National Institute for Health and Care Excellence

Draft for consultation

Ovarian cancer: identifying and managing familial and genetic risk

[I] Carrier probability - women with ovarian cancer

NICE guideline number tbc

Evidence reviews underpinning recommendation 1.4.5 in the NICE guideline

September 2023

Draft for consultation

These evidence reviews were developed by NICE

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Carrier probability - women with ovarian cancer

Review question

At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

Introduction

Up to 20% of ovarian cancers arise due to an inheritable cause; this is a significant minority. Identifying this significant minority is a clinical priority as it could have treatment implications for the patient and could enable risk reduction strategies in affected relatives. These causes of inheritable ovarian cancer are not always because of a single gene mutation (such as in the *BRCA* gene) but can be due to a complex interaction of a combination of small changes in the individuals DNA. Therefore, it is not always easy to illicit the underlying inheritable source.

Testing all ovarian cancer patients for an inheritable cause is one strategy to find those who have a germline cause for their cancer. However what test to do, how to interpret the results and the impact such testing would have on the provision of genomic services are all uncertain. Therefore, it may be that limiting testing to a probability that would increase the yield of positive results and make the interpretation of those results more reliable is preferable. This review question looks at the effects of applying various probabilities as a threshold for germline testing on the clinical outcomes.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women with ovarian cancer
Intervention	Germline pathogenic variant analysis
Comparator	No germline pathogenic variant analysis

Outcomes	**Critical**
	• Any other (non-ovarian) cancer incidence
	• Number of people carrying pathogenic variants
	• Rates of uptake of risk reducing treatments:
	  ○ Chemoprevention
	  ○ Surgery
	  ○ Surveillance
	Important
	• None

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are

described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Four studies were included in this review, 1 cross-sectional study (Chandrasekaran 2021) and 3 systematic reviews (Arts-de Jong 2016, Atwal 2022, Witjes 2022).

Chandrasekaran 2021 reported the prevalence of germline pathological variants of *BRCA1/2, RAD51C, RAD51D,* and *BRIP1* in women with high-grade non-mucinous epithelial ovarian cancer. The systematic reviews (Arts-de Jong 2016, Atwal 2022, Witjes 2022) reported the prevalence of germline pathological variants associated with ovarian cancer in women with ovarian cancer according to subgroups including: histological type of ovarian cancer, age at onset, family history. There is no overlap of studies included in the systematic reviews by Arts-de Jong 2016 and Witjes 2022.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Arts-De Jong 2016 Systematic review International	N=6218 women with all types of epithelial ovarian, fallopian tube or peritoneal cancer N=11 studies (including only published studies from January 2000, no upper limit reported)* Age, mean (SD): NR	Germline testing for PVs in *BRCA1/2*	Prevalence of PVs according to: • Age at onset of OC • Family and personal history of cancer • Histological type of OC	• Number of people carrying pathogenic variants
Atwal 2022 Systematic review International	N=10826 women from unselected and selected ovarian cancer populations (>18 years old)	Germline testing for PVs in *MMR* genes	Prevalence of PVs according to: • Unselected cases of OC • Selected cases of OC	• Number of people carrying pathogenic variants

Study	Population	Intervention	Comparison	Outcomes
	N=21 studies Age, mean (SD, years): 52 (not reported)		• Family history	
Chandrasekaran 2021 Cross-sectional study UK	N=303 women with high-grade non-mucinous epithelial ovarian cancer, who were newly diagnosed or under follow-up in the Northeast London Cancer Network Age, mean (SD; years): NR, but median (range): 61 (51-71) in no germline pathogenic variants group; 54 (51-62) in germline pathogenic variants group	Germline testing for PVs in *BRCA1/2, RAD51C, RAD51D, and BRIP1*	Prevalence of PVs according to: • overall • with and without a family history • high-grade • stage	• Number of people carrying pathogenic variants
Witjes 2022 Systematic review International	N=11351 women with ovarian cancer N=28 studies (including only studies published between January 2015 and November 2020)* Age, mean (SD): NR	• Germline testing for PVs in *BRCA1/2, BRIP1, RAD51C, RAD51D, PALB2, ATM, MLH1, MSH2, MSH6, and PMS2*	Prevalence of PVs according to histological type of OC: • high grade serous • carcinosarcoma • endometrioid • low-grade serous • clear cell • mucinous • other	• Number of people carrying pathogenic variants

MMR: mismatch repair N: Number; NR: not reported; OC: ovarian cancer; PV: pathological variant; SD: standard deviation
**There is no overlap between Arts-de Jong 2016 and Witjes 2022 systematic reviews*

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

There was a lack of studies comparing germline pathogenic variant analysis with no germline pathogenic variant analysis. However, there was a large body of evidence on the number of women with ovarian cancer who carry germline pathological variants (prevalence) of genes associated with ovarian cancer. This was reported both overall and within subgroups such as histological type of cancer, age at onset and family history of cancer. Pathological variants were seen in all of the subgroups analysed, suggesting that genetic testing could be useful in all cases of ovarian cancer.

There was a lack of evidence on incidence of other (non-ovarian) cancers and the rate of uptake of risk reducing treatments.

Prevalence of germline BRCA1/2 pathogenic variants in ovarian cancer overall, by histological subtype, age of onset and family history

There was low quality evidence that the overall prevalence of *BRCA1/2* pathological variants was around 13-17%. When grouping by histological type of ovarian cancer the highest prevalence of *BRCA1/2* pathological variants was around 22% in women with high grade serous cancers (low to high quality evidence).

Low quality evidence suggested that age of ovarian cancer onset was also associated with risk of *BRCA1/2* pathological variants, with the highest prevalence seen in the 40 – 50 year group, followed by the 50 – 60 year group. Very low quality evidence suggested that positive family history of breast or ovarian cancer was associated with a relatively high prevalence of *BRCA1/2* pathological variants (26%) when compared to those without a positive family history (6%).

Prevalence of germline MMR deficient pathogenic variants in ovarian cancer

Moderate quality evidence indicated that overall prevalence of *MMR* deficient pathological variants was 0.8% in unselected populations with ovarian cancer.

Prevalence of germline BRIP1, RAD51C, RAD51D, PALB2, ATM, MLH1, MSH2, MSH6, PMS2 pathological variants in ovarian cancer

Low quality evidence indicated that around 3% of women with ovarian cancer had germline pathological variants of *BRIP1, RAD51C, RAD51D, PALB2*, or *ATM* genes.

Prevalence of germline BRCA1, BRCA2, RAD51C, RAD51D or BRIP1 pathological variants in ovarian cancer

One study reported a prevalence of around 18% for pathological variants of *BRCA1, BRCA2, RAD51C, RAD51D* or *BRIP1* in women with ovarian cancer (moderate quality). In this study there was low to moderate quality evidence that women with high-grade serous cancer had a relatively high prevalence of pathological variants (around 20%) as did those with positive family history (46%).

See appendix F for full GRADE tables.

Economic evidence

Included studies

Five economic studies were identified which were relevant to this review (Eccleston 2017, Hurry 2020, NICE CG164 2013, Moya-Alarcon 2019, Sun 2023 in publication). The manuscript by Sun (2023) has been accepted for publication and the technical team has had a chance to review it before publication.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included economic evidence

The systematic search of the economic literature undertaken for the guideline identified the following studies:

Women with breast or ovarian cancer with a carrier risk ranging from 5% to 40% (eligible first- and second-degree relatives were included only as part of sensitivity analysis):

- One UK study on the cost-utility of *BRCA* genetic testing for women affected by breast or ovarian cancer (NICE CG164 2013).

