Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
AstraZeneca	Guideline	016	001 - 013	The draft guideline focusses almost exclusively on the identification of pathogenic variants in people who have a family history of ovarian cancer, or who come from a high-risk population, but who do not have a personal diagnosis of ovarian cancer. Specific recommendations for patients who have a personal diagnosis of ovarian cancer are covered in section 1.4.5; however this section is brief and omits several important considerations, including: There is no mention of the relationship between somatic and germline variants, and how this relates to the optimal sequencing of tumour and germline testing. It is critical that healthcare professionals are aware of the importance of tumour testing in patients with ovarian cancer, and the fact that if patients are referred solely for germline testing, detection of somatic variants can be missed. Identification of somatic variants informs patient eligibility for targeted treatments. The British Gynaecological society and British Association of Gynaecological Pathology published a consensus statement on this topic in 2021 (Sundar S et al. British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for germline and tumor testing for BRCA1/2 variants in ovarian cancer in the United Kingdom. Int J Gynecol Cancer. 2021 Feb;31(2):272-278). There is no comment on the interplay between the use	Thank you for your comment. This guideline is focused on assessment and management of risk. It is not addressing management of ovarian cancer and therefore does not include testing for the treatment of ovarian cancer. Somatic testing is relevant to the treatment of ovarian cancer (including the use of PARP inhibitors) but this is outside the remit of this guideline. Regarding the cited consensus statement publication, this did not meet any of the review protocol criteria. This type of study is not listed as being eligible for inclusion in any of the evidence reviews.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				of HRD (homologous recombination deficiency) and BRCA (BReast CAncer gene) testing. Most patients with high-grade advanced ovarian cancer are referred for HRD testing to establish their eligibility for targeted therapies. The results of a HRD test include somatic BRCA mutation status. Patients who are identified to have a somatic BRCA mutation via this route ought to be offered a follow-up germline BRCA test to establish if their mutation is familial, and to inform the need for cascade testing. Although section 1.4.5 of the draft guideline refers the reader to the separate NICE guideline on "ovarian cancer: recognition and initial management" for further information on the care of people with a personal diagnosis of ovarian cancer, neither of the points above are covered in that guideline either. Given that the final scope for this draft guideline on "Ovarian cancer: identifying and managing familial and genetic risk" specifically includes patients who have ovarian cancer and given that both points above can have a meaningful impact on the care offered to such patients and their families, AstraZeneca strongly recommend that they be included in the final guideline.	
Cancer Research UK	Guideline	013	012	Recommendation 1.3.3: It should be made clear that the risk tools examined in this consultation (evidence review D) predict the risk of BRCA1/2 mutations, and one questionnaire for Lynch Syndrome mutations. The risk tools cannot rule out the risk of a person having another mutation that increases risk of ovarian cancer.	Thank you for your comment. The committee concluded that the CanRisk tool would suit most people; however, the committee agreed it is not appropriate for everyone, such as those with Lynch genes. The committee emphasised that genetic services must be pragmatic in estimating these risks in

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					people who may be at risk of rarer ovarian cancers and choose the most suitable tool given a person's particular family history. However, the committee added to the criteria that are designed for the threshold used for testing that they should be based on 'specific clinical circumstances or a verified family history'.
Cancer Research UK	Guideline	013	012	Recommendation 1.3.3 suggests tools "such as Manchester scoring system, CanRisk (BOADICEA), BRCAPRO" should be used to assess a person's risk of having a pathogenic variant. The recommendations do not specify only these tests as the tests will develop, and others will become available, however, by not specifying it leaves this open to interpretation and use of other tests. Our concern would be that other risk calculators that are not reliable could be used (see comment 3). We recommend inclusion of a statement specifying what "demonstrated accuracy" means, i.e., "demonstrated accuracy of "X", in a prospective study of "X" size and population".	Thank you for your comment. The committee concluded that genetic services possess the necessary skills and expertise to choose a relevant tool for a particular person. The CanRisk tool would suit most people, but they also agreed that more research is need and made a research recommendation. Therefore they decided to not be prescriptive about this so as not to exclude any tools that are in development now or will be developed based on the research recommendation of the guideline. Recommendations do not go into the level of detail, such as study types, size of population and accuracy cut-offs. Cut-offs for low, medium and high accuracy are provided in Supplement 1 – Methods and cross-references to this supplement have been added to the relevant evidence reviews to signpost to these. However, the committee added to the criteria that are designed for the threshold used for testing that they should be based on 'specific clinical circumstances or a verified family history'.
Cancer Research UK	Guideline	013	012	We recommend that recommendation 1.3.3 includes a statement to select the risk assessment tool based on the specific clinical circumstances, as described in evidence review D, page 21.	Thank you for your comment. The wording 'specific clinical circumstances' has been added to this recommendation, as suggested.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Cancer Research UK	Guideline	017	011	Recommendation 1.6.3 says to "use a tool with demonstrated accuracy…(such as CanRisk)". However, only evidence for CanRisk was assessed, where there are still evidence gaps. It is important to be clear and specific about the risk factors that a tool needs to include as inputs for analysis, and what "demonstrated accuracy" actually means within recommendation 1.6.3 (see comment 10).	Thank you for your comment. The evidence review was about tools rather than individual risk factors, so it is not possible to list these. With regards to what constitutes demonstrated accuracy, the document 'supplement 1 – methods' outlines the thresholds for sensitivity and specificity (lower and upper), meaning that below the threshold a test was not considered to be accurate and above it was. Thresholds are also specified for other accuracy measures such as likelihood ratios and area under the curve to indicate what was considered a useful, moderately useful and not useful test for using these measures (see section on 'Assessing imprecision and importance in diagnostic reviews and prediction models'). Whilst the whole supplement was already referenced in the evidence report, a direct cross-reference to the evidence reviews where this is applicable (evidence reviews D, E and L) has been added to this section.
Cancer Research UK	Guideline	017	014	Recommendation 1.6.4 suggests that a tool that only accounts for a person's age and family history could be used. However, these tools were excluded from the evidence review (evidence review E). If tools including only a person's age and family history (and not pathogenic variant) can be used, the evidence for these should be evaluated. We recommend editing recommendation 1.6.4 to clarify whether a tool only accounting for a person's age and family history can be used or not.	Thank you for your comment. The wording 'their age and family history' has been removed to be consistent with the evidence which only included studies that incorporate information on pathogenic variants.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Cancer Research UK	Guideline	018	014	Recommendation 1.7.1 does not make it clear that aspirin is not recommended as a protective approach for ovarian cancer for people with Lynch Syndrome (as per the decision made in evidence review M, page 12).	Thank you for your comment. Not to use aspirin for the purpose of reducing risk of ovarian cancer has been added as suggested to improve the logical flow and provide advice to the healthcare professional.
Cancer Research UK	Guideline	021	019	Bullet point 5 of recommendation 1.8.6 should be clear that monitoring will involve 4-monthly blood tests that will be analysed with ROCA, as discussed in evidence review L, page 13 line 44.	Thank you for your comment. It has now been clarified that this would be analysed with an algorithm that takes account of patterns of CA125 levels over time. ROCA is currently the main algorithm doing this but there could be others in development so the committee did not want to be prescriptive about this.
Cancer Research UK	Guideline	022	006	The first bullet of recommendation 1.8.8 states "using an algorithm (for example, the Risk of Ovarian Cancer Algorithm [ROCA])". ROCA was the only algorithm examined in the relevant evidence file (evidence review L), and therefore, the statement should be clear that only ROCA should be used. Alternatively, if the aim is to leave this open to new algorithms that might be developed, we recommend inclusion of a statement stating that the algorithm used will need to have "demonstrated accuracy of "X" in prospective studies of "X" size and population".	Thank you for your comment. It has been added to this recommendation that it should be an algorithm with 'demonstrated accuracy'.
Cancer Research UK	Evidence review D	General	General	Not all risk tools have been evaluated in different demographic groups, and where they have, they show differing performance in different cohorts. Tools are now being developed for certain cohorts (such as the ARiCa tool in the Ang 2022 study). It should be made clear in the recommendations (1.3.3) that the risk tool should be chosen based on the demonstrated performance of the tool in the relevant demographic group.	Thank you for your response. The committee intentionally worded the recommendation to say 'a calculation method with demonstrated accuracy' to allow new tools to be used when they are being developed. It has also been added that tools should be selected based on specific clinical circumstances that are designed for the threshold used for testing. The study by Ang et al. 2022 Predicting the Likelihood of Carrying a BRCA1 or BRCA2 Mutation in Asian

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Patients With Breast Cancer is included in the review on the optimal methods of assessing the probability of having a pathogenic variant. The ARiCA tool was not included as an example in the recommendation because of the relatively small evidence base and the associated uncertainty. Although this means that the committee was less certain about this tool, they did not want to prohibit its use and to address this uncertainty they also made a research recommendation. This has now been made explicit in the 'The committee's discussion and interpretation of the evidence' section in the evidence report and the rationale has been updated accordingly.
Cancer Research UK	Evidence review D	018	010	The Finnish model is included in the summary of evidence (not all models are), but there are only 2 studies that include this test, the most recent is from 2007, and the other is retrospective (de la Hoya 2003, Parmigiani 2007). We therefore cannot determine the current performance of the Finnish model from these studies. The Finnish model is an example of where we cannot be sure of the accuracy of a test and therefore would have concerns about its use, particularly due to the vague nature of the proposed recommendation (1.3.3).	Thank you for your comment. The evidence showed that the Finnish model had a slightly poorer discrimination as compared to BOADICEA, BRCAPRO or Manchester Scoring System and, although it is mentioned in the summary of the evidence, it is not included in the recommendation as a specific example of demonstrated accuracy. Supplement 1 - methods describes what is classified as good accuracy and a cross-reference has now been added to this to the evidence review to make it clearer what would constitute 'demonstrated accuracy'.
Cancer Research UK	Evidence review D	General	General	Studies that evaluated previous versions of tests have been included in the evidence review. For example, the most recent version of BRCAPRO is 6.0, however there are studies included that date back to 2002 and use previous versions of the test for retrospective studies (e.g., Euhus 2022, Berry 2002). These studies	Thank you for your comment. The aim of this review was to gather all relevant evidence to help the committee to make a decision on the optimal methods of assessing the probability of having a pathogenic variant. Therefore, previous versions of tests are included in the review for completeness. In the

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				may not be representative of the current test's performance, and this should be kept in mind when making the decision to recommend a test.	recommendations the committee has focused on the models with the largest bodies of evidence, but left it flexible enough to allow for the use of other models that might suit the particular circumstances better, including newer versions of the included models.
Cancer Research UK	Evidence review E	General	General	The Lee (2022) paper on the CanRisk model is a 'partial validation' of the model. The validation did not include the more recent PRS and some common risk factors. Therefore, this model has not been validated fully.	Thank you for your comment. That is correct, the authors used a PRS with 15 variants rather than the more informative 36-variant PRS, and not all relevant risk factors were included. This information has been added to the evidence report in the quality of the evidence section. Only one tool that incorporates the risk factors specified by the committee in the review protocol was identified. Therefore, based on the above and the reasonable calibration of the tool, the committee decided to recommend this as an example tool.
Cancer Research UK	Evidence review E	General	General	Criteria for genetic testing in the guideline (1.4 Table 4) start from the age of 30. CanRisk has been partially validated using data for people aged 50 or over only. We recommend inclusion of a research recommendation to validate CanRisk fully (see comment 4), including in people aged 30 and over and in different demographic groups (those the model would be recommended for) to ensure equitable performance.	Thank you for your comment. There is a research recommendation associated with this review question and it focuses on the performance characteristics of tools or models assessing the absolute risk of ovarian cancer. The recommendation proposes to include women of any age who are at risk of ovarian cancer.
Cancer Research UK	Evidence review E	General	General	A RCT of the CanRisk model in the UK and US is underway (protocol outlined here https://www.mdpi.com/2072-6694/14/11/2716), that will study decision making based on risk scores, risk-management options, acceptability of the test and	Thank you for your comment. This was logged with the NICE surveillance team.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cost-effectiveness. This will be an important study to complement this consultation.	
Cancer Research UK	Evidence review E	006	026	Table 1 includes a list of factors linked to risk of ovarian cancer. Missing from this list is exposure to asbestos, which is linked to an increased risk of ovarian cancer (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230399/).	Thank you for your comment. Table 1 contains information based on qualitative evidence. Asbestos was not mentioned as a particular issue and did not come up in the evidence on what people felt they needed information on. The committee therefore did not comment on this.
Cancer Research UK	Evidence review E	008	001	Table 2 shows the single study included in evidence review E had a small number of participants, and the 95% CIs were not reported, making this low quality evidence to base recommendations on.	Thank you for your comment. The committee discussed the available evidence and noted it being of mainly low quality. Because this was the only tool and is also currently used for this purpose, they recommended the CanRisk tool as an example that could be considered in situations when it is already known that a person has a genetic pathogenic variant. A research recommendation was made and this may lead to further tools that could be used if they have demonstrated levels of accuracy. The 95% CIs were not reported for all outcomes, however it was reported for the AUC for discrimination between ovarian cancer cases and controls, as well as for E/O for predicted and observed cases of ovarian cancer over 5 years follow-up and for predicted and observed 5 years risk of ovarian cancer in lowest risk quintile. The quality of the evidence was downgraded due to the indirectness of the study population (the validation sample used in the study largely excluded women at high familial risk of ovarian cancer) and imprecision.
GENinCode Plc	Guideline	General	General	The interchangeable use of the words 'monitoring' and 'surveillance' is somewhat confusing.	Thank you for your comment. The wording has now been consistently changed to surveillance. This also

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				'Monitoring' has commonly used to evaluate progression/relapse in patients with ovarian cancer after first line treatment. Hence it is confusing to use it in this guideline. We support the use of the word 'surveillance' throughout. It might be helpful to define the word 'surveillance' in the list of Terms. There are 21 uses of the word 'monitoring' in the Guideline and we believe that 20 of them could sensibly be replaced with the word 'surveillance'. There is an additional use of the word 'monitoring' on page 6, line 12 and we believe its use here does not mean 'surveillance', but rather 'carrying out annual clinical reviews'	includes the word 'monitoring' on page 6 which was intentionally used in this context. This was to emphasise that surveillance should be the responsibility of the familial ovarian multidisciplinary team (review is also separately included in the bullet point).
GENinCode Plc	Guideline	General	General	**Additional Questions** The committee poses the following questions: Would it be challenging to implement of any of the draft recommendations? Please say why and for whom. Please include any suggestions that could help users overcome these challenges (for example, existing practical resources or national initiatives. Would implementation of any of the draft recommendations have significant cost implications? The ROCA Test is an algorithmic based test, using a standard CA125 blood result. It would be straight-forward and cost-effective to implement within the NHS by interfacing with existing technology e.g. NHS APP. GENinCode has developed the algorithm software to	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned. If the reference refers to Philpott et al. The avoiding late diagnosis of ovarian cancer (ALDO) project; a pilot national surveillance programme for women with pathogenic germline variants in BRCA1 and BRCA2, Journal of medical genetics, 60, 440-49, 2023, then it is included in the review on the benefits and risks of surveillance in the health economic section (evidence review K).

