that the evidence on aspirin did not show a protective effect in terms of ovarian cancer incidence, so did not recommend it for the general population of people at increased risk of ovarian cancer. However, they noted that there is existing NICE guidance on the use of aspirin to reduce the risk of colorectal cancer in people with Lynch syndrome. Because people with Lynch syndrome are included in the scope of this guideline, the committee felt it was important to link to the NICE guideline on colorectal cancer to ensure that they are aware of this recommendation.

#### Combined oral contraceptives

The committee agreed, based on their knowledge and experience, that oral contraceptives can be associated with a lower risk of ovarian cancer, but long-term use is associated with an increase in breast cancer. They therefore decided to only recommend oral contraceptives as a preventive medicine in particular circumstances: firstly, when the reduction in ovarian cancer risk (based on for example age, family history) may outweigh an increased breast cancer risk; and secondly, if risk-reducing surgery is not appropriate (for example, because of age and planned pregnancy).

The committee noted that oral contraception is commonly prescribed for birth control and can be prescribed for other purposes (for example, for polycystic ovary syndrome). In their experience, people are not always fully informed about the potential risks (increased risk of developing breast cancer) and benefits (reduced risk of developing ovarian cancer), which is necessary for informed decision making. There is existing guidance on how to discuss the risk of developing breast cancer for people using oral hormonal contraceptives in the NICE guideline on familial breast cancer.

### How the recommendations might affect practice

The committee discussed that the recommendations would not significantly change practice.

Return to recommendations

## Risk-reducing surgery

### Factors to take into account when considering risk-reducing surgery

Recommendations 1.8.1 to 1.8.5

#### Why the committee made the recommendations

The committee discussed general factors that need to be taken into account or discussed with the person when considering risk-reducing surgery. Risk-reducing surgery means that the person would become unable to become pregnant because their ovaries and fallopian tubes would be removed. The committee agreed that risk-reducing surgery should not be offered to people planning to conceive naturally because the incidence of ovarian cancer in people younger than 35 is relatively small. Based on the evidence, they also specified the criteria for offering risk-reducing surgery. These criteria could relate to people who have a pathogenic variant or those with a strong family history, and they noted that it is important to attempt to verify the family history if possible (by exploring testing with the person or their family).

The committee discussed the importance of supporting people to make informed decisions and agreed the information and support that people should receive.

The committee agreed that decisions around risk-reducing surgery can cause anxiety and stress. They discussed that the psychological impact of surgery should be taken into account in discussions with the person and that psychological support before surgery may be needed.

The committee also discussed information and support to aid decision making, particularly around menopause and managing symptoms for premenopausal people considering bilateral salpingo-oophorectomy.

The committee noted, based on their knowledge and experience, that decisions about risk-reducing surgery for people who are carriers of bi-allelic pathogenic variants in mismatch repair genes (for example, homozygous PMS2) are complex. However, they are also very rare so the committee agreed that a referral to a specialist multidisciplinary team would be needed for discussions about potential risk-reducing surgery.

#### How the recommendations might affect practice

The recommendations will reinforce common good practice and will lead to safer practice and better outcomes.

Return to recommendations

## Monitoring for people who choose to delay or not have risk-reducing surgery (ovarian cancer surveillance)

Recommendations 1.8.6 to 1.8.8

#### Why the committee made the recommendations

The recommendations are based on limited evidence of the effectiveness of monitoring (ovarian cancer surveillance) as well as how accurately the methods diagnose cancer. Not many studies were identified, and the available studies were limited in the applicability of the populations and the comparisons investigated.

The committee agreed that risk-reducing surgery is always superior to monitoring in relation to preventing cancer and therefore decided not to recommend monitoring because it could encourage people to delay or avoid risk-reducing surgery; the evidence supported this. The committee also discussed the evidence that monitoring

is associated with an earlier detection of cancer but also noted a lack of data on an associated survival benefit. However, the committee acknowledged that because people often have children later in life, they may delay or choose to not have risk-reducing surgery. The committee discussed, based on their expertise and the evidence, that the risk of ovarian cancer rises with age and incidence curves vary according to the pathogenic variant, and therefore suggested varying ages for onset of monitoring if surgery was delayed or declined.