Women with ovarian cancer or breast cancer and their eligible first- and second-degree relatives:

- One UK study on the cost-utility of parallel *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* panel-germline and somatic *BRCA* testing of all ovarian cancer patients (plus PARP-i treatment) and the subsequent testing and management of their first- and second-degree relatives if index patient or first-degree relative were positive (Sun 2023 - in publication);

- One UK study on the cost-utility of *BRCA* testing for all women with epithelial ovarian cancer and the subsequent testing and management of their first- and second-degree relatives if index patient or first-degree relative were positive (Eccleston 2017);

- One Canadian study on the cost-utility of *BRCA* testing for all women with ovarian or breast cancer and the subsequent testing and management of their first- and second-degree relatives if index patient or first-degree relative were positive (Hurry 2020);

- One Spanish study on the cost-utility of *BRCA* testing for all women with incident non-mucinous high-grade epithelial ovarian cancer and the subsequent testing and management of their first and second-degree relatives if index patient or first-degree relative were positive (Moya-Alarcón 2019).

See the economic evidence tables in appendix H. See Table 3 and Table 4 for the economic evidence profiles of the included studies.

Table 3: Economic evidence profile for *BRCA1/BRCA2* genetic testing in women with breast or ovarian cancer with carrier risks ranging from 5% to 40% (the impact on eligible first- and second-degree relatives included only as part of sensitivity analyses)

				Incremental			
Study	**Limitations**	**Applicability**	**Other comments**	**Costs**	**QALYs**	**Cost effectiveness (Cost/QALY)**	**Uncertainty**
NICE (CG164) 2013 UK Cost-utility analysis	Potentially serious [1]	Directly [2]	Modelling study (Decision tree and Markov) Time horizon: 50 years Outcome: QALYs Comments: - Base-case analysis includes index population only. -Sensitivity analysis considers costs and outcomes to eligible first- and second-degree relatives. - The analysis stratified the results by age.	Range for carrier risks of 5% to 40%: 40-49 years £997 to £1,373 50-59 years £1,046 to £1,469 60-69 years £1,105 to £1,547 70+ years £1,152 to £1,569	Range for carrier risks of 5% to 40%: 40-49 years 0.0519 to 0.0780 50-59 years 0.0400 to 0.0546 60-69 years 0.0262 to 0.0346 70+ years 0.0138 to 0.0180	40-49 years ICERs < £20k/QALY for 5-40% carrier risks 50-59 years ICERs > £20k but < £30k/QALY for 5-40% carrier risks 60-69 years At all carrier risks ICERs > £40k/QALY 70+ years At all carrier risks ICERs > £80k/QALY	Probabilities of being cost-effective at £20k/QALY threshold: - 40-49 years - 0.501 and 0.594 for carrier probabilities of 5% and 40%, respectively - 50-59 years - 0.311 and 0.262 for carrier probabilities of 5% and 40%, respectively - 60-69 years - 0.076 and 0.043 for carrier probabilities of 5% and 40%, respectively - 70+ years - 0.006 and 0.000 for carrier probabilities of 5% and 40%, respectively Including costs and QALYs to eligible first- and second-degree relatives: - 40-49 years – results the same - 50-59 years – carrier risks 10-40% ICERs < £20k/QALY, at 5% carrier risk the ICER was £19-21k/QALY - 60-69 years – not cost-effective at 5-10% carrier risks (ICERs > £30k/QALY), at 15% ICER £18- 21k/QALY, and 20-

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	QALYs	Cost effectiveness (Cost/QALY)	
							40% cost-effective with ICERs < £20k/QALY - 70+ years – not cost effective at 5-15% carrier risks (ICERs > £30k/QALY), at 20% the ICER of £19-24/QALY, and at 30-40% cost effective (ICERs < £20k/QALY). -The results were robust to changes in single parameter values including, genetic testing costs, palliative care cost, utilities associated with breast and ovarian cancer, decrement associated with genetic testing, and percent of eligible people who choose not to undergo genetic testing.

Abbreviations: CG: Clinical guideline; ICER: Incremental cost-effectiveness ratio; k: Thousand; QALY: Quality-adjusted life-year; UK: United Kingdom
[1] Due to the lack of data the same cancer incidence rates were assumed for some age groups and carrier risks
[2] UK study; QALYs

Table 4: Economic evidence profiles for genetic testing in women with ovarian cancer or breast cancer versus no genetic testing or family history/clinical criteria for genetic testing and including the impact on eligible first- and second-degree relatives (note: academic-in-confidence redaction for unpublished data related to Sun 2023)

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
Sun 2023 (in publication) UK Cost-utility analysis	Minor [2]	Directly [3]	Modelling study (Patient-level simulation) Genetic test: BRCA1/BRCA2/RAD51C/RAD51D/BRIP1 and BRCA1/BRCA2 somatic testing for ovarian cancer patients Time horizon: Lifetime time Outcome: QALYs Comment -Includes PARP-i treatment for ovarian cancer and sensitivity analysis without PARP-i treatment -Includes index population, and eligible first- and second-degree relatives	[redacted]	[redacted]	[redacted]	- Probability of being cost-effective was 18% at £30k/QALY threshold. - Panel germline testing (with PARP-i) was sensitive to both PARP-i cost and overall survival associated with PARP-i treatment. - Individual model inputs such as pathogenic variant prevalence, costs, utility scores, and transition probabilities had minimal impact on the cost-effectiveness of unselected panel-germline testing. - In a scenario analysis where adherence to hormone replacement was varied, and a scenario which modelled parallel testing in ovarian cancer patients <70 years and sequential somatic testing followed by germline testing in patients >70 years the conclusions were unchanged. - Excluding PARP-i, panel germline testing resulted in ICERs of [redacted] with 99%

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
							probability of being cost effective at £30k/QALY threshold.
Eccleston 2017 UK Cost-utility analysis	Minor [4]	Directly [5]	Modelling study (Patient-level simulation) Genetic test: BRCA1/BRCA2 Time horizon: 50 years Outcome: QALYs Comment: Includes index population, N=7,284 people with ovarian cancer and their cancer-free family members (N=3,768 first-degree and N=935 second-degree eligible relatives)	£3,061,420	706	£5,282	- The 95% CI for the ICER: £1,593–11,764. - Probability of being cost-effective: 99.9% at £20k/QALY threshold. - The findings were robust and the ICER remained under £20k/QALY in all deterministic sensitivity analyses including probability of having a BRCA mutation, risk reducing surgery uptake rates and effectiveness, mean age of the index population, survival rates, number of genetic counselling sessions, and including a disutility for BRCA testing.
Hurry 2020 Canada Cost-utility analysis	Minor [6]	Partially [7]	Modelling study (Patient-level simulation) Genetic test: BRCA1/BRCA2 Time horizon: 50 years Outcome: QALYs Comment: Includes index population, N=2,786 people with EOC and N=26,316 with breast cancer and their cancer-free family members (N=6,136 first-degree relatives and	£6,608k (for a cohort)	788 (for a cohort)	£8,384	- Probability of being cost-effective: 96% at willingness-to-pay of £28,054/QALY. - The results were robust in sensitivity analyses, which included varying the age of RRBM and RRBSO, rates of risk-reducing surgery uptake, age of index cases, germline sensitivity, cost estimates for ovarian and breast cancer, considering index cases of either OC or BC and BRCA

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
			N=1,052 second-degree relatives)				testing rate. In all these analyses, the ICER of genetic testing remained below £20k/QALY. Only when *BRCA* genetic testing cost increased to £898 (base-case: £379) the ICER of genetic testing increased to £32,028/QALY.
Moya-Alarcón 2019 Spain Cost-utility analysis	Potentially serious [8]	Partially [9]	Modelling study (Patient-level simulation) Genetic test: BRCA1/BRCA2 Time horizon: 50 years Outcome: QALYs Comment: Includes index population, N=130 people with ovarian cancer and their cancer-free family members (N=104 first-degree and N=19 second-degree eligible relatives)	£1,492,266 (for a cohort)	44 (for a cohort)	£33,915	- Probability of being cost-effective: 53% at £37,721/QALY. - The findings were robust to various sensitivity analyses explored including varying patients' age, cancer risk in BRCA carriers, preventive surgery uptake, costs of tests and cancer management, cancer risk after preventive surgery, and cancer utilities.