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				operate with an API, which enables a standard plug in model to be adopted. A centralised service was operated for the ALDO study (Philpott et al, 2022) and many of these operational procedures are capable of being re-instated easily as required.	
GENinCode Plc	Guideline	General	General	In describing the particular surveillance test being recommended by the guidance, the following terms are used: ' the CA125 ROCA Test, the Risk of Ovarian Cancer Algorithm [ROCA] In the interests of consistency, we would like to recommend use of the term "the ROCA Test' with the following definition (in bold) included in the section 'Terms used in this guideline' on page 27/28: The ROCA Test: A test that evaluates a combination of age, menopausal status and single or multiple serial measurements of CA 125 in serum specimens to assess a woman's risk of having ovarian or fallopian tube cancer. Throughout the literature, alternative terms are used to describe the ROCA Test, for example the risk of ovarian cancer algorithm, the CA125 ROCA. All can be considered synonymous with the ROCA Test.	Thank you for your comment. In the interest of consistency Risk of Ovarian Cancer Algorithm test (ROCA test) is used where it is first mentioned, and from then onwards use 'the ROCA test'. A definition in the 'Terms used in this guideline' section was not included because the ROCA test was only an example of such an algorithm. This is consistent with the sections related to assessment tools where some tools are given as examples.
GENinCode Plc	Guideline	021	019 - 021	We think it is confusing here to state… '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	Thank you for your comment. It has now been added that this would be analysed with an algorithm that takes account of patterns CA125 levels over time and a review at least once a year to discuss the recommendation of having risk-reducing surgery.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				to discuss having risk-reducing surgery'. It implies that the guideline is recommending repeat standard CA125 testing as the surveillance test, which it is not. We suggest the following alternative: 'surveillance will involve them having a blood test every 4 months, and a review at least once a year to discuss having risk-reducing surgery'.	
GENinCode Plc	Guideline	022	006 - 009	In the bullet:… 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 reviews with a call and recall mechanism. …the ROCA Test is given as an example of an algorithm that can analyse 4-monthly CA125 longitudinal data. In the supporting Evidence review L (page 14, line 23-24), the reasons given for giving the ROCA Test only as an example is because of 'other algorithms besides ROCA in use or in development'. The ROCA Test is an algorithmic test developed to UK regulatory standards and is clinically validated. We are not aware of any other such algorithms in clinical use for surveillance in high-risk women. This is supported	Thank you for your comment. The committee did not want to be prescriptive about the particular test because other algorithms could be developed. However, the committee acknowledged that the tests need to be suitable and appropriate and have therefore added that it should be an algorithm with 'demonstrated accuracy'. This is also consistent with other part of the guideline where tools with demonstrated accuracy are recommended and examples of such tools are provided. The study by Blyuss et al. 2018 was excluded from the review on benefits and risk of surveillance because the population did not match that specified in the review protocol, that is women with increased risk of familial ovarian cancer.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				by the Developer's assessment of the literature. None of the 13 included studies (Evidence review, page 8, Table 2) report on or support 'other algorithms' with evidence from prospective studies. We are aware of two other algorithms reported in the academic literature. These are referred to as MMT and PEB in the article published here (Comparison of Longitudinal CA125 Algorithms as a First-Line Screen for Ovarian Cancer in the General Population - PubMed (nih.gov)). However, this paper used a historic dataset (i.e. it does not report a prospective de novo evaluation of these algorithms, using a defined surveillance strategy); it was conducted in post-menopausal, normal risk women, not high risk BRCA carriers; and, there was no performance advantage of either MMT or PEB over the ROCA Test. Hence, we recommend the following wording of this bullet (see also comment 5 below): refer the person to the centrally coordinated service for 4-monthly surveillance using the ROCA Test. manage any necessary follow-on testing required for abnormal results.	
GENinCode Plc	Guideline	022	006 - 009	We find this bullet confusing. 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 reviews with a call and recall	Thank you for your comment. The committee reflected on this recommendation and made some changes to it. Recommendations 1.8.19 and 1.8.20 have been revised to (1) indicate who should be responsible for doing this because it would be impossible for primary care to be involved in this (2) to indicate more clearly

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				mechanism. If the ROCA Test is to be centrally-co-ordinated (which we agree with), then the familial ovarian cancer multidisciplinary team would only need to refer the person for that service. Results can be communicated back to the multidisciplinary team, allowing persons with any abnormal results to be managed accordingly. Hence, we recommend the following wording of this bullet (see also comment 4 above) refer the person to the centrally coordinated service for 4-monthly surveillance using the ROCA Test. manage any necessary follow-on testing required for abnormal results.	that this is a consideration and not a routine measure for all and (3) that this is not a central call and recall system but that it would need to be coordinated and audited so that its uptake and effectiveness can be assessed. Recommendation 1.8.20 has also been reworded to start with 'if surveillance is carried out...' to indicate that this is not necessarily being done for everyone. A centrally coordinated service would be equivalent to a national screening programme which is outside the remit of NICE and also the evidence it is based on was not considered strong enough to support such a programme. It was therefore agreed that this should be the responsibility of the familial ovarian cancer multidisciplinary team. There was no evidence related to the next steps following-on from abnormal test results, but the committee noted that further investigations after abnormal results is standard practice and would not have to be explicitly mentioned.
GENinCode Plc	Evidence review K	General	General	The word 'monitoring' is used 5 times in this review, compared to 'surveillance' which is used 319 times. We believe that all 5 instances of 'monitoring' could be replaced with 'surveillance'. The reasons for this are as stated in comment 1.	Thank you for your comment. The word 'monitoring' has been replaced with 'surveillance' as suggested (in this evidence review as well as in the guideline).
GENinCode Plc	Evidence review K	General	General	In describing the particular surveillance test being recommended by the guidance, the following terms are used: ROCA Test, ROCA: risk of ovarian cancer algorithm,	Thank you for your comment. References to this particular surveillance test have been replaced with 'the ROCA test', with the exception of the appendices, where the data has been extracted verbatim from the relevant studies. There were some variations to the test that were also retained.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				ROCA with CA125, ROCA: The Risk of Ovarian Cancer Algorithm, Risk of Ovarian Cancer Algorithm (ROCA Test), Risk of Ovarian Cancer Algorithm (ROCA®) test, the ROCA® test, ROCA, the CA-125 ROCA test, ROCA test, ROCA with CA125 measurements In the interests of consistency, we would like to recommend use of "the ROCA Test" with the following definition (in bold) included in the section 'Terms used in this guideline' on page 27/28: The ROCA Test: A test that evaluates a combination of age, menopausal status and single or multiple serial measurements of CA 125 in serum specimens to assess a woman's risk of having ovarian or fallopian tube cancer. Throughout the literature, alternative terms are used to describe the ROCA Test, e.g. the risk of ovarian	

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cancer algorithm, the CA125 ROCA. All can be considered synonymous with the ROCA Test.	
GENinCode Plc	Evidence Review K	017	045	'serious' should read 'serous'	Thank you for your comment. This has now been corrected.
GENinCode Plc	Evidence review L	General	General	The word 'monitoring' is used 2 times in this review, compared to 'surveillance' which is used 322 times. We believe that these two instances of 'monitoring' could be replaced with 'surveillance'. The reasons for this are as stated in comment 1.	Thank you for your comment. The word 'monitoring' has been replaced with 'surveillance' (in this evidence review as well as in the guideline).
GENinCode Plc	Evidence review L	General	General	In describing the particular surveillance test being recommended by the guidance, the following terms are used: ROCA Test, ROCA: risk of ovarian cancer algorithm, Risk of Ovarian Cancer Algorithm (ROCA), CA125 ROCA, ROCA, CA125 ROCA Test, ROCA test, ROCA (risk of ovarian cancer algorithm) In the interests of consistency, we would like to recommend use of "the ROCA Test" with the following	Thank you for your comment. References to this particular surveillance test have been replaced with 'the ROCA test', with the exception of the appendices, where the data has been extracted verbatim from the relevant studies. There were some variations to the test that were also retained.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				definition (in bold) included in the section 'Terms used in this guideline' on page 27/28: The ROCA Test: A test that evaluates a combination of age, menopausal status and single or multiple serial measurements of CA 125 in serum specimens to assess a woman's risk of having ovarian or fallopian tube cancer. Throughout the literature, alternative terms are used to describe the ROCA Test, e.g. the risk of ovarian cancer algorithm, the CA125 ROCA. All can be considered synonymous with the ROCA Test.	
GENinCode Plc	Evidence review L	011	022	CA124 should be CA125	Thank you for your comment. This has now been corrected.
Newcastle University	Evidence review M	007	020	Thank you for recognising the CAPP2 RCT. We did publish specific information on ovarian and endometrial cancers in the 2020 paper and in the 2011 paper (Burn et al Lancet 378(9809): 2081–2087. doi: 10.1016/S0140-6736(11)61049-0 interim 5 year analysis). In 2011 we reported that there had been 38 non-CRC Lynch related cancers including 18 cases of endometrial cancer, 13 of which were in the placebo arm. In the 2020 paper further details are to be found in the supplementary material. Supplement to: Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-	Thank you for your comment highlighting the details of this study. As reported in the evidence report in Table 8, Burn et al. 2011 Lancet and Burn et al. 2020 Lancet were excluded because the results were not reported separately for women.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				controlled trial. Lancet 2020; 395: 1855–63. Of the 861 participants in the aspirin limb of the trial, 476 (55.3%) were female. 199 of these (41.8%) were followed to the 20th anniversary. At 10 years follow up there had been 4 cases of ovarian cancer in the aspirin group and 3 in the placebo group. There had been 8 cases of endometrial cancer in the aspirin group and 17 in the placebo group -table S2 (p=0.08 unpublished). Figure S4 shows the Intention to Treat Graph with confidence intervals over 20 years (published p value 0.09). The effect of aspirin between 4 and 10 years mirrors that seen in the CRC cases, but numbers are too low to achieve significance. Our conclusion is that there is no evidence in CAPP2 that aspirin affects ovarian cancer based on very small numbers but that it is likely that aspirin reduces the burden of endometrial cancer	
Newcastle University	Evidence review M	013	009 - 013	We wish to support the proposed linkage to the DG151 recommendation published in 2020 of aspirin in Lynch as a preventive agent for CRC. As part of ongoing work to develop a national Lynch syndrome registry in England it appears that only around 30% of LS carriers are taking aspirin. This is, in part, due to dose uncertainty, which will hopefully be resolved by CaPP3 which reaches LPLV in 2024 and	Thank you for your comment highlighting that Lynch syndrome is not included as a off-label indication in the BNF monograph for aspirin, this has been fed back to the BNF.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				has involved 5 years of aspirin treatment at different doses among 1879 LS carriers. Nevertheless, the cumulative evidence supports commencement of aspirin and there is expert guidance, referenced in DG151, suggesting 150-300mg dose depending on body size as an interim. Unfortunately, a survey of GPs identifies the omission of aspirin use in Lynch syndrome from the British National Formulary as a barrier to use. It would be of great benefit to have the anti-cancer effects of aspirin recorded in the BNF as a basis for its use in those at highest risk.	
NHS England	Guideline	General	General	A general comment that we found this quite hard to read and believe it may be organised back to front: It would make sense to start with who is eligible for testing before going into responsibilities for genetic testing.	Thank you for your comment. A visual summary has been developed as a navigation aid for this guideline.
NHS England	Guideline	General	General	We strongly suggest the document makes reference to making reasonable adjustments. This is a legal requirement as stated in the Equality Act 2010. Adjustments aim to remove barriers, do things in a different way, or to provide something additional to enable a person to receive the assessment and treatment they need. Possible examples include allocating a clinician by gender, taking blood samples by thumb prick rather than needle, providing a quiet space to see the patient away from excess noise and activity.	Thank you for your comment. Making reasonable adjustments as required by the Equality Act is a statutory requirement and so this requirement would not need to be repeated in each individual NICE guideline.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We recommend including reference to the Reasonable Adjustment Digital Flag (RADF) and the RADF Information Standard which mandates all providers and commissioners of health services and publicly funded social care to identify, record, flag, share, meet and review Reasonable Adjustments, including details of their underlying conditions. DAPB4019: Reasonable Adjustment Digital Flag - NHS Digital	
NHS England	Guideline	General	General	We recommend including reference to the importance of Communication: Using simple, clear language, avoiding medical terms and 'jargon' wherever possible. Some people may be non-verbal and unable to describe verbally how they feel. Pictures may be a useful way of communicating with some people, but not all.	Thank you for your comment. We agree that people need to be communicated with in an appropriate way and given information in an appropriate format. Further detail on communication and treating people as individuals is covered in other NICE guidelines (which are cross referenced in recommendation 1.2.1) so this information is not repeated in all other NICE guidelines. In recommendation 1.2.1 the relevant sections in the linked guidelines have been specified. To further emphasise this, it was also already highlighted that information should be tailored to the person's needs for example, is in an accessible format (which could mean using pictures) or available in a different language.
NHS England	Guideline	General	General	Please note recent LeDeR research: kcl.ac.uk/ioppn/assets/fans-dept/leder-main-report-hyperlinked.pdf	Thank you for highlighting this. The committee noted that the annual LeDeR report relates to the lives and deaths of people with a learning disability in general, including deaths related to cancer in female reproductive organs. However, it does not reflect situations where there is a person at risk of having a

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					pathogenic variant. The report therefore does not specifically apply to this guideline.
NHS England	Guideline	004		Commissioners and service providers should ensure that appropriate training is provided for healthcare professionals to support genetic counselling of patients.	Thank you for your comment. The committee did not want to be prescriptive in terms of training required because this is outside the scope of this guideline and falls into the remit of the relevant professional training bodies. However, they felt strongly about health inequality and therefore recommended that '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...' (section 1.1).
NHS England	Guideline	005	007	Should this be "male or female reproductive organs)." since the dissociation of gender and birth biological reproductive organs may increase the risk of not coming forward for all.	Thank you for your comment. This is specifically related to people who cannot develop ovarian cancer and to raise awareness that these people could have a gene that if they pass it on could increase the risk of ovarian cancer. People not at risk of developing ovarian cancer may think that this guideline does not apply to them. Wording to the rationale has been added to clarify this.
NHS England	Guideline	005	009	Whilst appreciate the later comment about the need to be mindful of capacity in primary care, think that primary care services still have a valuable part to play in case-finding given that families disperse and lose contact. Perhaps "contributing to opportunistic case-finding"?	Thank you for your comment. The committee decided that whilst primary care can provide support to the person at risk of having or having a pathogenic variant, it is up to the person to inform their family rather than primary care.
NHS England	Guideline	005	009	It seems very likely that primary care will be responsible for longer term oversight of HRT prescribing following discharge from risk -reduction surgery.	Thank you for your comment. HRT prescription and oversight is a shared responsibility, as it is stated in Table 1 which refers to healthcare professionals in all settings. HRT prescribing in primary care following

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					discharge from hospital is routine practice. It has been added to section 1.10 that HRT should be started as soon as clinically appropriate after surgery which is likely to commence in hospital.
NHS England	Guideline	015	016	You highlight that Ashkenazi and Sephardi Jewish people are at risk, please can you add a footnote or other signpost to say 'People with Jewish ancestry are eligible for BRCA testing through the NHS England Jewish BRCA testing programme – www.nhsjewishbrcaprogramme.org.uk'	Thank you for your comment. The NHS England Jewish BRCA testing program is a pilot programme. Therefore, the committee could not include or refer to it in the recommendation at this stage. However, the recommendation's rationale in the guideline's supporting section titled 'Why the committee made the recommendation' refers to this. The related evidence review also cites this pilot (evidence review H).
NHS England	Guideline	015	018	If you are going to highlight Greenlanders as at specific risk, you should also include the Orkney Islands: https://www.genomicseducation.hee.nhs.uk/blog/distinctive-cancer-causing-variant-found-in-families-from-orkney/	Thank you for your comment. The risk of BRCA1 gene mutation in Orcadians living in the Northern Isles of Scotland, UK is based on a single study which found a prevalence of 0.96% [95% confidence interval of 0.59% to 1.48%], see the related evidence review H. This risk is substantially lower than the risks observed in other high-risk populations and is below the threshold for cost-effective genetic testing. Therefore, the committee has decided not to include this population in their recommendation at this point in time. Due to the fact that this has been reported in the media (as well as the highlighted HEE weblink), this explanation has been added to the 'other factors the committee took into account' section of evidence review H.
NHS England	Guideline	022	003	'Monitoring' for people who choose to delay or not have risk-reducing surgery (ovarian cancer surveillance) is 'low efficacy screening' by another name. We are uncertain how this will be organised and	Thank you for your comment. Recommendations 1.8.19 and 1.8.20 have been revised to (1) indicate who should be responsible for doing this because it would be impossible for primary care to be involved in