They were also concerned about the risk of false-positive surveillance results so recommended the test with the best performance characteristics in relation to false-positive and false-negative rates. The evidence showed that serial 4-monthly CA125 longitudinal testing using an algorithm was the most accurate test for this. The committee acknowledged that an infrastructure needs to be in place, so recommended a centrally coordinated call and recall mechanism to implement this. They recommended that there should be a review at least once a year to explore the option of risk-reducing surgery.

The committee agreed that people should be made aware that monitoring is not an alternative to risk-reducing surgery and that risk-reducing surgery is the only way to reduce their risk of developing ovarian cancer. It should also be explained that monitoring would involve 4-monthly blood tests and that there is a possibility that a test result could be false. The committee decided that this information is needed to encourage people not to delay risk-reducing surgery indefinitely.

The committee also made a recommendation for research to obtain more evidence on the long-term benefits and risks of ovarian cancer surveillance.

**How the recommendations might affect practice**

The committee discussed that because monitoring would be a change to current practice, the infrastructure for services is not established. Implementing the recommendations may be a challenge and associated with a considerable resource impact. Implementation would take up clinical as well as administrative time, for example, screening invitations, appointments, cost of tests (the CA125 ROCA test is currently not available on the NHS), interpretation of tests and providing the outcomes of tests. Monitoring has been shown to detect ovarian cancer at an earlier

stage but it has not been shown to translate into a survival benefit. The committee also noted that the majority of people would be expected to opt for risk-reducing surgery; hence, only very few people would require monitoring, potentially mitigating some of the resource impact.

Return to recommendations

## Types of risk-reducing surgery and timing in relation to the person's specific pathogenic variant

Recommendations 1.8.9 to 1.8.14

### Why the committee made the recommendations

The committee discussed that decisions related to risk-reducing surgery for ovarian cancer have to take into account the NICE guideline on familial breast cancer because some of the genes associated with ovarian cancer would also increase the risk of breast cancer. So, considerations around risk-reducing mastectomy should be made in line with the NICE familial breast cancer guideline.

The committee discussed the evidence that bilateral salpingo-oophorectomy improves overall survival. They noted that most of the evidence came from studies with carriers of the BRCA1 or BRCA2 variants. Based on the evidence, they recommended bilateral salpingo-oophorectomy for people at increased risk of ovarian cancer with BRCA1 and BRCA2, and also RAD51C, RAD51D, BRIP1 or PALB2, which are also associated with an increased risk of ovarian cancer.

The MLH1, MSH2 or MSH6 pathogenic variants are associated with Lynch syndrome, which is associated with an increased risk of endometrial as well as ovarian cancer. Although there was no evidence identified related to different types of surgery within this specific group, the committee decided that total hysterectomy as well as bilateral salpingo-oophorectomy should be recommended to prevent both of these types of cancers. They noted that PMS2 is also associated with Lynch syndrome (and is therefore on the associated gene panel). PMS2 increases the risk of endometrial cancer alone rather than endometrial as well as ovarian cancer. They therefore did not add it to the table of risk-reducing surgery for people at risk of ovarian cancer.

The committee made separate recommendations related to the PMS2 pathogenic variant because of its link to Lynch syndrome. People with this pathogenic variant have an increased risk of endometrial cancer alone, but could have an increased risk of ovarian cancer if there is also a family history of ovarian cancer. They therefore considered it to be safe to only recommend total hysterectomy for people with a heterogenous PMS2 pathogenic variant unless there is also a family history of ovarian cancer when additional bilateral salpingo-oophorectomy could be considered.

The committee used their knowledge and experience to agree the minimum ages for risk-reducing surgery, and discussed that there could be exceptional circumstances when risk-reducing surgery could be considered earlier, based on an individualised assessment.

The committee acknowledged that an argument could be made for having salpingectomy first and then delayed oophorectomy, which would avoid a surgical menopause. They noted that some of the evidence related to this showed promise. However, the evidence had very short follow-up and therefore, the important outcomes such as overall survival and ovarian cancer incidence could not be measured.