Abbreviations: BC Breast cancer; CAD: Canadian Dollars; CI: Confidence interval; EOC: Epithelial ovarian cancer; ICER: Incremental Cost-Effectiveness effectiveness Ratio; k: Thousand; N: Number of people; OC Ovarian cancer; PARP-i: Poly(ADP-ribose) polymerase inhibitor; QALY: Quality-adjusted life-year; RRBM: Risk reducing bilateral mastectomy; RRBSO: Risk reducing bilateral salpingo-oophorectomy; UK: United Kingdom; US: Unites States; WTP: Willingness to pay

[1] Costs were converted to UK pounds using OECD purchasing power parities (PPPs)
[2] Well conducted study, no notable methodological issues identified
[3] UK study; QALYs
[4] Source of some model inputs unclear, otherwise well conducted study, deterministic and probabilistic sensitivity analyses undertaken
[5] UK study; QALYs
[6] Well conducted study, no notable methodological issues identified
[7] Canadian study, 1.5% discount for costs and outcomes
[8] Some data sources were unclear, deterministic and probabilistic sensitivity analyses undertaken, no discounting applied to QALYs which may have overestimated cost-effectiveness

1 *[9] Spanish study*

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Economic

Women with breast or ovarian cancer with carrier risks ranging from 5% to 40% (the impact on eligible first- and second-degree relatives included only as part of sensitivity analyses)

- Evidence from a cost-utility analysis, based on modelling (NICE CG164 2013), suggests that *BRCA1/BRCA2* genetic testing is likely to be cost-effective compared with no genetic testing for women affected with ovarian or breast cancer (considering only costs and QALYs for index people) aged 40-49, with carrier risks of 5% to 40% in the UK. However, for women aged 50-69 and 70+ genetic testing is unlikely to be cost-effective for carrier risks ranging from 5% to 40%. This analysis is directly applicable to the NICE decision-making context and has potentially serious limitations.

- Evidence from a cost-utility analysis, based on modelling (NICE CG164 2013), suggests that *BRCA1/BRCA2* genetic testing is likely to be cost-effective compared with no genetic testing for women with ovarian or breast cancer (considering costs and QALYs for index people and all eligible relatives) aged 40-49, with carrier risks of 5% to 40% in the UK. Genetic testing is likely to be cost-effective for women aged 50-59 with carrier risks of 10% to 40%, except for those with a 5% carrier risk where it is borderline cost effective (ICER is £19-21k/QALY). For women aged 60-69 genetic testing is likely to be cost-effective for carrier risks of 20% to 40%, borderline cost-effective for a 15% carrier risk (ICER £18-21k/QALY) and unlikely to be cost-effective for carrier risks 5% to 10%. In women aged 70+ genetic testing is likely to be cost-effective for 30% to 40% carrier risks, borderline cost-effective for a 20% carrier risk (ICER of £19-24k/QALY) and unlikely to be cost effective for carrier risks 5% to 15%. This analysis is directly applicable to the NICE decision-making context and has potentially serious limitations.

Women with ovarian or breast cancer and their eligible first- and second-degree relatives

- Evidence from a cost-utility analysis based on modelling (Sun 2023 in publication) suggests that *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1* genetic testing (plus *BRCA1/BRCA2* somatic testing for ovarian cancer patients) is unlikely to be cost-effective compared with no genetic testing in women with ovarian cancer and their eligible relatives in the UK when including treatment with PARP-i. However, when treatment with PARP-i is excluded genetic testing becomes cost-effective. The study is directly applicable to the NICE decision-making context and has minor limitations.

- Evidence from a cost-utility analysis based on modelling (Eccleston 2017) suggests that *BRCA1/BRCA2* genetic testing is likely to be cost-effective compared with no genetic testing in women with ovarian cancer and their eligible relatives in the UK. The study is directly applicable to the NICE decision-making context and has minor limitations.

- Evidence from a cost-utility analysis based on modelling (Hurry 2020) suggests that *BRCA1/BRCA2* genetic testing is likely to be cost-effective compared with no genetic

testing in women with ovarian or breast cancer and their eligible relatives in Canada. The study is partially applicable to the NICE decision-making context and has minor limitations.

- Evidence from a cost-utility analysis based on modelling (Moya-Alarcón 2019) suggests that *BRCA1/BRCA2* genetic testing, compared with no genetic testing, is unlikely to be cost-effective in women with ovarian cancer and their eligible relatives in Spain, since it exceed exceeds NICE's upper cost-effectiveness threshold of £30,000 per QALY. The study is partially applicable to the NICE decision-making context and has potentially serious limitations.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Incidence of other (non-ovarian) cancers was a critical outcome because pathogenic variants associated with ovarian cancer are often associated with other types of cancer. Identifying pathogenic variants has the potential to reduce the incidence of these other cancers through risk reducing treatments, but this will also depend on the rate of uptake of these treatments. The number of people carrying pathogenic variants (prevalence) was also a critical outcome, because this informs the choice of testing strategy, such as testing all women with ovarian cancer or testing particular high-risk subgroups.

The quality of the evidence

The quality of the evidence was assessed using GRADE and ranged from very low to high quality. Evidence quality was downgraded predominantly because of inconsistency and imprecision. One of the included systematic reviews was considered at serious risk of bias because it did not address heterogeneity or the impact of risk of bias on its results.

Evidence was lacking for outcomes of other (non-ovarian) cancer incidence and rates of uptake of risk reducing treatments. Due to the gaps in the clinical evidence and the issues with evidence quality, the committee also drew on their experience when drafting the recommendations.

Benefits and harms

The committee, based on the clinical and health economic evidence, agreed to recommend genetic counselling and genetic testing to any woman diagnosed with invasive epithelial ovarian cancer. They agreed that detection of pathological variants could benefit the woman through risk reducing treatment and may directly inform her care, for example poly-ADP ribose polymerase (PARP) inhibitors for those with *BRCA* mutations. There are also benefits for the woman's relatives who have the option of risk reducing treatment if they are also found to carry the pathogenic variant.

The committee also discussed various carrier probability thresholds but decided against recommending any particular threshold and took a pragmatic view that the overall prevalence of pathogenic variants was high enough to justify testing for any woman diagnosed with any invasive epithelial ovarian cancer.

The committee, based on expertise, decided to recommend testing in specific subtypes of tumours seen in ovarian-cancer related syndromes such as ovarian Sertoli-Leydig cell tumour, small cell carcinoma of the ovary hypercalcaemic type, ovarian sex cord stromal tumour with annular tubules, embryonal rhabdomyosarcoma of the ovary and ovarian gynandroblastoma. These are associated with pathogenic variants that increase the risk of ovarian cancer. They noted that these ovarian cancer histotypes are rare and that genetic

counselling and genetic testing would help identify these pathogenic variants whilst not adding significant costs.

Cost effectiveness and resource use

There were five existing economic studies on the cost-effectiveness of *BRCA* genetic testing in women with breast or ovarian cancer.

Only one economic analysis explicitly assessed the cost-effectiveness of offering genetic testing at various carrier risks. All other studies compared offering genetic testing with no genetic testing or using family history/clinical criteria for genetic testing in people with ovarian or breast cancer, without explicitly mentioning what the carrier risk was. However, the committee was able to approximate carrier risks from the population descriptions provided in these studies.