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				coordinated – the guideline and evidence section proposes a national call and recall system. This should not be in a guideline unless it is proven to be of benefit and/or there is resource for its implementation.	this (2) to indicate more clearly that this is a consideration and not a routine measure for all and (3) that this is not a central call and recall system but that it would need to be coordinated and audited so that its uptake and effectiveness can be assessed. Recommendation 1.8.20 has also been reworded to start with 'if surveillance is carried out...' to indicate that this is not necessarily being done for everyone. All of these revisions are making it clearer that this is not a national screening programme.
NHS England	Guideline	025	004, 019	We are not sure that there is any evidence of the benefit of taking peritoneal washings at risk reducing surgery: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4712515/#:~:text=The%20main%20reason%20for%20performing,primary%20peritoneal%20carcinoma%20(PPC).	Thank you for your response. The committee recommended strongly that peritoneal washings should be taken because not doing this could lead to missing cancerous cells, such as serous tubal intraepithelial carcinoma (STIC) which would affect staging and ongoing management. We have added text to the rationale to clarify this. The study by Block et al. 2016 was not included in the review because all participants had undergone risk reducing surgery and therefore no relevant comparative data was reported.
NHS England	Guideline	028	013	Confusing glossary definition. Perhaps should read 'Mismatch repair genes code for proteins that are involved in correcting mistakes made when DNA is copied in a cell. ……' or similar	Thank you for your comment. This has been revised as suggested.
NHS England	Guideline	040	012	This relies on a readily available advice and guidance pathway for (primary care) clinicians to access a genetics service, this may not currently be available in all areas.	Thank you for your comment. In recommendation 1.1.1 it states that commissioners and services providers 'should ensure that there are referral pathways to genetics services' which would include a way to contact such services. The committee are aware of the

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					challenges to such services (both geographic and related to infrastructure). NICE is developing resource impact tools and supporting information on the timelines of guidance implementation, acknowledging that this will need to be a gradual process. Geographical inequalities has also been added as an issue to the Equality Impact Assessment form to highlight that this is currently an issue.
NHS England	Guideline	041	018	There will need to be awareness of the change in threshold in primary care to support referral of those previously not considered for testing to be referred and also care taken in wider comms/media because of the risk of increasing demand on primary care access for those unsure whether they meet the criteria.	Thank you for your comment. The committee have included a new recommendation related to awareness raising.
NHS England	Guideline	049	012	Clear lines of responsibility are very important for such monitoring to avoid undue patient anxiety, risk and unnecessary workload for NHS services. Historically primary care has provided blood test monitoring for PSA, it will need to be clear to GP services, secondary/tertiary care services and patients that this is not the route for Ca125 monitoring and care taken so that pathology services do not route the results to General Practice.	Thank you for your comment. It has now been clarified that this would be the responsibility of the familial ovarian cancer multidisciplinary team and the rationale has been updated accordingly.
NHS England – Genomics Unit	Guideline	004	006 - 009	Across the breadth of the Guideline it should be clearly defined if the statement is referring to affected or unaffected patients or both. In most cases, only unaffected people that require genetic testing need to be referred to clinical genetics. Affected patients can be tested in the oncology specialty and this supports mainstreaming of genetic services.	Thank you for your comment. The 'gynaecology oncology services' has been added to recommendation 1.1.1 and have also referred to mainstreaming as one of the responsibilities of the gynaecology oncology services for people with invasive epithelial ovarian cancer. It has also been clarified that genetic counselling and genetic testing of those diagnosed with non-epithelial ovarian cancers in

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					recommendation 1.4.5 should be within the remit of genetic services. A visual summary has also been developed as a navigation aid for this guideline.
NHS England – Genomics Unit	Guideline	014	006 – 014	We would need to change the eligibility criteria in the National Genomic Test Directory (NGTD) for familial ovarian cancer testing to align with the criteria proposed in this guideline and in particular for unaffected people. The updates to the NGTD criteria would need to be approved by the Rare Disease Test Evaluation Working Group and it is not certain that the Test Evaluation Working Group would agree with all the changes being proposed in the NICE Guideline. This could lead to a disconnect between the NHSE NGTD criteria for genetic testing and the NICE Guidelines.	Thank you for your comment. The committee has reviewed the latest evidence on the effectiveness and cost-effectiveness of genetic testing including a bespoke economic model for this topic (see Evidence review F for full details). Based on this evidence, they have established the eligibility criteria for genetic testing. The lower thresholds are driven by a significant decrease in genetic testing costs and are in line with other recent research. The committee noted that currently, BRCA1/2 testing should be offered to individuals with a 10% probability of having the BRCA1/2 gene mutation. However, in the committee's experience, some centres already use lower thresholds due to decreased panel testing costs. The committee acknowledges that this may pose implementation challenges. The committee hopes that the criteria for genetic testing will be aligned across organisations to ensure optimal outcomes for individuals at risk of familial ovarian cancer. The lower thresholds mean that more people will have access to genetic testing services. Although there may be initial pressures and costs, there will be overall significant cost-savings to the NHS due to more people taking preventative measures and fewer people developing ovarian (or breast cancer), which requires expensive care.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS England – Genomics Unit	Guideline	014	006 – 014	NHS England Genomics Unit has concerns about the proposed criteria for genetic testing: The use of % thresholds, stratified by age, to determine the probability of having a pathogenic/likely pathogenic variant in unaffected individuals, and where there is no affected relative available for testing, will be difficult to implement clinically. In part due to limited models to assess these thresholds that apply to all the target genes and in part due to the complexity that will require specialist expertise and longer time for the individual clinical appointments. The current eligibility criteria in the NGTD for Familial Ovarian Cancer (R207) does not include testing for unaffected where there is no living affected or material from deceased proband to test first. The criteria for Inherited breast cancer and ovarian cancer (R208) includes testing for unaffected and requires that the unaffected has a first degree relative who was affected. The proposed criteria in the NICE Guideline states that for testing of unaffected individuals that that person has a relative who has had breast or ovarian cancer but does not specify if this needs to be a first degree relative. There needs to be consideration about how the change of the criteria for R207 impacts on the criteria for R208 to ensure there is equity and appropriate testing across these two Clinical Indications. The proposed criteria will introduce inequity in testing by favouring testing of unaffected with a family history	Thank you for your comment. Some changes were made to the recommendations based on your feedback. Specifically, the referral criteria have been simplified for GPs and made it easier for them to identify people who may benefit from genetic testing. Our committee believes that tertiary services have the necessary skills and expertise to calculate the probability percentage of having a pathogenic variant, which is done routinely. The committee understands that implementing these recommendations may require some changes in practice, but these recommendations are based on the systematic consideration of effectiveness and cost-effectiveness evidence. The committee also acknowledge that there may be some potential inequity due to different eligibility criteria in familial ovarian and familial breast cancer guidance, but the committee's remit was to provide recommendations specifically for familial ovarian cancer. Your comment has been passed to the NICE surveillance team for further consideration and there is a general update to the breast cancer guidelines underway. The wording of the recommendations in question was modified and also included an explicit reference to the NICE guidelines on familial breast cancer. Anyone with ovarian cancer (as per related recommendations in section for people with ovarian cancer) should be offered genetic testing. Therefore, it

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				over a person who is affected with no family history but higher prior risk of having a genetic variant in the breast cancer genes. The proposed criteria for ovarian cancer will also introduce inequity in testing unaffected people with other cancers e.g. prostate, by favouring those considered at risk of ovarian cancer and not those at risk of other cancer types.	is unclear how the proposed criteria would favour testing unaffected individuals with a family history of cancer over those who are affected by cancer. Lastly, it has been clarified that these thresholds are assessed by genetic / cancer services who would be responsible mainly for epithelial invasive ovarian cancers. Also, people at risk of pathogenic variants associated with other rare cancers would most likely come to services via other routes, and again our committee's remit was to provide recommendations specifically for familial ovarian cancer. However, your comment has been passed on to the NICE surveillance team for further consideration on the potential inequalities this may create and an update to the breast cancer guidelines is currently underway.
NHS England – Genomics Unit	Guideline	014	006 – 014	There needs to be consideration in how the criteria for genetic testing will be implemented as this will lead to increase in testing activity for unaffected individuals and increase in referrals to clinical genetics.	Thank you for your comment. The committee was aware of the implementation issues that may arise. The NICE resource impact team will develop costings for key recommendations to support implementation. NICE is also exploring providing more information on the timelines for implementation, acknowledging that these changes will take time and will be gradual. Although there may be initial pressures and costs, there will be overall significant cost-savings to the NHS due to more people taking preventative measures and fewer people developing ovarian (or breast cancer), which requires expensive care.
NHS England –	Guideline	015	010 - 018	Testing unaffected people with no family history but who are from one of the specified populations; Ashkenazi Jewish, Sephardi Jewish or Greenlander, is	Thank you for your comment. The committee did not intend for this to be recommending a national screening programme. It has been reworded to clarify

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Genomics Unit				targeted population screening. Implementation would need to be with the National Screening Committee and National Screening Programmes and not the genomics specialised commissioners.	that this recommendation aims to raise awareness and promote recognition rather than targeted population screening.
NHS England – Genomics Unit	Guideline	015	010 - 018	The NHS Jewish BRCA Testing Programme is on going and we suggest that the Guideline references this programme to access testing for unaffected people who are from the Ashkenazi and Sephardi Jewish populations.	Thank you for your comment. The NHS England Jewish BRCA testing program is a pilot project. Therefore, the committee could not include or refer to it in the recommendation at this stage. However, the recommendation's rationale in the guideline's supporting section titled 'Why the committee made the recommendation' refers to this. The related evidence review also refers to this pilot (evidence review H).
NHS England – Genomics Unit	Guideline	015	013 - 015	Agree that testing unaffected people who are from the populations defined (Ashkenazi Jewish, Sephardi Jewish or Greenlander) should be tested for the founder mutations only.	Thank you. The committee agree, and this is supported by these populations having substantially increased risk of having pathogenic variants and also cost-effectiveness evidence which indicates that founder mutation screening is more efficient and less costly.
NHS England – Genomics Unit	Guideline	016	014 - 020	The Guidance suggests that clinicians select the gene panel from the NGTD and decide the most appropriate panel based on the family's history, i.e. either R207, R208 or R210. The criteria differ for each Clinical Indication (Ovarian R207, Breast and ovarian R208 or Lynch R210) and there needs to be consideration how the change of the criteria for ovarian testing will impact on the criteria for breast & ovarian and Lynch to ensure there isn't inequity.	Thank you for your comment. The committee were aware that the criteria from the NGTD differ to those in the guideline and the challenges that this will pose. The criteria for testing are based on clinical and cost effectiveness evidence. NICE is developing resource impact tools and supporting information on the timeliness of guidance implementation, acknowledging that this will need to be a gradual process.
OUTpatients	Guideline	General	General	We recommend use of "gynaecological organs" as opposed to "female reproductive organs" as not all who have these organs will identify as female.	Thank you for your comment. The terminology 'female reproductive organs' is our house style. Our style guide is evidence based and the language used in our guidance is in line with that. When deciding on the

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					terminology 'female reproductive organs', we took into account feedback that this wording is clearer English and easier to understand for a lay audience than 'gynaecological'. We have clarified the wording by adding 'born with'. We constantly review our style guide and language we use, and your comments will form part of that.
OUTpatients	Guideline	General	General	Guideline & Evidence Review I We accept that this evidence review is could only be conducted for women due to the lack of available data for trans men and non-binary people but this perhaps would benefit form a caveat explaining why this was the only population that could be included.	Thank you for your comment. The committee agreed that the findings could be generalised to trans men and non-binary people with some or all of the following female reproductive organs: ovaries, fallopian tubes and/or a uterus. The evidence review was therefore renamed to refer to 'people with ovarian cancer' rather than restricting it to women.
OUTpatients	Guideline	014	013	Table 4 (Genetic Testing Criteria) lists the percentage risk above which people should be offered genetic counselling, by female and male. However, it is not clear whether this is by gender or birth assigned sex. We believe that this should be by birth assigned sex because of the organs involved and so would suggest titling this as: People assigned female at birth/People assigned male at birth We would suggest this above titling it by possession of female/male reproductive organs as people may have the same level of risk of the variant, regardless of whether they still possess those organs.	Thank you for your comment. This has been revised to list all the relevant groups in the column headings.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
OUTpatients	Guideline	016	001 - 003	"This recommendation is for women, trans men and non-binary people with some or 2 all of the following female reproductive organs: ovaries, fallopian tubes and/or a 3 uterus." Does this only apply if these organs are still in situ? As the level of risk to family remains even if they have been removed. So perhaps better to say 'if they have ever had any of the following organs' for clarity. As this phrasing is repeated elsewhere in the document, the same applies to these sections.	Thank you for your comment. This wording has been reviewed and revised to read 'This recommendation is for women, trans men and non-binary people born with any female reproductive organs (ovaries, fallopian tubes, uterus)'.
OUTpatients	Guideline	019	013	1.8 – Risk Reducing Surgery It is worth noting that that trans men and non-binary people assigned female at birth may undertake surgeries that are risk reducing as part of their gender affirming care. This requires acknowledgment with an additional bullet point, including the fact that if these people do not meet the other criteria, then this should be accessed through gender identity services, but also, that of they do meet the criteria, they should not have to wait unduly for their surgeries, and that surgical planning should be done in collaboration with gender-affirming services. This has been noted in UK Consensus Guidance and an additional publication here: https://www.nature.com/articles/s44276-023-00002-0 https://link.springer.com/article/10.1007/s40142-021-	Thank you for your response and for drawing our attention to these publications. The committee agree that people can consider having the surgery that is most suitable for them with respect to gender affirming care as long as that is the reason for undertaking the surgery. So, anyone who is high risk may have surgery at a younger age if that is appropriate and advised by the specialist for gender affirming care. That is the context for having the procedure at that time point and that stands independent of risk reduction for ovarian cancer. The rationale for earlier surgery cannot be risk reduction as the risk is not high enough to reduce at that point in time. So that cannot be the justification for this surgery. Trans men and non-binary people registered female at birth can follow the gender affirming guideline (that is referenced in the comment) in that context, but it cannot be the recommendation related to risk reducing surgery. The 'benefits and harms' section of evidence review N has been revised to clarify that this would therefore be outside the scope