The committee noted that MLH1, MSH2, MSH6 and PMS2 increase the risk of endometrial cancer, and therefore a hysterectomy is indicated only for carriers of these pathogenic variants. The committee recommended against hysterectomy for carriers of other pathogenic variants unless there would be other reasons for this to be done.

**How the recommendations might affect practice**

The committee discussed that risk-reducing surgery is already current practice but that the timing of when it is offered varies. There is currently also no specific consideration for the timing related to specific pathogenic variants other than BRCA1 and BRCA2 and the committee noted that the recommendations will standardise this. Also, the recommended ages for risk-reducing surgery correspond with increasing cancer incidence and offer the greatest potential for cancer reduction and associated healthcare cost savings.

The committee noted that broader eligibility criteria for genetic testing will lead to more people opting for risk-reducing surgery. This could put additional pressure on existing services. However, risk-reducing surgeries are generally less complex and require less extensive preoperative and postoperative care compared with ovarian cancer surgery. It would also save costs associated with other cancer treatment as well as save lives. Therefore, in the long term, risk-reducing surgery is likely to result in better outcomes for people and cost savings for services.

Return to recommendations

## Tests before risk-reducing surgery, referral to the gynaecology oncology multidisciplinary team, and what to consider during surgery

Recommendations 1.8.15 to 1.8.20

### Why the committee made the recommendations

#### Tests before risk-reducing surgery

The committee used their knowledge and experience to agree the tests that should be carried out before risk-reducing surgery to minimise the risk of missing asymptomatic ovarian or endometrial cancer.

#### Referral to the gynaecology oncology multidisciplinary team

There was evidence that risk-reducing surgery is effective and will identify asymptomatic cancer in some people undergoing risk-reducing surgery. Based on this evidence, the committee recommended that if this is identified before or after surgery, a referral should be made to the gynaecology oncology multidisciplinary team so that cancer treatment can be planned.

#### During risk-reducing surgery

Based on their knowledge and experience, the committee agreed that minimal access surgery is generally preferred over a laparotomy. They noted that some of the evidence included peritoneal washing, but the study included this in both arms of the comparison. It was therefore unclear whether this would be more effective than not using it. However, the committee recommended to take peritoneal washings to prevent missing cancerous cells that may have spread to the peritoneal cavity.

The committee noted that it is general good practice to investigate any lesions that are noticed during surgery even if they are found outside the organs that are being removed, to increase the likelihood of finding any asymptomatic cancers.

#### How the recommendations might affect practice

The recommendations reflect current practice and will reduce variation.

Return to recommendations

## Pathology protocol for handling specimens from risk-reducing surgery

Recommendations 1.9.1 to 1.9.5

### Why the committee made the recommendations

The committee agreed, based on their knowledge and experience, that people undergoing risk-reducing surgery are at increased risk of having an occult precancerous or malignant lesion, so intensive pathological investigation is needed. The committee discussed that pathology protocols for the detection of microscopic lesions found within the fallopian tubes have changed over time. The SEE-FIM (Sectioning and Extensively Examining the FIMbriated End) protocol entails multiple sagittal sections of fimbriae combined with 2 mm-thick sections of the remainder. The committee agreed, based on their knowledge and experience, that this type of sectioning is necessary to maximise the detection of precancerous lesions and early cancers.

The committee discussed that immunohistochemistry is a relatively inexpensive, yet informative, investigation that is available in all NHS pathology laboratories. Immunohistochemistry for p53 and ki67 helps in the identification of serous tubal intraepithelial carcinoma (STIC) and high-grade serous ovarian carcinomas. The committee agreed that investigations of these markers are only necessary if a premalignant or malignant lesion is suspected on morphological examination. They should not be performed in morphologically normal fallopian tubes because immunohistochemistry would not provide any additional information.

The committee agreed that to enable accurate reporting, surgical specimens need to be correctly labelled. It is not possible to determine the laterality of an adnexa once it has been removed from the body. Therefore, at the time of removal, surgeons should ensure adnexal specimens are submitted in 2 separate containers and labelled as originating from either the left or right adnexa. This will enable pathologists to issue accurate reports.