The committee discussed the economic analysis that was undertaken for the NICE Familial Breast Cancer Guideline CG164 (2013). This analysis was directly applicable to the NICE decision-making context and had potentially serious methodological limitations. The committee noted that the analysis is outdated. It was also highlighted that some cancer incidence data was based on assumptions. The committee discussed that there is more recent effectiveness and cost data. The committee acknowledged the findings and found it encouraging that overall, the cost-effectiveness of offering genetic testing to women with ovarian or breast cancer was within NICE cost-effectiveness threshold values. Particularly so when considering the costs and outcomes to eligible first- and second-degree relatives.

The committee acknowledged another UK study which found that *BRCA* genetic testing for women with epithelial ovarian cancer, the subsequent testing and management of their first and second-degree relatives, if the index patient or first-degree relative were positive, was cost-effective. In this study the incremental cost-effectiveness ratio was well below the lower NICE cost-effectiveness threshold. Also, the probability of genetic testing being cost effective was approaching 100% at £20,000 per QALY threshold. This evidence was directly applicable to the NICE decision-making context and only had minor methodological limitations.

The committee also discussed another UK study which found that offering genetic testing to women with ovarian cancer was not cost-effective. This study was directly applicable to the NICE decision-making context and had only minor methodological limitations. The committee discussed that in this study genetic testing also included somatic *BRCA* testing of all ovarian cancer patients (not necessarily how genetic testing would be done in clinical practice). Also, currently only *BRCA* testing is undertaken in people with ovarian cancer diagnosis. This analysis, however, did include a panel of genes.

The committee also discussed that the inclusion of PARP inhibitors was the main driver of the results. They have also noted that if genetic testing is not offered to women with ovarian or breast cancer then more PARP inhibitors will need to be given in future, due to people being identified late with more advanced stage ovarian cancers. This would result in even greater pressure on the NHS.

The committee also noted that there is uncertainty in some model inputs. For example, the impact of PARP inhibitors on overall survival. As a result, the committee was more inclined to use the results of the analysis which excluded PARP inhibitors and found that genetic testing was cost-effective in women with ovarian cancer.

The committee also acknowledged evidence from Canada which found that *BRCA* testing for people with ovarian or breast cancer and the subsequent testing and management of their first and second-degree relatives if the index patient or first-degree relative were positive was potentially cost-effective. The committee noted that this evidence was only partially applicable to the NICE decision making.

The committee acknowledged the Spanish study which suggested that *BRCA* testing for women with ovarian cancer and their eligible relatives might not be cost-effective, since it exceeds NICE's upper cost-effectiveness threshold of £30,000 per QALY. However, this study's partial applicability to NICE's decision-making context, together with potential serious methodological limitations (such as non-discounted QALYs, unclear data sources and lack of sensitivity analyses), limited the committee's ability to draw firm conclusions from this study.

The committee noted that offering genetic testing to people with invasive epithelial ovarian cancers aligns with current practice and that the economic evidence supports this approach. Moreover, genetic counselling is an integral component of genetic testing for pathogenic variants and the implementation of this recommendation will not require additional resources. Also, in their evaluations of the cost-effectiveness of genetic testing, all included economic studies considered genetic counselling as part of the strategy under evaluation.

The committee discussed that genetic testing for women diagnosed with rarer non-epithelial ovarian cancers may be less cost effective. However, the committee explained that there will be very few women with these other rarer cancers and decided to recommend genetic testing and counselling in these women too.

The committee acknowledged that most of the economic evidence relates to *BRCA* genetic testing. However, implementing the recommendation in this area will mean testing for other genes included in the panel as well. The committee explained that *BRCA* genes are the most prevalent and determine the cost-effectiveness of genetic testing. Even though panel testing costs may be higher, the overall costs of genetic testing have substantially decreased over time. This suggests that the costs used for *BRCA* genetic testing in the included older economic analyses may be comparable to those of panel testing. Consequently, the reported cost-effectiveness will likely be improved since additional pathogenic variants would be identified for similar testing costs.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.4.5 in the NICE guideline.

References – included studies

Effectiveness

Arts-de Jong 2016

Arts-de Jong, M, de Bock, GH, van Asperen, CJ et al. (2016) Germline BRCA1/2 mutation testing is indicated in every patient with epithelial ovarian cancer: A systematic review. European Journal of Cancer 61:137-45

Atwal 2022

Atwal, A, Snowsill, T, Dandy, MC et al. (2022) The prevalence of mismatch repair deficiency in ovarian cancer: A systematic review and meta-analysis. International Journal of Cancer 151(9):1626-1639

Chandrasekaran 2021

Chandrasekaran, D, Sobocan, M, Blyuss, O et al. (2021) Implementation of Multigene Germline and Parallel Somatic Genetic Testing in Epithelial Ovarian Cancer: SIGNPOST Study. Cancers 13(17):4344

Witjes 2021

Witjes, VM, van Bommel, MHD, Ligtenberg, MJL et al. (2021) Probability of detecting germline BRCA1/2 pathogenic variants in histological subtypes of ovarian carcinoma. A meta-analysis. Gynecologic Oncology 164(1):221-230

Economic

Eccleston 2017

Eccleston, A., Bentley, A., Dyer, M., Strydom, A., Vereecken, W., George, A., et al., A cost-effectiveness evaluation of germline BRCA1 and BRCA2 testing in UK women with ovarian cancer, Value in Health, 20, 567-76, 2017

Moya-Alarcón 2019

Moya-Alarcón, C., González-Domínguez, A., Simon, S., Pérez-Román, I., González-Martín, A., Bayo-Lozano, E., et al., Cost–utility analysis of germline BRCA1/2 testing in women with high-grade epithelial ovarian cancer in Spain, Clinical and Translational Oncology, 21,1076-84, 2019

Hurry 2020

Hurry, M., Eccleston, A., Dyer, M., Hoskins, P., Canadian cost-effectiveness model of BRCA-driven surgical prevention of breast/ovarian cancers compared to treatment if cancer develops, International journal of technology assessment in health care, 36,104-12, 2020

NICE 2013

NICE 2013, Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer CG164, Last updated: 2019

Sun 2023 - in publication

Sun, L., Sobocan, M., Rodriguez, I.V., Wei, X., Kalra, A., Oxley, S., et al., Cost-effectiveness of unselected multigene germline and somatic genetic testing for epithelial ovarian cancer, in publication

1

Appendices

Appendix A Review protocol

Review protocol for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

Table 5: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022371244
1.	Review title	Carrier probability at which women with ovarian cancer should be offered genetic testing
2.	Review question	At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?
3.	Objective	To identify at what carrier probability threshold women with ovarian cancer (with or without breast cancer) should be offered genetic testing
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE in Process & MEDLINE Epub Ahead of Print • Epistemonikos • International Health Technology Assessment (INAHTA) database Searches will be restricted by: • English language studies • Human studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.