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				00201-6 Some suggested wording should be as follows: "Trans men and non-binary people assigned female at birth may undertake surgeries as part of their gender-affirming care that are also risk-reducing, whether or not they meet the above criteria. Where the individual otherwise meets the criteria for risk reducing surgery, work alongside gender identity services and surgical providers to offer to provide timely surgery that is in line with the persons body goals." And "Consider risk-reducing surgery in people younger than the ages in recommendation 1.8.9 where that person wishes to undertake these procedures for the purposes of gender-affirming care".	of this guideline. The first reference (Giblin et al. 2023 UK recommendations for the management of transgender and gender-diverse patients with inherited cancer risks) is a consensus statement and these types of publications are not included in any evidence review on the basis of not matching any of the review criteria. The second reference (Coad et al. 2021 Considerations in Management for Trans and Gender Diverse Patients with Inherited Cancer Risk) is an overview about the best practice for supporting trans patients including tailored risk assessments and management recommendations and does not match any of the review protocols in this guideline.
OUTpatients	Guideline	024	015	Section 1.8.16 – An endometrial biopsy may not be acceptable to those who experience genital dysphoria. This should be noted in footnote.	Thank you for your comment. The committee were aware of evidence that 3% to 5% incidental cancer is detected by biopsy. Depending on the outcome of the biopsy ongoing management could also be different. They therefore considered this to be essential and did not add the footnote to prevent any confusion.
OUTpatients	Guideline	026	007	Section 1.10.1 - Standard HRT is unlikely to be acceptable to trans men and non-binary people but an additional subpoint here may be useful: "Trans men and non-binary people who are already accessing gender-affirming hormone therapy (GAHT)	Thank you for your comment. This topic relates to the use of HRT after risk reducing surgery which would lead to significant sudden loss of hormones from the ovaries. This is regardless of the gender identity of the person. The committee therefore agreed that the offer of HRT should apply to everyone and it is then up to

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				need not be offered HRT. Those not accessing GAHT should have appropriate specialist endocrine review within gender identity services to access appropriate bone protection, and any additional hormone therapy that is aligned with their body goals'.	the individual to decide whether this is the option that they want to take up.
OUTpatients	Guideline	029	001	Key Recommendations for Research We would suggest that the impact of familial ovarian cancer on trans men and non-binary people, and the experience of this population within genetics services be included as a topic further research. We would also recommend that the exploration of this in other minority populations is included.	Thank you for your comment. The committee agreed that there was a general lack of research in trans men and non-binary people. Whilst there was one topic related to information and support, we did not have a general review question about the impact of familial ovarian cancer so the committee could not add your suggested research recommendation. We had already documented in some of our research recommendations that the committee particularly welcomes more research in populations covered by the Equality Act 2010. It was checked that this was consistently done for all research recommendations and have specifically highlighted as examples trans and non-binary people (or specifically trans-men where the question applied to them) as well as people from different ethnic backgrounds.
Ovacome Ovarian Cancer Charity	Guideline	General	General	Comment from our members: "I thought the support and ongoing surveillance ideas were good and the commitment to ask about mental health at each appointment. But as we know this often doesn't happen in practice. I know they are very keen to get women to accept risk reducing surgery but child bearing is already such a high pressure subject for most young women that this needs to be handled sensitively.	Thank you for your comment. Whilst the committee included recommendations related to surveillance, they wanted to ensure that the message is clear that 'people should not view surveillance as an alternative to risk-reducing surgery'. This is because surveillance cannot stop cancer developing. So, the committee agrees that these discussions need to be balanced and handled sensitively. The committee thought it was important to raise

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				I applaud the focus on cluster communities such as Ashkenazi Jewish people and on those women who might struggle to access good information. They have focused on women with close relatives affected but I wonder if this may close down access for some, where a relative doesn't share their BRCA status or families with high numbers of OC diagnoses who haven't been tested?"	awareness about at-risk populations so that they can come forward for testing and they have revised the relevant recommendation to highlight this point. People with a family history with high numbers of OC diagnoses are not excluded from testing. There are legal issues about sharing genetic information so the committee could not comment on people who may not share their BRCA status with their families. However, the committee already recommended that people should be given 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 (see Table 2). This is aimed to support people to share this information.
Ovacome Ovarian Cancer Charity	Guideline	General	General	Comment from our members: "It is encouraging to see such a detailed and comprehensive review. […Regarding the] genetic counsellor consultation […] Provision of coaching pre sharing of this highly impactful information if preferable. This requires further recruitment and coordination of appointments. I would suggest booked a geneticist appointment alongside the blood draw as both take approximately 3 months. If the results show no cancer driver mutations the geneticist could be cancelled and the results related by the oncology clinician."	Thank you for your comment. Whilst the committee acknowledges the challenge of long waiting lists, it will be a matter for local implementation to decide how appointments should be organised.
Ovacome Ovarian	Guideline	General	General	Comment from our members: "If I had the knowledge of the breast cancer link to OC and had genetic testing offered in 2005 […]I would have surgery. It would have	Thank you for sharing this.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Cancer Charity				saved me all I have gone through and are still going through. At a very great savings for NHS/ government."	
Ovacome Ovarian Cancer Charity	Guideline	General	General	Comment from our members: Currently, the RMI in the guidelines only takes into account: CA125, ultrasound and menopause. No BRCA status, no family history and no symptoms. When referred to the local hospital Gynaecology Department with: an Ovarian Cyst, a BRCA2 mutation, family history of (aggressive) Ovarian Cancer, a slightly elevated CA125 level and pelvic pain. I scored less than half the required points on the RMI to initiate further investigations. Six months later from the first referral and only through the determination and great efforts of my GP (who did take into my account my BRCA2 status), I was finally seen at the Gynaecology Department and diagnosed with Stage 1b (aggressive) Ovarian Cancer. I was diagnosed with a BRCA2 mutation back in 2006 so it makes me very depressed to realise that in 2023 it still hasn't made it to the RMI.	Thank you for your comment and for sharing your experience. The Risk of Malignancy index is a tool related to ovarian cancer which is not specific to familial and genetic risk. It is therefore outside the remit of this guideline but is included in the NICE guideline for ovarian cancer: initial assessment and referral.
Ovarian Cancer Action	Guideline	General	General	Would it be challenging to implement of any of the draft recommendations? Please say why and for whom. Please include any suggestions that could help users overcome these challenges (for example, existing practical resources or national initiatives. Section 1.2: We agree with the detailed information specified that should be communicated to patients, the open-ended nature of referrals recommended and	Thank you for your comment. The committee reflected on section 1.2 particularly the information provision in all settings. It was decided to make this more suitable for primary care. The relevant sections of the cross-referred guidelines have been specified to make these clearer and references to information related to pathogenic variants were removed. Having to provide information related to relevant trials was also moved from Table 1 to Table 2. This will make it easier for this

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				ongoing support that is sorely needed. In terms of practicalities and challenges, we feel that this will be difficult to maintain in some parts of the country. We are concerned that there will be a postcode lottery in terms of the care available to patients, the waiting times, and the access to open referral appointments along their journey. The impact of waiting for information and the need for support along the process is clearly demonstrated multiple times in Evidence review A. Without addressing how this open support will work in practice equally across the country, our concern is that this anxiety will increase for some patients. Recommendation 1.2.10: Group genetic counselling sessions. We agree this may result in a better experience for patients. We have concern that this may be difficult for some centres to set up and run regularly. This may mean there are fewer opportunities for patients to attend and longer waits.	information to be provided and maintained. The committee were aware of the challenges genetic services face. NICE is developing resource impact tools and supporting information on the timeliness of guidance implementation, acknowledging that this will need to be a gradual process. In relation to group genetic counselling sessions, there was evidence that this is an effective and cost effective option. It could be argued that fewer resources would be taken up once this is implemented because it is more efficient than individual face-to-face sessions. Therefore, it may mean shorter rather than longer waiting times. However, the committee used the word 'consider' indicating that they may not be suitable for everyone and in every centre.
Ovarian Cancer Action	Guideline	General	General	Would implementation of any of the draft recommendations have significant cost implications? We believe that cost implications would include:- Section 1.4: Lowering the testing threshold would increase the numbers of people accessing genetic testing, certainly in the short term, and therefore increased resource needs for risk-reducing surgery and screening services. As mentioned in the evidence reviews, this will, over the long term, save money due to greater uptake of risk-reducing surgery and lower	Thank you for your comment. Both the threshold model for testing and the population testing were based on economic analyses. It is therefore the case that in the long run these strategies will save money because earlier identification will lead to fewer cases of cancer the treatment of which would be associated with significantly higher costs. However, the committee recognises the challenges that services face and added to the recommendation that family history should be verified and clarified that the population testing is not a national screening programme but a

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cancer incidence. However, in the short term this may produce a backlog, longer waits for initial appointments and adding to waiting lists for risk-reducing surgery. In some areas this impact will be greater than others. Our supporters tell us that waiting for appointments and surgery impacts their mental health during a time they are making difficult decisions. - Recommendation 1.4.4 (populations to test) This will increase costs and numbers of people in the system, at least in the short term. In the long term we acknowledge that it will be cost saving. However, the usual number of people coming through the system, plus the additional numbers due to threshold reduction, plus additional testing due to these populations, will in the short term cause a bottleneck that could impact all services and the mental health of those going through the process. -Recommendation 1.8.8 (Serial CA125 plus yearly review if not taking up Risk-reducing Bilateral Salpingo-oophorectomy (RRBSO))As acknowledged, this will increase costs and we question whether the infrastructure will cope with any significant number of women opting to delay risk-reducing surgery and choose surveillance, even in the short term. Even if these numbers are small, any delay in setting up an efficient system of testing and recall may also increase anxiety levels for patients and their family members.	matter of awareness raising so that a referral can be made if people from these populations have concerns. In relation to recommendation 1.4.4 the committee recognises that some services may experience an initial increase in demand in areas with a high concentration of high-risk populations (and associated longer waiting lists with a potential impact on levels of anxiety of people affected by this). These services will need help to meet the demand. However, the committee is taking a long-term view, as an increased uptake of preventative measures will ultimately lead to a significant reduction in cancer cases. This approach is supported by cost-effectiveness evidence from the UK. In relation to ovarian cancer surveillance recommendations 1.8.19 and 1.8.20 have been revised to (1) indicate who should be responsible for doing this because it would be impossible for primary care to be involved in this (2) to indicate more clearly that this is a consideration and not a routine measure for all and (3) that this is not a central call and recall system but that it would need to be coordinated and audited so that its uptake and effectiveness can be assessed. NICE is developing resource impact tools and supporting information on the timeliness of guidance implementation, acknowledging that this will need to be a gradual process.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Ovarian Cancer Action	Guideline	General	General	NICE Guidelines are aimed at healthcare professionals but also the public. Data tells us that around half of the UK population struggles to understand health information with around 7.1 million adults reading at, or below, the level of an average 9 year old (NIHR Evidence: Health information: are you getting your message across?; June 2022; doi: 10.3310/nihrevidence_51109). Although we acknowledge that this guideline is by nature extensive and complex, we would welcome additional efforts to make each section more accessible for the general public. E.g. flowcharts, visual explanations, diagrams and simplified versions. Comments from our community on how easily they understood the guidelines included: "The guideline is mostly for professionals so fair enough that I don't fully understand it." "There is a lot of technical language in here""There's just so many variants, it's hard to grasp how it will affect me""I was unable to read all of them as so long." Several comments related to presenting the information that the guideline contained in a clearer way for the individual. Suggestions for improvements include:"A questionnaire that asks you questions then sends you to the relevant part for you and your diagnosis" "A simplified version would be good for lay people (ie	Thank you for your comment and for the offer to work collaboratively in producing accessible versions of the guideline. To aid navigation of the document, a visual summary has been developed. When the guideline is published online there is also an 'information for the public' tab which provides information and resources for lay people. However, the guideline topic is related to familial and genetic risk which means that some of the language is inherently complex and some of the scientific concepts have been defined in the 'terms used in the guideline' section (hyperlinked to the relevant word or phrase).

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				basic FAQs with links to the Evidence Tables)" Ovarian Cancer Action are happy to work collaboratively with NICE in producing accessible versions of this guideline.	
Ovarian Cancer Action	Guideline	General	General	We appreciate and support the clarity in the wording around who this guideline, and each section, is relevant for in terms of gender and sex, and that this is discussed further in the Equality Impact Assessment. We have continuously raised awareness of the impact of hereditary cancer and genetic testing in men, trans women and non-binary people with male reproductive organs. Equally it is important to clarify, as you have done in the guideline, that anyone born with ovaries is at risk of ovarian cancer. Your wording makes both of these things clear. It is noted that no evidence was identified for trans people. We acknowledge the reference to training and information available for healthcare professionals to improve access to people who may not come forward due to not realising their risk. We would add to this training further to encourage understanding that the reasons people may not come forward may also have significant impacts on their experience through the life-long process of managing their risk of cancer.	Thank you for your comment in support of the inclusive language used in this guideline. The committee agree that awareness raising and training is very important. They have therefore added a recommendation stating that commissioners and service providers should raise awareness among healthcare professionals (particularly those in primary care) and the general public about which groups of people may be at risk of having a pathogenic variant.
Ovarian Cancer Action	Guideline	007	002	Section 1.2: We fully support that healthcare professionals should provide ongoing information and support relating to the topics specified. However, based on years of feedback from our supporters, we are aware that knowledge levels in primary care vary	Thank you for your comment. In light of stakeholder comments, section 1.1 of the guideline has been revised and the following recommendation has been added: '1.1.3 Commissioners and service providers should raise awareness among healthcare

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				significantly. This raises questions as to how effective this information and support will be. For example, we have been told multiple times of GPs reassuring patients that a family history of cancer on their father's side means they are not at risk, or that due to a BRCA gene fault they cannot prescribe them HRT post BSO. We would support additional training being provided in primary care.	professionals (particularly those in primary care) and the general public about which groups of people may be at risk of having a pathogenic variant.
Ovarian Cancer Action	Guideline	008	002	Recommendation 1.2.2: We appreciate the care that has gone into this entire section, particularly ensuring that information is in a format suitable for the person's needs. We do query that this requires either the person to have sufficient knowledge of their learning/ information needs as to make a specific request, or otherwise for the healthcare professional to spend additional time establishing how best to provide the information. While this may seem minor, we know every additional time requirement can add up and have a knock-on effect on services.	Thank you for your comment. It is critical that people receive the information in a format they understand and whilst this may require additional time it is essential in a shared decision making process. To make this easier, specific sections in the cross-referred NICE guidelines have been highlighted for easy access to such information (for example on communication needs). Part of this is a duty under the Equality Act 2010. The committee also thought that adapting information to the person's level of understanding is part of everyday clinical practice.
Ovarian Cancer Action	Guideline	008	010	Recommendation 1.2.3 We support the opportunity for patients to self-refer and initiate follow-ups (in line with the evidence review 1, p22 that information provision should be ongoing). In reality, however, the wait times for non-urgent referrals, alongside potentially further increased wait times due to more people coming through for genetic testing (due to the reduced threshold) may make this very difficult for patients. Patients will only request referral at a time of need, and therefore waiting several weeks or months to speak to a professional or ask questions may increase anxiety. In the meantime, they may turn to less reliable sources	Thank you for your comment. The committee are aware of the challenges that services face and potentially long waiting times. The recommendation related to self- and re-referral is about providing information rather than recommending when and why this should be done. This recommendation was based on qualitative evidence where people reported that they wanted more information related to this to improve the opportunities for discussions. There was no information about the provision or its effectiveness of regular information provision sessions