The committee also agreed that peritoneal cytology is needed to correctly stage any precancerous or cancerous lesions and detect occult peritoneal cancers.

The committee noted that people with Lynch syndrome are at increased risk of developing endometrial cancers. In Lynch syndrome, there is a propensity for endometrial cancers to arise within the lower uterine segment. The committee decided that the entire endometrium, including the lower uterine segment, should be submitted for pathological examination to ensure that such cancers and precancerous lesions are identified.

### How the recommendations might affect practice

There is already widespread use of the SEE-FIM protocol by pathologists in dealing with risk-reducing surgery specimens. Where this is not currently used, it will improve detection of occult precancers and cancers and therefore may lead to earlier treatment. Therefore, the recommendations will standardise the use of this pathology protocol.

Return to recommendations

## Hormone replacement therapy after risk-reducing surgery

Recommendations 1.10.1 to 1.10.4

### Why the committee made the recommendations

There was little evidence about hormone replacement therapy (HRT) after risk-reducing salpingo-oophorectomy. Studies were small and most had follow-up that was too short for some of the outcomes investigated, such as cardiovascular events for which the baseline risk is relatively low at a younger age. They also noted that the evidence showed that HRT is effective in decreasing vasomotor symptoms and

agreed that this is in line with the general literature on managing troublesome vasomotor symptoms. There was evidence that HRT is associated with fewer diagnoses of osteoporosis as well as higher bone mineral density. Despite the relatively small evidence base, this was consistent with the committee's experience and knowledge. They recommended that HRT should be offered to prevent loss of bone density and manage symptoms and, based on their knowledge and experience, decided that it should be offered until the average age of menopause (which is usually around 51 years).

The committee agreed that premenopausal women and people with female reproductive organs without a history of breast cancer should be offered HRT after risk-reducing surgery. They agreed that those with a history of certain types of breast cancer may sometimes be prescribed HRT after risk-reducing bilateral salpingo-oophorectomy, but that this should only be offered after advice from their breast cancer team. This is to ensure that HRT would not increase the risk of breast cancer recurrence given other potential risk factors (for example, oestrogen receptor-positive breast cancer).

The committee noted that oestrogen-only HRT is appropriate after a hysterectomy, whereas only combined preparations are appropriate for those with a uterus.

The committee were aware that genitourinary symptoms are effectively treated by vaginal oestrogen. This is consistent with the conclusions from the NICE guideline on menopause.

Because of the sparsity of evidence, the committee made a recommendation for research on the effectiveness and safety of HRT after risk-reducing surgery.

### How the recommendations might affect practice

The committee noted that these recommendations align with other NICE guidance and therefore should not change current practice.

Return to recommendations

# Context

Familial ovarian cancer affects people with female reproductive organs (ovaries, fallopian tubes and/or a uterus). Although in this guideline, the term ovarian cancer is used throughout, there is now evidence that most high-grade serous cancers (the most common type of ovarian cancer) arise from the distal fallopian tube from a precursor lesion referred to as serous tubal intraepithelial carcinoma (STIC).

In the UK, between 340,000 and 440,000 women, have a pathogenic variant associated with an increased risk of ovarian cancer. This includes pathogenic variants in BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2, MLH1, MSH2 and MSH6 genes. It is estimated that 15% to 20% of those with high-grade epithelial ovarian cancer also carry a pathogenic variant associated with increased risk of ovarian cancer.

Most of the people who carry a pathogenic variant for ovarian cancer do not have a family history suggestive of a genetic risk. This means many people have not sought testing for high-risk ovarian cancer pathogenic variants. Current best estimates are that only 3% of people with a pathogenic variant know that they are carriers. This proportion will increase with improved availability of genetic testing.

Most women and people with female reproductive organs who carry a pathogenic variant will not develop ovarian cancer. This guideline recommends how to assess the risk of having a pathogenic variant and the risk of developing ovarian cancer, what risk-reducing interventions should or should not be offered, and what information and support should be given.

# Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE topic page on cancer.

For details of the guideline committee, see the committee member list.