		The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Familial ovarian cancer
6.	Population	**Inclusion**: Women with ovarian cancer Exclusion: None
7.	Intervention	Germline pathogenic variant analysis
8.	Comparator	No germline pathogenic variant analysis
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Systematic reviews/meta-analyses of RCTs In the absence of RCTs non randomised studies will be included
10.	Other exclusion criteria	**Inclusion**: • Full text papers • Observational studies should control for baseline differences in patient groups **Exclusion**: • Conference abstracts • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/ study quality. • Non-English language articles
11.	Context	This question potentially updates CG 164 recommendations: 1.5.11 “Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a combined *BRCA1* and *BRCA2* mutation carrier probability of 10% or more. [2013]” 1.5.13 “Offer genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more. [2013]”
12.	Primary outcomes (critical outcomes)	• Any other (non-ovarian) cancer incidence • Number of people carrying pathogenic variants • Rates of uptake of risk reducing treatments:

		○ Chemoprevention ○ Surgery ○ Surveillance
13.	Secondary outcomes (important outcomes)	• None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-Reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • The non-randomised study design appropriate checklist. For example, Cochrane ROBINS-I tool for non-randomised controlled trials. The quality assessment will be performed by one reviewer and this will be checked by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity,

		respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: 0.8 and 1.25 for all relative dichotomous outcomes, for continuous outcomes any published validated MIDs, if none are available then +/- 0.5x control group SD.
17.	Analysis of sub-groups	Evidence will be stratified by: Different histopathological types of ovarian cancer • Personal history of breast cancer Evidence will be subgrouped by the following only in the event that there is serious heterogeneity in outcomes: • Groups identified in the equality considerations section of the scope ○ socioeconomic and geographical factors ○ age ○ ethnicity ○ disabilities ○ people for whom English is not their first language or who have other communication needs. ○ trans people (particularly trans men) ○ non-binary people Where evidence is stratified or subgrouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.
18.	Type and method of review	☒ Intervention ☐ Diagnostic

		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	16 October 2022	
22.	Anticipated completion date	13 March 2024	
23.	Stage of review at time of this submission	**Review stage**	**Started** / **Completed**
		Preliminary searches	☑ / ☑
		Piloting of the study selection process	☑ / ☑
		Formal screening of search results against eligibility criteria	☑ / ☑
		Data extraction	☑ / ☑
		Risk of bias (quality) assessment	☑ / ☑
		Data analysis	☑ / ☑

24.	Named contact	**5a. Named contact** National Institute for Health and Care Excellence (NICE) **5b Named contact e-mail** focl@nice.org.uk **5e Organisational affiliation of the review** NICE
25.	Review team members	• Senior systematic reviewer, guideline development team NGA • Systematic reviewer, guideline development team NGA
26.	Funding sources/sponsor	This systematic review is being completed by NICE
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: NICE guideline webpage.
29.	Other registration details	None
30.	Reference/URL for published protocol	https://whttps://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=371244
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Genetic testing, familiar ovarian cancer
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	None
36.	Details of final publication	https://www.nice.org.uk

1 *GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; RoB: risk of bias; SD: standard deviation*

Appendix B Literature search strategies

Literature search strategies for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

Database: Ovid MEDLINE ALL

Date of last search: 03/10/2022

#	Searches
1	exp Ovarian Neoplasms/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).ti,ab,kf.
3	or/1-2
4	Germ-Line Mutation/
5	((germline* or germ line* or pathogenic) adj2 (carrier* or variant* or mutat*) adj3 (test* or analys?s or assess* or evaluat*)).ti,ab,kf.
6	(probabilit* adj2 threshold*).ti,ab,kf.
7	exp Genetic Testing/
8	(genetic adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)).ti,ab,kf.
9	exp Sequence Analysis/
10	((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) adj2 (sequenc* or technique* or technolog* or method* or applicat*)).ti,ab,kf.
11	((sanger or dna) adj2 (sequenc* or method* or technique* or technolog* or applicat*)).ti,ab,kf.
12	chain termination method*.ti,ab,kf.
13	((multi* adj3 probe amplification*) or MLPA).ti,ab,kf.
14	(next generation sequenc* or NGS).ti,ab,kf.
15	Precision Medicine/
16	((precision or predict* or individual* or personal*) adj2 medicine).ti,ab,kf.
17	(p health or phealth).ti,ab,kf.
18	exp Risk Assessment/ and ge.fs.
19	or/4-18
20	3 and 19
21	letter/
22	editorial/
23	news/
24	exp historical article/
25	Anecdotes as Topic/
26	comment/
27	case report/
28	(letter or comment*).ti.
29	or/21-28
30	randomized controlled trial/ or random*.ti,ab.
31	29 not 30
32	animals/ not humans/
33	exp Animals, Laboratory/
34	exp Animal Experimentation/
35	exp Models, Animal/
36	exp Rodentia/
37	(rat or rats or mouse or mice or rodent*).ti.
38	or/31-37
39	20 not 38
40	limit 39 to English language
41	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.

#	Searches
42	drug therapy.fs.
43	(groups or placebo or randomi#ed or randomly or trial).ab.
44	Clinical Trials as Topic/
45	trial.ti.
46	or/41-45
47	Meta-Analysis/
48	Meta-Analysis as Topic/
49	(meta analy* or metanaly* or metaanaly*).ti,ab.
50	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
51	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53	(search* adj4 literature).ab.
54	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
55	cochrane.jw.
56	or/47-55
57	40 and (46 or 56)
58	Observational Studies as Topic/
59	Observational Study/
60	Epidemiologic Studies/
61	exp Case-Control Studies/
62	exp Cohort Studies/
63	Cross-Sectional Studies/
64	Controlled Before-After Studies/
65	Historically Controlled Study/
66	Interrupted Time Series Analysis/
67	Comparative Study.pt.
68	case control$.tw.
69	case series.tw.
70	(cohort adj (study or studies)).tw.
71	cohort analy$.tw.
72	(follow up adj (study or studies)).tw.
73	(observational adj (study or studies)).tw.
74	longitudinal.tw.
75	prospective.tw.
76	retrospective.tw.
77	cross sectional.tw.
78	or/58-77
79	40 and 78

1 **Database: Ovid Embase**

2 **Date of last search: 03/10/2022**

#	Searches
1	exp ovary tumor/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).ti,ab,kf.
3	or/1-2
4	germline mutation/
5	((germline* or germ line* or pathogenic) adj2 (carrier* or variant* or mutat*) adj3 (test* or analys?s or assess* or evaluat*)).ti,ab,kf.
6	(probabilit* adj2 threshold*).ti,ab,kf.
7	exp genetic screening/

#	Searches
8	(genetic adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)).ti,ab,kf.
9	exp sequence analysis/
10	((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) adj2 (sequenc* or technique* or technolog* or method* or applicat*)).ti,ab,kf.
11	((sanger or dna) adj2 (sequenc* or method* or technique* or technolog* or applicat*)).ti,ab,kf.
12	chain termination method*.ti,ab,kf.
13	((multi* adj3 probe amplification*) or MLPA).ti,ab,kf.
14	(next generation sequenc* or NGS).ti,ab,kf.
15	personalized medicine/
16	((precision or predict* or individual* or personal*) adj2 medicine).ti,ab,kf.
17	(p health or phealth).ti,ab,kf.
18	exp *risk assessment/
19	exp *genetics/
20	18 and 19
21	or/4-17,20
22	3 and 21
23	letter.pt. or letter/
24	note.pt.
25	editorial.pt.
26	case report/ or case study/
27	(letter or comment*).ti.
28	or/23-27
29	randomized controlled trial/ or random*.ti,ab.
30	28 not 29
31	animal/ not human/
32	nonhuman/
33	exp Animal Experiment/
34	exp Experimental Animal/
35	animal model/
36	exp Rodent/
37	(rat or rats or mouse or mice or rodent*).ti.
38	or/30-37
39	22 not 38
40	limit 39 to English language
41	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
42	40 not 41
43	random*.ti,ab.
44	factorial*.ti,ab.
45	(crossover* or cross over*).ti,ab.
46	((doubl* or singl*) adj blind*).ti,ab.
47	(assign* or allocat* or volunteer* or placebo*).ti,ab.
48	crossover procedure/
49	single blind procedure/
50	randomized controlled trial/
51	double blind procedure/
52	or/43-51
53	systematic review/
54	meta-analysis/
55	(meta analy* or metanaly* or metaanaly*).ti,ab.
56	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
57	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
58	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
59	(search* adj4 literature).ab.