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				of information. It may be more efficient to have pre-planned group information sessions (not only before testing as discussed in 1.2.10) at regular intervals that are open to all relevant patients, but invitations specifically sent to patients at certain ages e.g. several years before minimum BSO age. This could include signposting to reliable organisations for information and support, plus would give opportunity for peer support and connection, which we are told by patients is invaluable. Additional referrals could still be open if required in between these. However, we appreciate that there are resource implications which would be a barrier in some areas so this would need consideration.	at key stages and therefore the committee did not directly comment on this. However, your suggestion relating to information sessions at key stages to provide opportunities for people at key stages will be considered by NICE where relevant support activity is being planned.
Ovarian Cancer Action	Guideline	010	005	Recommendation 1.2.7 Table 2We support the inclusion how important contacting relatives is, and discussing how to do so, as this has been communicated to us as a major source of concern and anxiety. At times this results in people not contacting relatives about their results, so support in this area is much needed.	Thank you for sharing this.
Ovarian Cancer Action	Guideline	010	013	Recommendation 1.2.9 We welcome the recommendation to consider the best format for appointments for patients as this will allow the patient to be more comfortable, and more able to access the support and information. This should be an option at all appointments (that don't require examination) and given as an option each on occasion as circumstances may change.	Thank you for your comment. It is a general recommendation that would apply to all appointments and is not restricted to new appointments.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Ovarian Cancer Action	Guideline	011	007	Recommendation 1.2.10 We query the cost and staffing practicalities of group counselling sessions. Although (as acknowledged) this may reduce the time needed for individual sessions, for some teams the workload may be prohibitive at set up. This may mean sessions have to happen less often, which in turn may mean a longer wait for patients which would cause concern. As such we support the concept, but it should not reduce capacity or accessibility of the service in exchange for this different option.	Thank you for your comment. There was robust randomised controlled trial and cost effectiveness evidence to support the proposition of group information sessions that the committee drew on for this recommendation. The committee also discussed that a group session would free up resources that would otherwise be taken up by individual sessions and other workload or resources. So, the committee decided that this would not reduce capacity or accessibility of the service but would potentially increase it.
Ovarian Cancer Action	Guideline	012	003	Recommendation 1.2.12 Table 3In the section on risk-reducing surgery, we would suggest making it very clear regarding the effectiveness of surveillance. We appreciate this is mentioned in more detail in 1.8.6, however people may not cross reference, so it would be useful to add an extra qualification here.	Thank you for your comment. To address this point the bullet point was reworded and a cross-reference to recommendation 1.8.18 was added for further information.
Ovarian Cancer Action	Guideline	012	003	Recommendation 1.2.12 Table 3Although impact on sexual intimacy is mentioned very briefly, we would welcome (based on feedback from our community) a link to support services and signposting to further information services regarding who to speak to about these issues.	Thank you for your comment. This section relates to topics of information only. Once published there will be an information for the public tab on the NICE website which will include links to the main support organisations. It is also described in recommendations 1.8.3 and 1.8.4 that psychological support should be considered and specialist menopause counselling should be offered before and after surgery.
Ovarian Cancer Action	Guideline	013	001	Section 1.3/ 1.4 We had multiple comments from our supporters questioning how a lay person or GP would know their probability of having a pathogenic variant. For example:	Thank you for your comment. The committee appreciate that some sections of this guideline may be complex, however GPs are not expected to calculate a person's risk and this has now been clarified in the organisation of services section. This responsibility falls within the remit of genetic services (as is

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				"What I could not see was the tool which will be used to assess inherited family risk. Not sure if I missed it/them but I could not see it in the list of evidence." "…no clarification on how the 2% chance is calculated/by whom or the route to get this assessed.""I think there needs to be total transparency on how the % is calculated." We can see that the calculation from genetics services onwards is explained, however it isn't clear for the layperson or primary care how this will done, or how to identify for themselves whether they reach the required threshold. 1.3.1 states that "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 (1.4)." We noted that Evidence review D, in reference to calculating a person's risk of carrying a pathogenic variant, states "referral to genetic services would be needed because of the complexities of the tools and related risk calculations, and the limited time available during primary care consultations". Recommendation 1.3.3 states that "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	highlighted in recommendation 1.3.3). Furthermore, in light of stakeholder comments, sections 1.3 and 1.4 of the guideline have been revised to clarify which service would be responsible for the recommendations. The committee also added a recommendation with clear referral criteria to genetic services. Thank you also for your offer to work jointly with NICE to develop a patient- focussed tool or to make a clearer guide on how to calculate this. This will be considered where relevant support activities are being planned.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				history that are designed for the threshold used for testing." What is needed is a simple way for the layperson and their GP to understand what family history qualifies them for the different probability levels in table 4. In some areas this may be provided to GPs as a guide on who to refer, but this may not be available universally, and isn't accessible for patients in this guideline. Ovarian Cancer Action have a patient- aimed risk-tool (that will be updated in line with the new guidelines) and would be happy to work jointly with NICE to develop a patient- focussed tool or to make a clearer guide on how to calculate this.	
Ovarian Cancer Action	Guideline	014	006	Section 1.4 Ovarian Cancer Action support the reduced testing threshold for the specified age/sex groups as this gives access to more people who can take action to reduce their risks of cancer. Our supporters agree: "I think it is important that more people are eligible for genetic testing as this improves life chances. This is especially the case since there is no reliable screening programme for OC." "This is really positive news and a step in the right direction." "I think this will be really good for the future of getting	Thank you for your comment. It is good to hear that this guidance will have a positive impact. Recommendations on eligibility criteria have been revised to make them more streamlined and accessible, for example for referral from primary care. An awareness campaign was beyond the scope of economic modelling. However, a new recommendation has been included that emphasises the importance of raising awareness among healthcare professionals and the general public about the groups of people who might be at risk of having a pathogenic variant. This could be achieved through various initiatives. It would be appreciated if stakeholders like yourselves would help publicise this guidance and eligibility criteria for referral to genetic services and testing, so all eligible people undergo testing.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				early diagnoses." "The more people tested the better in my opinion. If you know you have a faulty gene you can make the decision to take action at an earlier stage." We also received comments from people who wanted to have genetic testing but weren't able to access it, for whom these changes may make the difference: "I am an only child of an only child. My Mum died from Ovarian Cancer. I cannot access testing as I don't have 2 close family members with it. This seems very wrong. I don't fit a box, therefore I get refused. I would like to see testing be for everyone who has any family member with Ovarian Cancer." "I was previously denied genetic ovarian testing because only one female relative (my mum) had been diagnosed with, and died from, ovarian cancer. However, as I have no sisters, daughters or maternal (nor paternal) aunts, I felt that this was discriminatory. But if I'd had other female relatives, we would all have to wait until another one of us was diagnosed before we were eligible for testing. It seemed short sighted not to assess the risk earlier." We would welcome an awareness campaign to notify people who had previously tried to access genetic testing, and were not eligible, to let them know that	

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				they now may be. We would highlight that this should be factored into any economic modelling.	
Ovarian Cancer Action	Guideline	015	010	Recommendation 1.4.4We welcome the explicit mention of the populations that are eligible for genetic testing regardless of family history. We do have concerns about the increase in people coming through the system in the short term, which will impact services through the whole journey. We also would suggest some clarification on the description of the populations. While we acknowledge the explanation that the committee did not want to be too prescriptive due to lack of evidence, it would be useful to include a short explanation that "Jewish" does not imply observation of the religion but instead refers to heritage, and what that means. This may also be an issue in primary care where knowledge levels vary greatly. Perhaps an example would help both the public and clinicians here. It is mentioned in the rationale that these people will only be tested for founder mutations and not a full panel test, but it is vital that anyone who has this testing and receives a negative result understands that they could still carry a different variant. It is therefore important to still ask about family history from these groups, and they need to understand what to look out for in terms of family members' health that may indicate they should have a full panel test in the future.	Thank you for your comment. This recommendation has been revised and more details has been added on the eligibility criteria (having at least 1 grandparent from the respective populations) to ensure that it is easily understandable by both the public and healthcare professionals. The committee recognises that some services may experience an initial increase in demand in areas with a high concentration of high-risk populations, and these services may need help to meet the demand. However, the committee is taking a long-term view, as an increased uptake of preventative measures will ultimately lead to a significant reduction in cancer cases. This approach is supported by cost-effectiveness evidence from the UK. In the section on information and support about familial ovarian cancer, the committee has made several recommendations. Some of this focuses on family history and that the risk could change if family history changes. This includes information on the risk of inheriting a pathogenic variant associated with ovarian cancer for individuals from Ashkenazi Jewish, Sephardi Jewish, and Greenlander family backgrounds. The section also provides details on referral for genetic counselling and testing, which could include explaining that these individuals will only be

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					tested for founder mutations and the associated implications. Additionally, a reference has been included to other useful resources, such as ovarian cancer symptom awareness information that may be beneficial for people to recognise potential symptoms of the disease in their family members.
Ovarian Cancer Action	Guideline	016	005	Recommendation 1.4.5We are aware that currently not all of the people diagnosed with ovarian cancer who are eligible for genetic testing are offered it in this country. We would welcome an awareness campaign (in conjunction with Ovarian Cancer Action) to help inform both clinicians and patients of their eligibility.	Thank you for your comment. To strengthen issues around awareness the committee added a recommendation that commissioners and service providers should raise awareness among healthcare professionals and the general public about which groups of people may be at risk of having a pathogenic variant. NICE will also explore ways to raise awareness of this guidance and support the implementation. It is also hoped that stakeholders, such as yourself, would help disseminate this guidance and information about eligibility for genetic testing.
Ovarian Cancer Action	Guideline	016	005	Recommendation 1.4.5It would be helpful to provide clarification (or signposting) in the guideline regarding explanations of different types of ovarian cancer. One of our supporters said they would appreciate "Making it known that certain cancers in ovarian do not need tested for Braca Gene"Even people who have received a diagnosis of ovarian cancer often find the classification of their diagnosis confusing, and they may be unsure as to where their diagnosis fits in the sub-categories. Although this is second nature to clinicians, to the layperson it provides a layer of complexity that reduces accessibility and	Thank you for your comment. The terminology related to ovarian cancer is complex. However, it was beyond the scope of this guidance (risk assessment and risk management) to provide definitions for the different types and stages of ovarian cancer which is more of a management issue. We have made recommendations for information provision and included links to NICE advice on Ovarian cancer: recognition and initial management (CG122), which provides guidance on information provision and includes some information on classification of diagnosis and sub-categories. As suggested, a visual summary has been developed to

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				understanding. We would recommend presenting this visually and as simply as possible and would be happy to work with NICE to create this.	make them more accessible to both laypeople and healthcare professionals.
Ovarian Cancer Action	Guideline	016	005	Recommendation 1.4.5We had comments from our community questioning whether people with a diagnosis of mucinous ovarian cancer were eligible for genetic testing based on this guideline. The recommendation says "Offer genetic counselling and testing to anyone diagnosed with: • invasive epithelial ovarian cancer..." The rationale states: "The recommendation reflects current practice", but we are unclear as to how this isn't a change of practice. The Genomic Test Directory R207 specifies "High grade non mucinous epithelial ovarian cancer (EOC) at any age" or alternatively "Epithelial ovarian cancer (EOC) AND…" with specific family history requirements. The Lynch syndrome section of the directory (R210) qualifies Lynch-related cancer diagnoses (including EOC) testing eligibility with age of diagnosis or additional family history. As such, it appears that the Genomic Test Directory doesn't have provision to test all epithelial ovarian cancer currently. Although mucinous ovarian cancer is rare, representing only 2-3% of ovarian cancer cases, that equates to up to 220 people per year who may be trying to understand where sit in this guideline, and who currently do not qualify: "Was told [today] no need	Thank you for your comment. Mucinous ovarian cancer is a type of invasive epithelial cancer. The committee has recommended that all people diagnosed with any invasive epithelial ovarian cancer should undergo genetic testing, as the risk of pathogenic variants is high enough to justify this. Therefore, people with mucinous ovarian cancer would also be eligible for genetic testing. The committee has suggested that offering genetic testing to individuals with this type of invasive epithelial ovarian cancers is already a common practice. Specifying non-mucinous would disadvantage people with Lynch syndrome genes which would increase the risk of mucinous rather than non-mucinous epithelial ovarian cancer. However, in services where people with mucinous epithelial ovarian cancer are not currently being tested, it would represent a small change in practice due to the small number of people with mucinous ovarian cancer. The committee is aware that there are many other rare sub-types of ovarian cancer, and the Genomic Test Directory does not have a provision for testing all types of these cancers. However, the committee has noted that these rare types of ovarian cancer would be accessing services via other routes and most likely would have undergone whole genome testing. The committee has also made several recommendations on raising awareness among healthcare professionals

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				to be tested as mine was a mucinous ovarian cancer."If it is the case that mucinous ovarian cancer will qualify for testing, we urge NICE to create a plan to ensure clinicians across the country are aware of this and how to make sure no patients are missed. It would be helpful to make the distinction between different types of ovarian cancer clearer for the lay person.	and the general public,. NICE is exploring ways to raise awareness of this guidance and support its implementation. It is also hoped that stakeholder organisations will support us in publicising this guidance and eligibility for genetic testing. As suggested, a visual summary of this guidance was developed to make it more accessible to both laypeople and healthcare professionals. This section has been updated to explain that this is not common practice according to the current test criteria and an explanation was provided why the committee decided to change this as described above.
Ovarian Cancer Action	Guideline	020	007	Recommendation 1.8.3 Psychological support around the time of RRBSO is vital, and we appreciate this being included. However, we have concerns that the psychological support available varies greatly across the country. We know that some centres have excellent links and specialist support, others do not. This may result in a long wait for general mental health support, which may subsequently cause an increased wait to get on a surgical list for RRBSO.	Thank you for your comment. The committee were aware of the challenges these services face. However, it was considered unethical to not refer people who are in need of these services. Geographical inequalities have been added to the Equality Assessment Impact form. The committee discussed the issue of delay to wait for mental health services versus delay for risk reducing surgery and concluded that it would be difficult to prioritise one over the other or be prescriptive about timings. This would vary from individual to individual and is a complex weighing up of the risks to mental and physical health.
Ovarian Cancer Action	Guideline	020	011	Recommendation 1.8.4 We welcome the recommendation to offer specialist menopause counselling before and after RRBSO, however we are aware that not all areas of the country have NHS menopause clinics. We have many anecdotal examples of BRCA+ women being told	Thank you for your comment. The committee were aware of potential geographical inequity of services and has added this to the Equality Impact Assessment form. However, in the context of risk reducing surgery a referral could be made as soon as a person is considering this rather than as soon as the risk

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				factually incorrect information by GPs and gynaecologists (e.g. carrying a BRCA gene fault, even with no cancer diagnosis, means you cannot have HRT at all). Even in areas with specialist services, the wait times are already very long. The concern is that there will be inequity of service, longer waiting times and patients may end up delaying surgery, having surgery without the specialist advice, or resorting to unreliable sources of information such as social media to make their decisions.	increases to a level where risk reducing surgery is recommended. This does not have to be immediately before surgery. The aim of the guideline is to improve access to such services which means the implementation of new services where they are not currently available.
Ovarian Cancer Action	Guideline	021 - 021	006 - 019	Recommendation 1.8.6-1.8.8 We appreciate the careful thought that has gone into detailing the drawbacks of monitoring at the present time to ensure that patients do not actively consider this option as equal to RRBSO. We are concerned at the additional resource implication of the call/recall set up for monitoring. We appreciate this may not be a large number of patients but the system would need to be up and running without delay.	Thank you for your comment. In relation to ovarian cancer surveillance recommendations 1.8.19 and 1.8.20 have been revised to (1) indicate who should be responsible for doing this because it would be impossible for primary care to be involved in this (2) to indicate more clearly that this is a consideration and not a routine measure for all and (3) that this is not a central call and recall system but that it would need to be coordinated and audited so that its uptake and effectiveness can be assessed. NICE is developing resource impact tools and supporting information on the timelines of guidance implementation, acknowledging that this will need to be a gradual process so that services (including GP services) are not overwhelmed.
Ovarian Cancer Action	Guideline	026	004	Recommendation 1.10 HRT is a vast and important topic for patients in this situation. There are many questions and information needs, and one of our supporters commented that:	Thank you for your comment. It has been added to this section that HRT should be started as soon as clinically appropriate after surgery to emphasise this point. Information provision is covered in section 1.2 which includes information related to HRT. It is also recommended that people should be offered specialist