#	Searches
60	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
61	((pool* or combined) adj2 (data or trials or studies or results)).ab.
62	cochrane.jw.
63	or/53-62
64	42 and (52 or 63)
65	Clinical study/
66	Case control study/
67	Family study/
68	Longitudinal study/
69	Retrospective study/
70	comparative study/
71	Prospective study/
72	Randomized controlled trials/
73	71 not 72
74	Cohort analysis/
75	cohort analy$.tw.
76	(Cohort adj (study or studies)).tw.
77	(Case control$ adj (study or studies)).tw.
78	(follow up adj (study or studies)).tw.
79	(observational adj (study or studies)).tw.
80	(epidemiologic$ adj (study or studies)).tw.
81	(cross sectional adj (study or studies)).tw.
82	case series.tw.
83	prospective.tw.
84	retrospective.tw.
85	or/65-70,73-84
86	42 and 85

1 **Database: Cochrane Database of Systematic Reviews Issue 10 of 12, October 2022**
2 **and Cochrane Central Register of Controlled Trials Issue 10 of 12, October 2022**

3 **Date of last search: 03/10/2022**

#	Searches
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2	(ovar* NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Germ-Line Mutation] this term only
#5	((germline* or germ line* or pathogenic) NEAR/2 (carrier* or variant* or mutat*) NEAR/3 (test* or analys?s or assess* or evaluat*)):ti,ab,kw
#6	(probabilit* NEAR/2 threshold*):ti,ab,kw
#7	MeSH descriptor: [Genetic Testing] explode all trees
#8	(genetic NEAR/2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)):ti,ab,kw
#9	MeSH descriptor: [Sequence Analysis] explode all trees
#10	((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) NEAR/2 (sequenc* or technique* or technolog* or method* or applicat*)):ti,ab,kw
#11	((sanger or dna) NEAR/2 (sequenc* or method* or technique* or technolog* or applicat*)):ti,ab,kw
#12	chain termination method*:ti,ab,kw
#13	((multi* NEAR/3 probe amplification*) or MLPA):ti,ab,kw
#14	("next generation sequenc*" or NGS):ti,ab,kw
#15	MeSH descriptor: [Precision Medicine] this term only
#16	((precision or predict* or individual* or personal*) NEAR/2 medicine):ti,ab,kw
#17	(p health or phealth):ti,ab,kw

#	Searches
#18	MeSH descriptor: [Risk Assessment] explode all trees
#19	MeSH descriptor: [Genetics] explode all trees
#20	#18 AND #19
#21	{OR #4-#17, #20}
#22	#3 AND #21
#23	conference:pt or (clinicaltrials or trialsearch):so
#24	#22 NOT #23

1 **Database: Epistemonikos**

2 **Date of last search: 03/10/2022**

#	Searches
1	(advanced_title_en:((ovar* AND (cancer* OR neoplas* OR carcino* OR malignan* OR tumor* OR tumour* OR adenocarcinoma* OR sarcoma* OR angiosarcoma* OR lymphoma* OR leiomyosarcoma* OR metasta*))) OR advanced_abstract_en:((ovar* AND (cancer* OR neoplas* OR carcino* OR malignan* OR tumor* OR tumour* OR adenocarcinoma* OR sarcoma* OR angiosarcoma* OR lymphoma* OR leiomyosarcoma* OR metasta*))))
2	(advanced_title_en:(("germline mutation analysis" OR sanger OR "next generation sequenc*" OR "sequence analysis" OR NGS OR MLPA)) OR advanced_abstract_en:(("germline mutation analysis" OR sanger OR "next generation sequenc*" OR "sequence analysis" OR NGS OR MLPA)))
3	1 AND 2

3 **Database: INAHTA International HTA database**

4 **Date of last search: 03/10/2022**

#	Searches
1	"Ovarian Neoplasms"[mhe]
2	((ovar* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR ((ovar* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
3	#2 OR #1
4	"Germ-Line Mutation"[mh]
5	(((((germline* or germ line* or pathogenic) AND (carrier* or variant* or mutat*) AND (test* or analys?s or assess* or evaluat*))))[Title] OR ((((germline* or germ line* or pathogenic) AND (carrier* or variant* or mutat*) AND (test* or analys?s or assess* or evaluat*))))[abs]
6	((probabilit* AND threshold*))[Title] OR ((probabilit* AND threshold*))[abs]
7	"Genetic Testing"[mhe]
8	((genetic AND (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)))[Title] OR ((genetic AND (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)))[abs]
9	"Sequence Analysis"[mhe]
10	(((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) AND (sequenc* or technique* or technolog* or method* or applicat*)))[Title] OR (((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) AND (sequenc* or technique* or technolog* or method* or applicat*)))[abs]
11	(((sanger or dna) AND (sequenc* or method* or technique* or technolog* or applicat*)))[Title] OR (((sanger or dna) AND (sequenc* or method* or technique* or technolog* or applicat*)))[abs]
12	("chain termination method*")[Title] OR ("chain termination method*")[abs]
13	((multi* AND probe amplification*))[Title] OR ((multi* AND probe amplification*))[abs]
14	(MLPA)[Title] OR (MLPA)[abs]
15	(("next generation sequenc*" or NGS))[Title] OR (("next generation sequenc*" or NGS))[abs]
16	"Precision Medicine"[mh]
17	(((precision or predict* or individual* or personal*) AND medicine))[Title] OR (((precision or predict* or individual* or personal*) AND medicine))[abs]
18	((p health or phealth))[Title] OR ((p health or phealth))[abs]
19	#18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4
20	#19 AND #3