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				"The guidelines regarding access to / use of HRT post prophylactic surgery still aren't very clear. This is something that I have had to battle to have prescribed, resulting in buying privately. Clear guidelines for all GP surgeries would be so helpful for all women in this situation." However, we understand there is a new Menopause guideline due in 2024. It would be helpful to refer to this guideline for further information/ guidance about HRT.	menopause counselling before and after surgery so that any related questions can be discussed. The focus of this section was HRT after risk-reducing surgery. HRT as part of treatment for general menopause symptoms is outside the scope of the guideline.
Royal College of General Practitioners	Guideline	General	General	The use of the genomics testing directory (GTD) could be made easier if the weblink opens in the ovarian page rather than the front page of the GTD	Thank you for your comment. It is common practice to link to the landing page. This is because content may change or move around within a respective document.
Royal College of General Practitioners	Guideline	General	General	It is important to provide clarity on whether the online referral form is a national form or is it one that is locally produced.	Thank you for your comment. The recommendation gives the 'referral form' as an example of a facilitator for referral pathways to genetic services. The committee were therefore not prescriptive about whether this would be national or locally produced form.
Royal College of General Practitioners	Guideline	007	010	Rec 1.2.1 We are concerned that the suggested information and support to be given 'in all settings' in Table 1 is beyond the remit or knowledge of primary care. A GPs responsibility is to identify those who meet the threshold for a genetics clinic, refer, and signpost on to any sources of information. GPs are not going to be able to give more details about 'the risk of having a pathogenic variant associated with ovarian cancer from a person's family history' and 'details of any trials or	Thank you for your comment. The content of Table 1 has been reviewed and a few details that were considered more specialist (risk of pathogenic variant and details of any trial or studies that might be appropriate) have been removed or moved to another Table 2. It was agreed that the remaining information is very general and GPs should be able to provide this as part of the routine care of someone with concerns about familial ovarian cancer. There are now specific

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				studies that might be appropriate' – We believe that is the role of genetics clinics. Furthermore, this recommendation is challenging as it suggests that healthcare professionals in primary care should be giving advice about NG86 which is about the experience of social care. We believe this is not appropriate and should come from a SPLW or social worker, not a healthcare professional.	sections that have been added to each of the cross-referred guidelines. The link to the social care guideline is now to a particular section that covers enabling people to make decisions which includes a recommendation on communication which the committee considered to be useful in all settings by any healthcare professional.
Royal College of General Practitioners	Guideline	013	005	Rec 1.3.1 We uncertain about how applicable this is to primary care – It primarily focuses on who genetics services should offer testing to and testing based on percentage risks of cancer.	Thank you for your comment. A recommendation with simple referral criteria has now been included.
Royal College of General Practitioners	Guideline	013	008	Rec 1.3.2 This recommendation is challenging. It is important to clarify if the recommendation suggests that GPs should continue to use the referral criteria set out in CG164 (which is what is currently done). If so, it will be useful to replicate it in this guidance, or explicitly mention that GPs should be using it.	Thank you for your comment. A recommendation with simple referral criteria has now been included.
Royal College of General Practitioners	Guideline	013	012	Rec 1.3.3 We are concerned that this recommendation suggests using tools that GPs are not familiar with e.g CanRisk.	Thank you for your comment. The recommendation states that this should be the responsibility of 'genetic services' rather than primary care.
Target Ovarian Cancer	Guideline	General	General	We welcome the draft guideline, and the approach will help ensure that those with a familial risk of ovarian cancer are able to find this out and act in the information. There remains a lack of knowledge in the general public that ovarian cancer can be hereditary. There is not enough public awareness that a BRCA variation can lead to ovarian cancer as well as breast	Thank you for your comment. This is a new NICE guideline and as part of this one aim was to raise awareness. The guideline has been reviewed and 1 recommendation was added and another reworded to specifically emphasise raising awareness about who may be at risk (see the sections on organisation of services and at-risk populations).

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cancer and very limited awareness of other variations. If the guideline is to be effective consideration must be given to the public information need and how public awareness can be improved.	
Target Ovarian Cancer	Guideline	General	General	Primary care will be central to the successful role out of the guideline, so it is vital that GPs have access to education, information, and support to help them identify those that the need to be referred to genetic services. Target Ovarian Cancer's research has found that just 61 per cent of GPs are aware of aware that for ovarian cancer family history is relevant on both the father's and the mother's side. It is clear that there is an education need. Primary care is already under significant pressure and the rollout of wider access to testing means that information and support must be ready when the final guideline is published given there is likely to be a an large initial demand for referrals.	Thank you for your comment. The committee agreed that the consultation draft, did not outline the role of the GP in the referral process clearly enough. The draft was amended to include more detail on family history taking to clarify that this would mean both paternal and maternal family. A visual summary was also added to aid navigation of the guideline. NICE is also planning implementation support to facilitate uptake of some of the recommendations in the guideline.
Target Ovarian Cancer	Guideline	General	General	Preventive options for ovarian cancer remain limited and can have life altering affects for patients, there is a need for research into prevention options and this should be considered as part of the guideline.	Thank you for your comment. A research recommendation related to primary preventive medicines was added to encourage further work in this area (see evidence review M for details).
Target Ovarian Cancer	Guideline	011	007	Consideration should be given to the appropriateness of recommending information being given in a group in light of an individual circumstances/cultures	Thank you for your comment. There was robust randomised controlled trial and cost effectiveness evidence to support the proposition of group information sessions that the committee drew on for this recommendation. They agree that this may not

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					work for everyone so they decided that this could be considered as an option.
Target Ovarian Cancer	Guideline	013	012	Will there be one standardised calculation method agreed prior to publication of the final guideline and will primary care be expected to undertake the calculation before referral?	Thank you for your comment. The committee recommended that this is carried out in genetic services rather than primary care and agreed that healthcare professionals in these services possess the necessary skills and expertise to choose a relevant tool for a particular person. The CanRisk tool would suit most people, but they also agreed that more research is need and made a research recommendation. Therefore, they decided to not be prescriptive about this so as not to exclude any tools that are in development now or will be developed based on the research recommendation of the guideline.
Target Ovarian Cancer	Guideline	015	010	Specific information on the risks for these groups in needed.	Thank you for your comment. The recommendation has been revised to make eligibility criteria clearer (having at least 1 grandparent from the respective populations).However, the recommendation states that all individuals from at-risk population groups are eligible for genetic testing and counselling, therefore, specific information on risks for these groups is not relevant here. Nevertheless, further details on the risks is provided in the related section of the guideline titled 'Why the committee made the recommendation' and the evidence for this is systematically reviewed and discussed in evidence review H.
Target Ovarian Cancer	Guideline	026	004 - 020	The guideline is not clear on who should take primary responsibility for prescribing HRT or combined oral contraceptives. GPs may have the specialist knowledge required to prescribe in situations where a	Thank you for your comment. The committee revised the recommendation by adding 'start HRT as soon as clinically appropriate after surgery' which is likely to happen soon after surgery and therefore is prescribed

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				patient has a mutation and has undergone risk reducing surgery. Given that onset of menopause symptoms are likely to be immediate and aggressive, we would suggest that this should start in secondary care with guidance from a menopause specialist, and then perhaps transfer to the GP.	in secondary care first and then transferred to the GP. HRT prescribing in primary care is otherwise standard practice.
UK Cancer Genetics Group	Guideline	General	General	We have collated feedback from the UK Cancer genetics group and Cancer Genetics lead clinicians across the UK. The feedback in this document therefore represents the views of the UK Cancer Genetics Services. Our key messages are summarised here upfront: Concerns re: complexity of the eligibility criteria for genetic testing Time consuming and extensive resource required to make accurate age based assessments No current model which can allow you to calculate the risk figure in these guidelines. No available model assess the risk of a clinically actionable variant on the current tested gene panel (R207). CanRisk does not include MMR genes. Manchester score only assesses BRCA1/2. No one uses BRCAPRO. Issues which ensue when NICE guidelines deviate from the prescribed National Genomic Test Directory	Thank you for comment. With regards to complexity, the committee concluded that genetic services possess the necessary skills and expertise to calculate the probability percentage of having a pathogenic variant, which is done routinely using tools. Any tool used would require time and resources to calculate and some are more complex than others. Once calculated age and sex criteria can then be applied in accordance with Table 4 of the guideline. The CanRisk tool would suit most people; however, the committee agreed it is not appropriate for everyone, such as those with Lynch genes, and other tools can be used. The committee emphasised that genetic services must be pragmatic in estimating these risks in people who may be at risk of rarer ovarian cancers and choose the most suitable tool given a person's particular family history. However, the committee added to the criteria that are designed for the threshold used for testing that they should be based on 'specific clinical circumstances or a verified family history'. They have also made 2 recommendations for further research 1) about the optimal tools to use to assess mutation carrier probability and 2) about identifying the

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(and therefore the funding for NHS testing). The committee liaised with the Test Directory team prior to guidelines and the suggested eligibility is very different to current practice. Inequity of test eligibility criteria compared to other tumour types for both cancer patients and unaffected patients (e.g. breast cancer patients or unaffected relatives of breast cancer patients). Possible confusion about the most appropriate panel to test given inequity across related TD eligibility criteria (e.g. R208). It is possible cancer patient's ineligible for diagnostic testing for their own tumour type may still meet 2% criteria for unaffected ovarian cancer testing e.g. 41 ER+ve breast cancer patient, with no family history does not meet current R208 criteria as ~7.5% mutation likelihood but now would meet unaffected ovarian cancer testing criteria as >2%. Guidance to exclude breast cancer patients from testing when they are at equivalent risk to their unaffected relative could be deemed discriminatory. The population testing of founder populations and the subsequent resource implications. Founder screening would require entirely new laboratory processes to current with impact on laboratory resourcing. Who would deliver this testing? Population testing falls outside of the remit of clinical genetics services	performance characteristics of tools or models to assess the absolute risk of developing ovarian cancer The committee recognised the pressure that genetic services might face due to changes in eligibility criteria. Adjustments were made to recommendations on referral and verification of family history, which could alleviate some of the pressure on genetic services. The committee acknowledged that the criteria are different to the current criteria prescribed by the National Genomic Test Directory. However, the thresholds for testing were based on a bespoke economic model which provided robust evidence for these (see Evidence review F for full details). The committee concluded that once implemented this would be a cost saving strategy because earlier identification could prevent cancer. The NICE guideline on familial breast cancer has stipulated a higher threshold for testing because the economic model this is based on is not up-to-date. The breast cancer guidelines are in the process of being updated and 'genetic testing for people with early and locally advanced breast cancer' is one of the topics that is planned to be updated. However the timeline for updating this topic is not yet known. The ovarian guideline has been revised to ensure that people with breast cancer are not excluded as it currently looked like in section 1.4 and a cross-reference is made to the familial breast cancer guideline to signpost that people

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				For the monitoring of patients with US/ca125, there were concerns raised about inadequate systems for implementation and recall, the potential for clinical harm through delayed risk reducing surgery and the lack of resource to implement given the ages suggested would allow for monitoring of all eligible carriers 5 years prior to the age of expected risk reducing surgery. The lack of nuance for pre-menopausal women with the lack of 5 to 10 year OC risk estimates to enable them to balance short term OC risk against the risks of premature menopause. There needs to be some acknowledgement that despite lack of perfect data, discussion about age specific risks for premenopausal women with respect to absolute cancer risk before age 50 is vital for informed decision making about the benefits/risks of early surgical menopause, particularly for women with moderate risk gene/risk due to family history. The current regional inequities in access and ability to provide a familial multi-disciplinary team with the required specialised input (menopause services, psychological services etc)	with familial breast cancer would be assessed and risk managed as specified in that guideline. The committee highlighted that people from some populations should be offered testing. They highlighted that awareness should be raised and it should be recognised that people from at-risk populations have a higher probability of having a pathogenic variant and that if they do have concerns and seek healthcare advice, they should be offered referral for genetic testing. This was based on long-term RCT data and an economic model and in line with this model the guideline has also been revised to include a definition of the population (having at least 1 grandparent) to make this clearer. The committee was not anticipating this to be population testing. To make that explicit, it was clarified in the wording that the focus is on recognising and raising awareness only, so that people from high-risk populations will have to seek out access to genetic testing themselves. This would then fall into the remit of genetic services. The committee decided that founder pathogenic variant testing would be a simpler and less costly option which they agreed should fall into the remit of genetic services. This would require new lab processes and result in resource impact. The committee recognises that some services may experience an initial increase in demand in areas with a high concentration of high-risk populations, and these services may need help to meet the demand.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					However, the committee is taking a long-term view, as an increased uptake of preventative measures will ultimately lead to a significant reduction in cancer cases. This approach is supported by cost-effectiveness evidence from the UK. In relation to ovarian cancer surveillance using longitudinal CA125 testing using an algorithm, recommendations 1.8.19 and 1.8.20 have been revised to (1) indicate who should be responsible for doing this because it would be impossible for primary care to be involved in this (2) to indicate more clearly that this is a consideration and not a routine measure for all and (3) that this is not a national central call and recall system but that it would need to be locally coordinated, audited and interpreted by the familial ovarian cancer multidisciplinary team so that its uptake and effectiveness can be assessed. The committee disagreed that there was a lack of nuance for pre-menopausal women. There is no data available on the 5 and 10 year Ovarian cancer risk estimates in relation to the impact on risk reducing surgery. The threshold figures of 4% and 5% lifetime risk for premenopausal versus postmenopausal women in the recommendation is evidence based but the committee recognised that different thresholds for pre and post menopausal women may lead to confusion and unintended consequences. They have therefore standardised this to 5% overall. There is a section in Table 3 of the guideline related to what

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					information should be given and it has also been stipulated that specialist menopause counselling should be offered before and after surgery. The committee agreed that there should be discussions with people who have not been through the menopause about balancing the risks associated with a younger age of menopause and the benefits of risk-reducing surgery. All these discussions would allow the women to balance the benefits of risk-reducing surgery with the potential risks associated with early menopause. Whilst there is geographical variation in the provision of familial ovarian cancer multidisciplinary teams, the committee agreed that where they exist they provide the most appropriate care and make the pathway between services more efficient (which is also apparent in the new the visual summary). The committee acknowledged that the recommendations may incur initial set-up costs. However, these are unlikely to be significant and improved outcomes will offset these. 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, i.e. these meetings can be virtual/remote. NICE is developing resource impact tools and supporting information on the timeliness of guidance