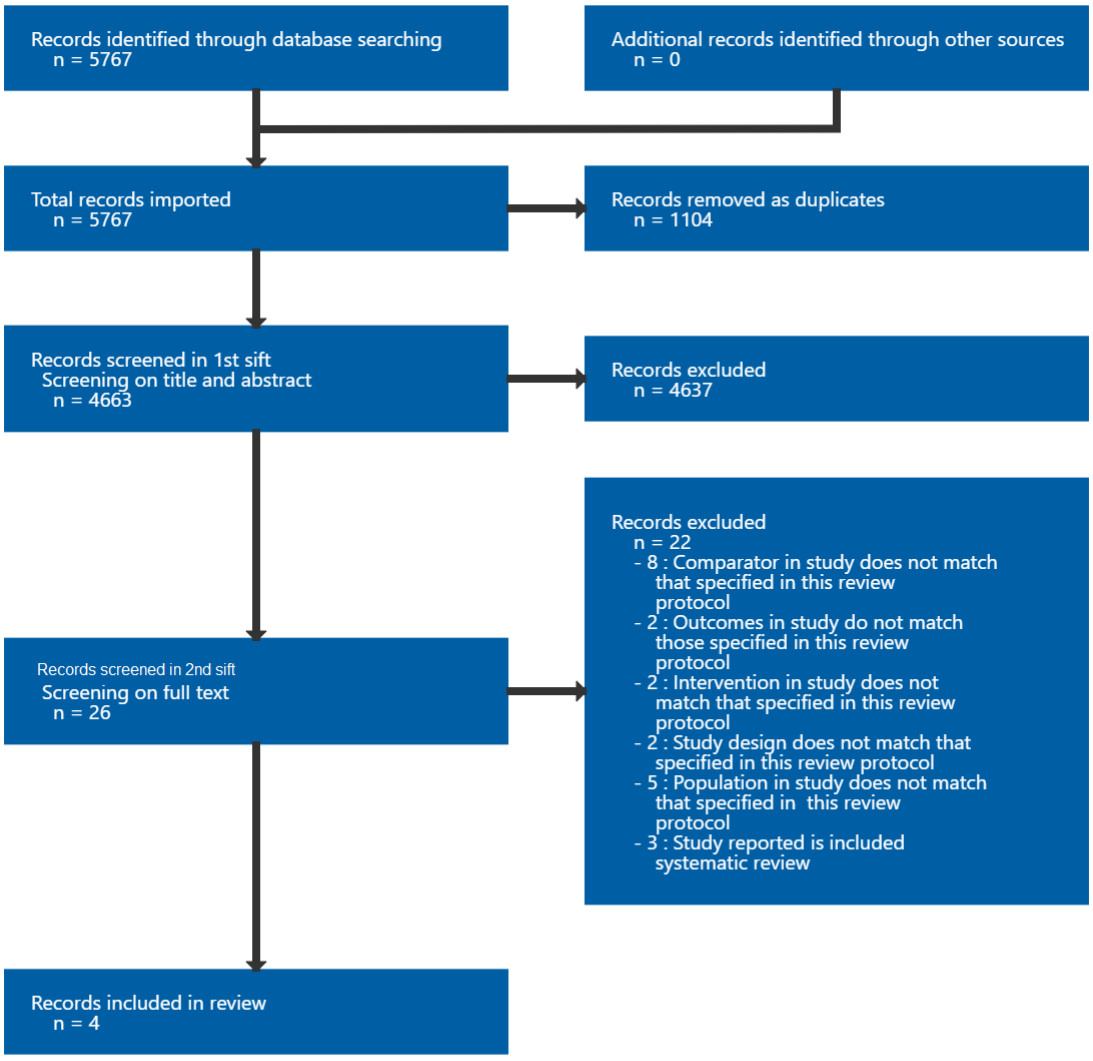
5

6

Appendix C Effectiveness evidence study selection

Study selection for: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

Arts-De Jong, 2016

Bibliographic Reference	Arts-De Jong, M.; De Bock, G.H.; Van Asperen, C.J.; Mourits, M.J.E.; De Hullu, J.A.; Kets, C.M.; Germline BRCA1/2 mutation testing is indicated in every patient with epithelial ovarian cancer: A systematic review; European Journal of Cancer; 2016; vol. 61; 137-145

Study details

Country/ies where study was carried out	Studies included from Australia, Canada, Denmark, Poland, Sweden, UK, USA,
Study type	Systematic review of cross-sectional studies
Study dates	Studies published between 2000 and 2015
Inclusion criteria	Population- and hospital-based studies in women with all types of epithelial ovarian, fallopian tube or peritoneal cancer who underwent comprehensive germline testing for both *BRCA1* and *BRCA2* mutations.
Exclusion criteria	Studies solely in Ashkenazi Jewish women. Studies with fewer than 75 participants.
Patient characteristics	11 studies with a total of 6218 women were included. No patient characteristics were reported.
Intervention(s)	Comprehensive germline testing: next-generation sequencing, Sanger sequencing, MLPA (multiplex ligation-dependent probe amplification) Reported for the following subgroups:

	• Age at onset of ovarian cancer, • family and personal history of cancer, • histology
Duration of follow-up	Not applicable
Sources of funding	Not reported
Results	**Prevalence (95% CI) of germline *BRCA1/2* PV in women with epithelial ovarian cancer– overall** 9 studies (N not reported): 12.7% (9.5 – 15.9) **Prevalence (95% CI) of germline *BRCA1/2* PV in women with epithelial ovarian cancer – age of onset ≤ 40 years** 8 studies (N not reported): 10% (3.2 – 16.9) **Prevalence (95% CI) of germline *BRCA1/2* PV in women with epithelial ovarian cancer – age of onset 40 to 50 years** 8 studies (N not reported): 19.7% (15.1 – 24.3) **Prevalence (95% CI) of germline *BRCA1/2* PV in women with epithelial ovarian cancer – age of onset 50 to 60 years** 9 studies (N not reported): 14.8% (7.8 -21.7) **Prevalence (95% CI) of germline *BRCA1/2* PV in women with epithelial ovarian cancer – age of onset ≥ 60 years** 9 studies (N not reported): 7.1% (4.4 – 10.0) **Prevalence (95% CI) of germline *BRCA1/2* PV in women with epithelial ovarian cancer – positive family breast/ovarian cancer history (variously defined in studies from 1st to 3rd degree relatives)** 10 studies (N not reported): 26.4% (20.5 – 32.3)

	Prevalence (95% CI) of germline *BRCA1/2* PV in women with epithelial ovarian cancer – negative family breast/ovarian cancer history (variously defined in studies from 1st to 3rd degree relatives)
	9 studies (N not reported): 6.2% (3.2 – 9.1)

CI, confidence interval; EOC: epithelial ovarian cancer; PV: pathological variants

Critical appraisal - NGA Critical appraisal - ROBIS checklist

Section	**Question**	**Answer**
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Unclear *(No details about data extraction, no risk of bias assessment assessment)*
Synthesis and findings	Concerns regarding the synthesis and findings	High *(Heterogeneity not addressed, impact of risk of bias assessment not considered, no details of analysis reported)*
Overall study ratings	Overall risk of bias	High
Overall study ratings	Applicability as a source of data	Fully applicable

Atwal, 2022

Bibliographic Reference	Atwal, A.; Snowsill, T.; Dandy, M.C.; Krum, T.; Newton, C.; Evans, D.G.; Crosbie, E.J.; Ryan, N.A.J.; The prevalence of mismatch repair deficiency in ovarian cancer: A systematic review and meta-analysis; International Journal of Cancer; 2022; vol. 151 (no. 9); 1626-1639

1 **Study details**

Country/ies where study was carried out	Studies in included from Canada, Finland, Germany, Italy, Japan, Poland, Netherlands, Spain, Sweden, Switzerland, UK, USA
Study type	Systematic review of cross-sectional studies
Study dates	No date restriction - studies were published between 1996 and 2020
Inclusion criteria	Studies investigating mismatch repair deficiency (MMRd) in both unselected and selected ovarian cancer (OC) populations. Studies had to be in the English language, in female adults (>18 years old).
Exclusion criteria	Studies with fewer than 50 women with OC or those concentrated on synchronous ovarian tumours with other primary malignancies.
Patient characteristics	Overall 54 articles were included in the meta-analysis including 17532 women with ovarian cancer. For germline analysis there were 21 studies including 10826 women with ovarian cancer. The mean age of participants was 52 years (36 studies reported this). Histotype of ovarian cancer: 53% were high grade serous, 18% were endometrioid, 14% were clear cell, 1% were low grade serous and 13% were of other histotype (46 studies reported this). Ethnicity was only reported in 3 studies
Intervention(s)	Germline analysis of path_MMR status. Reported for the following subgroups: • Unselected cases of OC (studies of universal testing for MMRd) • Selected cases of OC (testing for MMRd based on predefined criterion/criteria, for example histotype specific) • Cases with family history

Duration of follow-up	Not applicable
Sources of funding	No specific funding was used for this review.
Results	**Prevalence (95% CI) of germline MMR PV in women with ovarian cancer – unselected populations** 9 studies (57/7047) 0.8% (0.5 – 1.3), I^2 = 59% **Prevalence (95% CI) of germline MMR PV in women with ovarian cancer – selected populations (based on predefined criteria such as histological type)** 3 studies (24/1904) 2% (0.5 – 7.1), I^2 = 94%; individual effects were 6.9% (3.7 – 11.5), 0.5% (0.3 – 1), 2.6% (0.3 – 9.1)

CI, confidence interval; MMR: mismatch repair; PV: pathological variants

Critical appraisal - NGA Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

1 **Chandrasekaran, 2021**

Bibliographic Reference	Chandrasekaran, D.; Sobocan, M.; Blyuss, O.; Miller, R.E.; Evans, O.; Crusz, S.M.; Mills-Baldock, T.; Sun, L.; Hammond, R.F.L.; Gaba, F.; Jenkins, L.A.; Ahmed, M.; Kumar, A.; Jeyarajah, A.; Lawrence, A.C.; Brockbank, E.; Phadnis, S.; Quigley, M.; El Khouly, F.; Wuntakal, R.; Faruqi, A.; Trevisan, G.; Casey, L.; Burghel, G.J.; Schlecht, H.; Bulman, M.; Smith, P.; Bowers, N.L.; Legood, R.; Lockley, M.; Wallace, A.; Singh, N.; Evans, D.G.; Manchanda, R.; Implementation of multigene germline and parallel somatic genetic testing in epithelial ovarian cancer: Signpost study; Cancers; 2021; vol. 13 (no. 17); 4344