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					implementation, acknowledging that this will need to be a gradual process. This is also aimed at reducing geographical inequities which has also been highlighted as an issue in the Equality Impact Assessment form.
UK Cancer Genetics Group	Guideline	General	General	There is no mention in this document of the importance of verification of reported diagnoses. We know that a significant number of patient reported ovarian cancers in relatives are not confirmed as ovarian cancer and may be misreported when they are endometrial or cervical. Without clear guidance on confirming family history the risk calculations will be incorrect which could have serious consequences for both irreversible surgery and unnecessary demand on services. Please can a comment be inserted that for accurate risk assessment, accurate input information is vital which may require cancer confirmations via the Cancer Registry or other medical document.	Thank you for your comment. The draft has been amended to include that this should be a verified family history. It has also been added that this could be through confirmation via the Cancer Registry or other medical document as examples of verifications in the rationale section.
UK Cancer Genetics Group	Guideline	General	General	Will you produce a 1-2 page short summary of this complex guidance for ease of medical professionals?	Thank you for your comment. A visual summary has been developed as a navigation aid for this guideline.
UK Cancer Genetics Group	Guideline	General	General	The use of specific age related risk calculations for eligibility for germline genetic testing can only really be performed by the CanRisk software. And CanRisk software cannot currently give the information required to check eligibility as it does not include MMR genes, and also would require specific exclusion of breast cancer only genes (i.e. CHEK2). Clinical genetics services express that the implications of ubiquitous CanRisk use for services who do not have digital data	Thank you for your comment. The committee concluded that genetic services possess the necessary skills and expertise to calculate the probability percentage of having a pathogenic variant, which is done routinely. The CanRisk tool would suit most people; however, the committee agreed it is not appropriate for everyone, such as those with Lynch genes. The committee emphasised that genetic services must be pragmatic in estimating these risks in

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				collection is collectively vast and hugely resource intensive. Outside of genetics use of CanRisk is minimal and therefore using the eligibility criteria for referral pathways is not feasible at the current time.	people who may be at risk of rarer ovarian cancers and choose the most suitable tool given a person's particular family history. However, the committee added to the criteria that are designed for the threshold used for testing that they should be based on 'specific clinical circumstances or a verified family history'. The committee recognised the pressure that genetic services might face due to changes in eligibility criteria. Adjustments have been made to recommendations on referral and verification of family history, which could alleviate some of the pressure on genetic services. NICE is developing resource impact tools and supporting information on the timeliness of guidance implementation, acknowledging that this will need to be a gradual process.
UK Cancer Genetics Group	Guideline	General	General	Many regions do not have access to psychology and menopause services. Highlighting this inequity and supporting services to have additional resources would be helpful.	Thank you for your comment. The committee were aware of the challenges these services face. However, it was considered unethical to not refer people who are in need of these services. Geographical inequalities have been added to the Equality Assessment Impact form to highlight that these services are less available in some areas. NICE is developing resource impact tools and supporting information on the timeliness of guidance implementation to support pathways to services being set up.
UK Cancer Genetics Group	Guideline	General	General	There is push back against use of the word "should" where this might not be possible or clinically appropriate in certain situations. "Could offer" has been suggested as an alternative.	Thank you for your comment. The wording 'offer' or 'should offer' is used in NICE to reflect the strength of the recommendation usually based on strong clinical and economic evidence. 'Could offer' would weaken this substantially, meaning that attempts to implement the recommendation do not have to be made. This

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					would potentially mean that a lot of people at risk of having a pathogenic variant would not be identified.
UK Cancer Genetics Group	Guideline	General	General	These guidelines are complex, and currently mix up pathways for both affected and unaffected women and a flow chart of diagram is required to assist clinicians across primary, secondary and tertiary care to follow them as currently it is difficult to clearly pull out the roles and remits of different services with respect to the different patient cohorts.	Thank you for your comment. A visual summary has been developed as a navigation aid for this guideline.
UK Cancer Genetics Group	Guideline	004	006	This sentence "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" does not clearly differentiate upfront the different pathways for cancer patients versus unaffected patients. We are concerned this may risk the hard work undertaken in the NHS to mainstream ovarian cancer genetic testing. This guideline states on page 005 Line 27 1.1.5 that the gynae-oncology team are responsible for mainstream testing and management of ovarian cancer patients. Can you be explicit up front about the different pathways for the affected/unaffected patients. Affected patients do not need referral to genetics services for testing. Otherwise you need to make it much clearer that the first section is talking about UNAFFECTED people not patients with OC.	Thank you for your comment. The 'gynaecology oncology services' has been added to recommendation 1.1.1 and have also referred to mainstreaming as one of the responsibilities of the gynaecology oncology services for people with invasive epithelial ovarian cancer. It has also been clarified that genetic counselling and genetic testing of those diagnosed with non-epithelial ovarian cancers in recommendation 1.4.5 should be within the remit of genetic services. The committee have also produced a visual summary to aid navigation of the guideline.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Cancer Genetics Group	Guideline	006	001	1.1.6 Multiple centres in the UK commented that a "Familial ovarian cancer multidisciplinary team" does not currently exist in their service. Was the additional associated resource for set up and implementation of this service considered in health economic analyses. How would this be appropriately resourced and actioned? Many regional genetics services cover multiple district general hospitals and do not have sufficient genetic resource to cover all Trusts across large regional services. Clearly some places have this set up and feel it is the most appropriate model but set up, resourcing and implementation from scratch requires significant financial and staff resource.	Thank you for your comment. The economic literature review did not identify any existing economic evaluations on familial ovarian cancer multidisciplinary teams (MDTs). The review question on familial ovarian cancer MDTs was also not prioritised for economic modelling due to there being other higher-priority economic modelling areas. The committee acknowledged that not all trusts have dedicated familial ovarian cancer MDTs and there is variation in practice. The committee noted that similar teams already exist for breast cancer and have improved outcomes. The committee acknowledged that the recommendations may incur initial set-up costs. However, these are unlikely to be significant and improved outcomes will offset these. 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, i.e. these meetings can be virtual/remote.
UK Cancer Genetics Group	Guideline	007	002	Different sections of this document are open to different interpretations of which patients are included. First it is stated that the guidelines are for familial ovarian cancer and it is the responsibility of the teams to assess lifetime risk of ovarian cancer. In this section it states "these recommendations are for	Thank you for your comment. This was changed to read 'who has a familial or genetic risk' to make this clearer.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				anyone who has a risk of having a pathogenic variant associated with ovarian cancer". This appears to exclude those with a strong family history of ovarian cancer in whom genetic testing has excluded a monogenic pathogenic variant but who may still have polygenic familial risk. Should this be amended to "anyone who has a risk of having an enhanced genetic risk of ovarian cancer".	
UK Cancer Genetics Group	Guideline	010	006	Table 2: The term "mutation finding" is not one used in clinical practice. Do you mean comprehensive analysis of ovarian cancer associated genes to identify LP/P variants? Predictive testing would be better described as targeted variant analysis of a known LP/P variant as this could then apply to germline testing of a familial variant or confirmatory germline testing of a somatically identified variant	Thank you for your comment. The committee reflected on this and agree that this would not be readily understood and could cause confusion. It was therefore removed.
UK Cancer Genetics Group	Guideline	011	007	1.2.11 Why was group counselling included over other methods that can help with resources, e.g. digital pathways like BRCA Direct to streamline the consent pathway for diagnostic testing. Some services have reported they do not think group counselling has been helpful in this setting.	Thank you for your comment. There was robust randomised controlled trial and cost effectiveness evidence to support the proposition of group information sessions that the committee drew on for this recommendation. They agree that this may not work for everyone so they decided that this could be considered as an option. The committee were aware that BRCA Direct is a specific platform and pathway re-design, which has not yet been trialled widely and no evidence related to this was identified. They therefore did not comment on this.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Cancer Genetics Group	Guideline	011	013	You have used the term "pathogenic variant" throughout and not defined the term "likely pathogenic variant" which you then use in line 13, page 11. On genetic test reports the terms "likely pathogenic variant" and "pathogenic variant" will be used to describe clinically actionable variants. If the term "pathogenic variant" is going to be used in this document it would be helpful to clarify that this also refers to likely pathogenic variants in this context. Can you define "likely pathogenic variant" as well if you are going to use it in certain places in the document.	Thank you for your comment. In the 'terms used in this guideline' section it has been added that for the purpose of this guideline 'pathogenic variant also includes 'likely pathogenic variant' and defined what this means. Repeating it otherwise in each instance would make the document difficult to read. The committee discussed the terminology 'clinically actionable variant' and decided that this would be less readily understood. So, it was decided not to use this terminology.
UK Cancer Genetics Group	Guideline	012		Table 3 is only for people who have a likely pathogenic or pathogenic variant identified. Is there advice or information for individuals with no LP/P variant identified but who still have a significantly increased lifetime ovarian cancer risk on the basis of their family history and/or other risk factors? Many parts of this document refer only to assessment of high grade epithelial ovarian cancer, but you have then included in Page 16, Section 1.4.5 the other subtypes. Should you more clearly define when the recommendations apply only to high grade epithelial ovarian cancer and when other subtypes are included?	Thank you for your comment. The wording 'a strong family history of ovarian cancer' has been added to this section heading to clarify that this could relate to people who have a strong family history of ovarian cancer but may not have a known pathogenic variant. It has also been clarified which sections apply to invasive epithelial cancer. These changes were made to section 1 where it has been clarified which service would be responsible for the non-epithelial cancer types in recommendation 1.4.6 (used to be 1.4.5) and also to sections 1.7 and 1.8.
UK Cancer Genetics Group	Guideline	013	012	1.3.3 None of the methods listed here give an accurate risk of the likelihood of identifying a LP/P variant on the standard R207 ovarian cancer panel. Manchester scoring is for BRCA1/2 only. CanRisk does not have the MMR Lynch Syndrome genes assessed. No centres report use of BRCAPRO.	Thank you for your comment. The committee concluded that genetic services possess the necessary skills and expertise to calculate the probability percentage of having a pathogenic variant, which is done routinely. The CanRisk tool would suit most people; however, the committee agreed it is not appropriate for everyone, such as those with Lynch

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				To what degree was the lack of available accurate risk calculation for standard of care testing taken into account? These tools may well miss a Lynch family history with multiple cases of endometrial or colorectal cancer in the family.	genes. The committee emphasised that genetic services must be pragmatic in estimating these risks in people who may be at risk of rarer ovarian cancers and choose the most suitable tool given a person's particular family history. However, the committee added to the criteria that are designed for the threshold used for testing that they should be based on 'specific clinical circumstances or a verified family history'.
UK Cancer Genetics Group	Guideline	014	013	Table 4. The age related risk calculations in this table are complicated and different to any other eligibility criteria used across the National Genomic Medicine Service. It is hard to rationalise these criteria within the current National Genomic Medicine Service. There will be perceived inequity for other patients, and scenarios where unaffected people with a family history of ovarian cancer receive testing denied to our breast cancer patients. Breast charities/public may not be comfortable with these discrepancies either. Some patients with a family history of breast cancer will not meet R208 breast cancer testing, but will meet R207 ovarian cancer testing due to this discrepancy. The most clinically appropriate test may not be undertaken in this setting. Test directory eligibility criteria will need to alter if these guidelines are to be implemented.	Thank you for your comment. With regards to complexity, the committee concluded that genetic services possess the necessary skills and expertise to calculate the probability percentage of having a pathogenic variant, which is done routinely using tools. Any tool used would require time and resources to calculate and some are more complex than others. Once calculated age and sex criteria can then be applied in accordance with Table 4 of the guideline. In relation to the difference in eligibility criteria for R207 (ovarian cancer) and R208 (breast cancer), the NICE guidance on familial breast cancer was published over a decade ago, and since then, research has progressed and costs have changed. As a result, the thresholds for genetic testing are now lower in ovarian cancer than in breast cancer. The committee knew of other recent studies showing that offering genetic testing to high-risk populations with similar carrier risks is cost-effective. This difference has been highlighted

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The increase in numbers not only for patients with familial ovarian cancer, but with related cancer diagnoses (such as breast) which may mean the meet the age related familial ovarian cancer test eligibility criteria will be significant and put strain on existing laboratory and clinical services. There is not an accurate method of assessing risk of an LP/P variant in all genes on the current R207 OC panel. Some of the models you have suggested do not allow for age related risk adjustments – only CanRisk gives age related risk adjustments and this does not include MMR genes. So applying these very specific age-changeable thresholds is not feasible in practice and may lead to a lot of confusion. These risk calculations also only apply to high grade serous epithelial ovarian cancers – it is not clear that they do not apply to the other subtypes mentioned in this report. There is no way that primary or secondary care will be able to apply these criteria in order to know who to refer – which will mean clinical genetics will be referred anyone who someone wants an assessment in which will also impact on resources. What evaluation has been undertaken to look at impact on clinical genetics services and the resources required to implement this? Collectively, the clinical	to the NICE surveillance team and there is currently a general breast cancer guideline update underway. The committee recognises that test criteria would have to be altered and that some services will experience an initial increase in demand which puts a strain on them. However, the committee is taking a long-term view, as an increased uptake of preventative measures will ultimately lead to a significant reduction in cancer cases. This approach is supported by cost-effectiveness evidence from the UK. In relation to methods of assessing risk and risk calculations, the committee concluded that tertiary services possess the necessary skills and expertise to calculate the probability percentage of having a pathogenic variant, which is done routinely. The CanRisk tool would suit most people; however, the committee agreed it is inappropriate for everyone, such as those with Lynch genes. The committee emphasised that genetic services must be pragmatic in estimating these risks in people who may be at risk of rarer ovarian cancers and choosing the most suitable tool. The committee was aware of several developments in the field, including the creation of the patient-facing CanRisk tool. In relation to primary care the committee revised the referral criteria so that they could be efficiently utilised and clarified that risk calculations will be carried out by genetic services. They have also made adjustments to

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				genetics community has serious reservations of how this could be delivered in practice.	the information that primary care should provide and specified that primary care would not have any involvement in surveillance activities. The committee recognised the pressure that genetic services might face due to changes in eligibility criteria. Adjustments were made to recommendations on referral and verification of family history, which could alleviate some of the pressure on genetic services. NICE is developing resource impact tools and supporting information on the timeliness of guidance implementation, acknowledging that this will need to be a gradual process.
UK Cancer Genetics Group	Guideline	015	003	"No intervening blood relative (or their tissue)" – the resource implications of obtaining tumour blocks and performing DNA extraction on tissue from deceased individuals is often hugely more costly than testing – just putting this in brackets as an aside means we cannot act appropriately to test at 25% risk where intervening relative is deceased and we don't know if tissue is available or it is going to be hugely time/resource consuming to get tissue.	Thank you for your comment. We have reworded the second bullet of this recommendation to include 'or testing of the relative is impossible or not clinically appropriate (for example consent is declined)' to address this point.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Can you alter to something like "can test where it is not possible or clinically appropriate to test an affected intervening relative (or their tissue)"	
UK Cancer Genetics Group	Guideline	015	010	1.4.4 Many respondents from cancer genetics services disagree with this eligibility criteria. This is out of step with current breast cancer guidelines. Colleagues in areas highly enriched for these populations have said they will be overwhelmed and unable to meet demand, for example to service and support the Ashkenazi Jewish population in North London. You have not defined how people meeting this criteria will be identified? Do they need 1 grandparent, 2 grandparents? 4 grandparents? What is the cut off for saying someone comes from one of these groups? Clinical genetics services feel this is population screening and do not feel they should be responsible for population screening in the absence of a family history of a condition. Founder mutation screening does not exist in the GLHs currently. How will this be implemented in the test directory?	Thank you for your comment. The familial breast cancer guideline was developed a long time ago and genetic testing is less costly now. Consequently the thresholds are different which means higher thresholds for people in relation to familial breast cancer. However, the remit of our committee was to make recommendations on effective and cost-effective care for people who may be at risk of familial ovarian cancer. The committee was aware that some services may have an initial high demand in areas with a high concentration of these populations. These services may need help to absorb all the demand. However, this aligns with current developments in the NHS, such as the NHS Jewish BRCA testing program pilot work. The committee was of the view that linking up with such projects may make implementation easier. The definition and eligibility criteria have been reworded and more detail has been provided to clarify that this would mean that a person would have to have at least 1 grandparent from the respective populations. The committee was not anticipating this to be a national screening program. It was clarified in the wording that the focus is on recognising and raising awareness only, to make that explicit, so that people

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					from high-risk populations will have to seek out access to genetic testing themselves. The committee noted that clinical guidelines aim to promote advances in care, which may require changing and modifying current practices. Also, this recommendation is based on clinical and cost effectiveness evidence and our recommendations will represent overall cost savings to the NHS due to preventing cancers and associated high costs and adverse health outcomes. The committee decided that founder mutation screening would potentially be more efficient and cost saving. However, during an implementation phase this does not preclude whole gene panel testing where founder mutation screening is not available.
UK Cancer Genetics Group	Guideline	016	005	1.4.5 You need to link here to the information below (Section 1.5) about the specific germline genes/panels from the TD which would be tested in these different scenarios. You have not specified that you mean germline/constitutional genetic testing which is important when you are discussing genetic testing in cancer patients. You therefore need to distinguish this testing from somatic testing of their tumour DNA. There is no mention of the mutation likelihood of identifying a LP/P variant in these different tumour subtypes. None of the modes of assessing risk prediction for the R207 panel are relevant outside of	Thank you for your comment. Some additions have been made to clarify that we are referring to germline testing. The committee decided that for the rare cancer types it would be straightforward to find the relevant gene panel and that would not need to be specified in a recommendation. They thought that this would be clear from 'decide which gene panel to use in relation to each person's family or personal history'. Genetic services or gynaecology oncology multidisciplinary teams can then select the most appropriate gene panel. People with rarer cancer sub-types would come into the services via non-standard routes and would most

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				high grade epithelial ovarian cancers. How will people assess the likelihood of an unaffected relative of an individual with one of these subtypes developing ovarian cancer as per your eligibility criteria in Table 4? Is it actually the situation that non high grade epithelial subtypes are beyond the scope of this guideline and there should be clarity that most of the guidance does not apply outside of this context?	likely have had whole genome testing. As a result, any eligible relatives would be eligible for cascade testing. The committee decided that it does not have to be pointed out that non high grade epithelial subtypes are beyond the scope as they are not mentioned anywhere in the document.
UK Cancer Genetics Group	Guideline	016	018	1.5.2 This section seems to imply that testing for Lynch Syndrome is different to testing for ovarian cancer alone, but R207 contains the MMR genes	Thank you for your comment. Whilst R207 contains the MMR genes, panel R210 is specific to Lynch Syndrome. Therefore, all three relevant panels have been referred to, but it was explained that this should be decided according to each person's family or personal history.
UK Cancer Genetics Group	Guideline	018	020	1.7.2 Previous NICE breast guidelines stated that women should not be prescribed the oral contraceptive pill purely for prevention of cancer so is this contradicting/updating this guidance?	Thank you for your comment. There was some evidence that showed that the combined oral contraceptive pill had some preventative effectiveness. The committee was aware of the breast cancer guideline but have now made it clearer that it should only be used for some women when a reduction in ovarian cancer outweighs the risk of breast cancer.
UK Cancer Genetics Group	Guideline	019	018	1.8.1 We note the discrepancy between the 4% recommended risk threshold and recent national guidelines. There needs to be joining up and dissemination of the new threshold and agreement on this or confusion will ensue.	Thank you for your comment. The recommendation was based on evidence showing that at a 5% or higher lifetime risk of ovarian cancer, risk-reducing salpingo oophorectomy is cost effective. The model divided this up into pre and post menopausal people and this resulted in differential thresholds. However, the committee reflected on this and agreed that this would

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				In this section you only consider the lifetime risk of developing ovarian cancer for a person making decisions re: risk reducing surgery. It is hugely important, particularly for a premenopausal patient to consider the shorter term risks of developing ovarian cancer (i.e. 5 year risks, 10 year risks) so that they can make an informed decision of the risk of developing ovarian cancer VERSUS the risks of premature menopause, since premature menopause has side effects and an impact on quality of life. 5-10 year risk estimates are much more relevant for decision making between the ages of 35-55 than lifetime risk is. By only referring to lifetime cancer risks you are depriving women the chance to make more nuanced decisions. Do these figures refer to total lifetime risk e.g. from age 20 or residual lifetime risk? Should there be guidance to how to calculate "lifetime risk" so this is performed consistently across services. Does this guideline mean that women who are eligible at 4% lifetime risk pre-menopausally but then delay risk reducing surgery to avoid premature menopause, will then become ineligible for risk reducing surgery post-menopausally as their risk will be 4% not 5%? What impact will this have on their decision making – will they feel pressured into premenopausal surgery to avoid this scenario? Reducing thresholds for premenopausal women will	be difficult to implement and result in potential inequalities and other unintended consequences. Therefore, they agreed to change to an overall lifetime risk of 5% because it is unclear whether changing it overall to 4% would be cost effective. The evidence did not divide into 5- or 10-year risks and it is therefore difficult to say what would be cost effective. This refers to total lifetime risk rather than residual lifetime risk because there is not data available for residual lifetime risk. Specifying the role of menopause services is outside the remit of this guideline, but the committee felt that it is essential that there are 'established relationships with and agreed referral pathways to' such services. Specialist menopause counselling before and after surgery as recommended does not have to be restricted to specialist menopause services and could be given by other healthcare professionals with expertise in menopause. Lifetime risk is calculated in various ways taking into account a number of different factors. In the section on 'assessing the person's risk of developing ovarian cancer' the guideline says that a tool should be used to assess this risk and CanRisk is given as an example. This would allow the lifetime risk to be calculated. The section on risk reducing surgery only applies to the risk of epithelial ovarian cancer because the other rarer subtypes mentioned in recommendation 1.4.5 and their families would go through genetic services and their

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				impact on clinical genetics referrals. Most respondents feel keeping to 5% for both would have less potential for clinical harm. We feel there needs to be greater emphasis on the role of specialised menopause services here and very clear who has the responsibility for managing this aspect of the pathway e.g. primary care or gynae How is lifetime risk of ovarian cancer calculated in families with mixed ovarian cancer subtypes? CanRisk cannot be used in this setting as it only assess risk of high grade epithelial ovarian cancer. We are unclear whether RRBSO would be offered for a family history of all ovarian cancer subtypes without a molecular diagnosis.	risk reducing surgery may be different, but no evidence was identified specifically relating to these.
UK Cancer Genetics Group	Guideline	019	021	1.8.6 How will this system of appointments, recall and screening be managed? Who will be responsible for this? There needs to be clearer recognition of the impact on cancer genetics services who are often left to implement carrier databases and recall systems with no additional funding or resourcing and do not have the expertise to request and interpret results. The roles and responsibilities of this monitoring need to be more explicit.	Thank you for your comment. This recommendation has been revised to clarify that this would be the responsibility of the familial ovarian cancer multidisciplinary team.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Cancer Genetics Group	Guideline	021	024	1.8.7 We feel the age to start monitoring in this section is too low. It matches the age at which surgery could be offered, but in practice many women would delay surgery due to risks from premature menopause/completing families to closer to 40 (BRCA1), 45 (BRCA2) 50 (mod risk genes). (Lynch genes not mentioned here? Why?) This is cumulatively a huge volume of work for patients in whom it is not unreasonable to delay surgery for up to 5 years. Despite saying that monitoring is only for women who refuse surgery at that time, there is a chance that the numbers of women choosing "monitoring" over surgery will be significant. Will all women over these ages need to be referred whilst they are awaiting risk reducing surgery or delaying surgery for up to 5 years? What is an acceptable time period between assessment and surgery before "monitoring" is necessary? Concerns have been raised that this "monitoring" would be considered screening for which there is no evidence Why aren't the MMR genes mentioned here?	Thank you for your comment. Table 5 is intentionally worded using the phrase 'no earlier than…' which does not mean that the person would have to have the surgery at this age. The surveillance section would then have to match this because it would otherwise be unclear what the gap between thinking about surgery and surveillance would mean. It is also worded as 'only consider' doing this to clarify that not all women over these ages need to be referred but that it can be decided in a shared decision making process for each person given their particular risks, preferences and circumstances. Recommendations 1.8.19 and 1.8.20 have also been revised to (1) indicate who should be responsible for doing this because it would be impossible for primary care to be involved in this (2) to indicate more clearly that this is a consideration and not a routine measure for all and (3) that this is not a central call and recall system but that it would need to be coordinated and audited so that its uptake and effectiveness can be assessed. This is also making it clearer that this is not a national screening programme. The MMR genes are intentionally not mentioned because there was no evidence of the effectiveness of surveillance for people with Lynch genes and the committee also noted that the biology related to the Lynch genes is different which may impact effectiveness. Without the evidence the committee decided not to comment on this in the recommendation.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Cancer Genetics Group	Guideline	023	006	Table 2: For MMR genes, PLSD (2021) examining the impact of RRS on cancer incidence and mortality showed that there is little mortality benefit in preforming RRS before 40, and no measurable benefit in performing premenopausal BSO in MSH6 GPV carriers. DOI: 10.1038/s41436-020-01029-1 Most recent PLSD data (2023) has also reported <10% of OC risk up to age 80 in MSH6 and MLH1 carriers	Thank you for your response. The committee did not state that it should be at exactly age 35 but should not be considered earlier than age 35. This age also takes into account that the endometrial cancer risk in some families will be higher at an earlier age. The study by Dominguez-Valentin et al. 2021 was not included in the review because all participants had undergone risk reducing surgery and therefore no comparative data was reported.
UK Cancer Genetics Group	Guideline	023	008	1.8.10 Why is this section relevant in a guideline about familial ovarian cancer?	Thank you for your comment. PMS2 is one of the Lynch genes and this recommendation is therefore included for completeness to clarify that only total hysterectomy alone is needed if there is no family history of ovarian cancer. This may be something that would be missed if not stated in a recommendation and could put people with such a pathogenic variant at risk.
UK Cancer Genetics Group	Guideline	024	012	1.8.16 Suggest "consider" endometrial biopsy: risk of detecting asymptomatic cancer is low and wouldn't change management anyway, and is usually uncomfortable and invasive. In post menopausal women USS for endometrial thickness should suffice. We presume this guidance is only here due for women with Lynch Syndrome, and feel there is a risk this guidance becomes discrepant with more focussed Lynch Syndrome guidelines.	Thank you for your comment. The committee were aware of evidence that 3% to 5% incidental cancer is detected by biopsy which could be missed if ultrasound is used on its own. Ultrasounds is also particularly unreliable in Lynch syndrome. Depending on the outcome of the biopsy ongoing management could also be different. We have added this to the rationale to clarify why this is needed.
UK Cancer Genetics Group	Guideline	026	004	It would be helpful if this section could be expanded a little to cover (the RCOG Scientific Impact paper is really helpful, and some info from there could be	Thank you for your comment. The committee made some revisions to this section including clarification that HRT can be started as soon as clinically

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				included): Guidance on HRT use in women beyond the age of the menopause in the following subgroups: those who have had risk reducing mastectomy and no breast cancer (ie treat as normal, as breast Ca risks associated with HRT likely to be negligible). In my experience clinicians are often anxious about this, therefore say 'no' to these women which limits their access to a QoL intervention. It would be helpful to acknowledge the lack of evidence, but support a pragmatic, individualised approach Timing of HRT in relation to surgery – can usually be commenced immediately Add in (somewhere) – when counselling women about the option of HRT, where women choose the use the Mirena IUS, consider offering to place this at the time of surgery to minimise discomfort Emphasis on menopausal support for women who are unable to take HRT (usually breast cancer patients) – symptoms and long term health (esp bone health)	appropriate after surgery, that there should be a discussion about the individual risks and benefits of HRT use beyond the average age of menopause and that insertion of an LNG-IUS at time of surgery should be considered. This section was specifically about HRT but elsewhere in the document it was stated that people should be offered specialist menopause counselling before and after surgery where other options could be discussed.
UK Cancer Genetics Group	Guideline	028	016	On genetic test reports the terms "likely pathogenic variant" and "pathogenic variant" will be used to describe clinically actionable variants. If the term "pathogenic variant" is going to be used in this document it would be helpful to clarify that where in the document you refer to "pathogenic variants" whether	Thank you for your comment. This has now been included in the glossary ('terms used in this guideline' section) to state that for the purposes of this guideline the term pathogenic variant also includes likely pathogenic variant.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				you are also including "likely pathogenic variants" in this context	
Wales Cancer Network	Guideline	General	General	to make the opportunity for making every moment count to ensure there is access to information on prevention and maintaining healthy lifestyles messages eg each HB should have info and clear access to universal information on Prehabilitation – thus at point 1.2.2/ 1.8.3/ 1.8.9 / 1.8.17 prior to surgery- can apply to any / all of these	Thank you for your comment. Section 1.2 is related to the provision of information and a new recommendation has been added to section 1.1 related to raising awareness 'about which groups of people may be at risk of having a pathogenic variant'. This would mean that 'every moment' would count because people are better informed about and aware of risk. Prehabilitation was not part of the remit of this guideline so the committee could not comment on it.
Wales Cancer Network	Guideline	014	013	Table 4 Genetic testing criteria. The suggestion to vary the testing eligibility threshold by age is different to our usual practice and previous similar NICE guidance (CG164 on Familial Breast Cancer). The thresholds proposed seem very low and, if implemented, are likely to result in a significant increase in the number of tests required, which will be challenging for genomics laboratories to deliver.	Thank you for your comment. The NICE guidance on Familial Breast Cancer (CG164) was published over a decade ago, and since then, research has progressed and costs have changed. As a result, the thresholds for genetic testing are now lower. Other recent studies show that offering genetic testing to high-risk populations with similar carrier risks is cost-effective. This difference has been highlighted to the NICE surveillance team and there is currently a general breast cancer guideline update underway. The committee aimed to make effective and cost-effective care recommendations. They were aware that these recommendations would be a source of pressure to all services involved and attempted to mitigate this. Although there will be pressure on genetic services, there will be less pressure on the NHS in the long term due to fewer ovarian (and breast cancer) cases. These recommendations may justify increasing the capacity of genetic services.

Ovarian cancer: identifying and managing familial and genetic risk

Consultation on draft guideline - Stakeholder comments table
15/09/2023 – 27/10/2023

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The committee was also aware that genetics is a fast-changing field, always exploring how to streamline processes, and with time, this could be successfully implemented. NICE is exploring ways to provide supporting information on implementation timelines, acknowledging that implementing these recommendations will be a gradual process.
Wales Cancer Network	Guideline	016	006	The current NHSE Genomics Test Directory recommends genomic testing for all women with high-grade non-mucinous epithelial ovarian cancer but this guidance is proposing that testing should be offered to all women with any type of invasive epithelial ovarian cancer, which will be a significant increase in the number of tests required, which will be challenging for genomics laboratories to deliver.	Thank you for your comment. The committee decided that it should remain invasive epithelial ovarian cancer. Specifying non-mucinous would disadvantage people with Lynch syndrome genes which would increase the risk of mucinous rather than non-mucinous epithelial ovarian cancer. However, in services where people with mucinous epithelial ovarian cancer are not currently being tested, it would represent a small change in practice due to the small number of people with mucinous ovarian cancer.