2 **Study details**

Country/ies where study was carried out	UK
Study type	Cross-sectional study
Study dates	Not reported
Inclusion criteria	Women ≥18 years with high-grade non-mucinous epithelial ovarian cancer, who were newly diagnosed or under follow-up in the North East London Cancer Network (NELCN).
Exclusion criteria	None reported
Patient characteristics	N=303 Women without germline pathological variants (N=249): • Median (IQR) age at ovarian cancer diagnosis (years): 61 (51–71) • Ethnicity (N): 164 white, 23 black, 39 south Asian and 23 'other'. Women with germline pathological variants (N=54): • Median (IQR) age at ovarian cancer diagnosis (years): 54 (51–62) • Ethnicity (N): 32 white, 5 black, 13 south Asian and 4 'other'.
Intervention(s)	Germline testing for *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* genes and concomitant *BRCA1/BRCA2* somatic genetic testing (results not extracted for this evidence review).

	Reported for the following groups: • overall • with and without a family history • high-grade • stage
Duration of follow-up	Not applicable
Sources of funding	Funded by The Barts Charity, grant ECMG1B6R.
Results	**Prevalence (95% CI) of germline BRCA1, BRCA2, RAD51C, RAD51D or BRIP1 PV in women with ovarian cancer (overall)** 54 / 303: 17.8% (13.5 – 22.1) **Prevalence (95% CI) of germline BRCA1, BRCA2, RAD51C, RAD51D or BRIP1 PV in women with ovarian cancer and positive family history (1st or 2nd degree relative with breast or ovarian cancer)** 24 / 52: 46.2% (32.6 – 59.7) **Prevalence (95% CI) of germline BRCA1, BRCA2, RAD51C, RAD51D or BRIP1 PV in women with ovarian cancer and negative family history** 30 / 251: 12.0% (7.9 – 16.0) **Prevalence (95% CI) of germline BRCA1, BRCA2, RAD51C, RAD51D or BRIP1 PV in women with high-grade serous ovarian cancer** 52 / 259: 20.1% (15.2 – 25)

	Prevalence (95% CI) of germline BRCA1, BRCA2, RAD51C, RAD51D or BRIP1 PV in women with early stage serous ovarian cancer 10 / 67: 14.9% (6.4 – 23.5) **Prevalence (95% CI) of germline BRCA1, BRCA2, RAD51C, RAD51D or BRIP1 PV in women with advanced stage serous ovarian cancer** 44 / 236: 18.6% (13.7 – 23.6)

1 *CI, confidence interval; MMR: mismatch repair; PV: pathological variants*

2 **Critical appraisal - NGA Critical appraisal – JBI checklist for prevalence studies**

Section	Answer
Overall risk of bias	Low (all 9 questions answered as yes)

3 **Witjes, 2022**

Bibliographic Reference	Witjes, V.M.; van Bommel, M.H.D.; Ligtenberg, M.J.L.; Vos, J.R.; Mourits, M.J.E.; Ausems, M.G.E.M.; de Hullu, J.A.; Bosse, T.; Hoogerbrugge, N.; Probability of detecting germline BRCA1/2 pathogenic variants in histological subtypes of ovarian carcinoma. A meta-analysis; Gynecologic Oncology; 2022; vol. 164 (no. 1); 221-230

4 **Study details**

Country/ies where study was carried out	Studies were included from Europe (Czech Republic, Italy, Germany, Netherlands, Poland, Portugal, UK) Asia (China, Korea, Japan, Thailand) and USA
Study type	Systematic review of cross-sectional studies
Study dates	Studies were published between 2015 and 2020
Inclusion criteria	Studies published after 2014 in English language and in human subjects. Studies were included if all information required for computing the prevalence of germline *BRCA1/2* pathological variants (PVs) per histological subtype of ovarian cancer

	(OC) was provided. Germline *BRCA1/2* PVs were defined as class 4 and 5 variants, and OC was defined by the WHO 2014 and 2020 guidelines
Exclusion criteria	Studies were excluded if the population did not consist of ovarian cancer patients, when the number of ovarian cancer patients was unclear, when no germline testing was performed, when testing was restricted to pre-specified (founder) mutations, or when the information on histology was insufficient to compute proportions per subtype. Review articles, case-reports, opinion pieces and letters to editors were excluded, as were conference abstracts.
Patient characteristics	28 studies were included with 11,351 ovarian patients. Most studies included all ovarian patients, otherwise mucinous ovarian carcinoma was the most common exclusion criterion. No patient characteristics were reported.
Intervention(s)	Germline analysis for *BRCA1/2* pathological variants and for pathological variants in other ovarian cancer risk genes (*BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*). Histotype of ovarian carcinoma (WHO 2014 histology classification system). Reported for the following subgroups: • high grade serous • carcinosarcoma • endometrioid • low-grade serous • clear cell • mucinous • other
Duration of follow-up	Not applicable
Sources of funding	Grant from the Dutch Cancer Society (KUN2019–12732)
Results	**Prevalence (95% CI) of germline BRCA1/2 PV in women with EOC (of any histological subtype)** 28 studies (2105 / 11351): 16.8% (14.6 - 19.2); significant heterogeneity I^2 = 88% therefore range of effects is also reported: prevalences ranged from 6.5% (3.4 - 10.5) to 28.6% (25.5 - 31.8)

	Prevalence (95% CI) of germline BRCA1/2 PV in women with high grade serous ovarian cancer 28 studies (1738 / 7914): 22.2% (19.6 - 25.0); significant heterogeneity I^2 = 88% but range of effects not shown so cannot be reported **Prevalence (95% CI) of germline BRCA1/2 PV in women with carcinosarcoma ovarian cancer** 10 studies (9 / 77): 11.9% (5.8 - 22.6) **Prevalence (95% CI) of germline BRCA1/2 PV in women with endometrioid ovarian cancer** 27 studies (67 / 764): 5.8% (3.3 - 9.9) **Prevalence (95% CI) of germline BRCA1/2 PV in women with low-grade serous ovarian cancer** 23 studies (34 / 422): 5.2% (2.3 - 11.3) **Prevalence (95% CI) of germline BRCA1/2 PV in women with clear cell ovarian cancer** 27 studies (29 / 794): 3.0% (1.6 - 5.6) **Prevalence (95% CI) of germline BRCA1/2 PV in women with mucinous ovarian cancer** 17 studies (11 / 244): 2.5% (0.6 - 9.6) **Prevalence (95% CI) of germline BRCA1/2 PV in women with "other histological type" ovarian cancer** 25 studies (19 / 272): 7.0% (4.5 - 10.7) **Prevalence (95% CI) of germline BRIP1 PV in women with ovarian cancer** 9 studies (42 / 4658): 0.9% (CI NR)

	Prevalence (95% CI) of germline RAD51C PV in women with ovarian cancer 9 studies (44 / 5257): 0.8% (CI NR) **Prevalence (95% CI) of germline RAD51D PV in women with ovarian cancer** 9 studies (34 / 5195): 0.7% (CI NR) **Prevalence (95% CI) of germline PALB2 PV in women with ovarian cancer** 9 studies (27 / 4658): 0.6% (CI NR) **Prevalence (95% CI) of germline ATM PV in women with ovarian cancer** 9 studies (14 / 4658): 0.3% (CI NR) **Prevalence (95% CI) of germline MSH6 PV in women with ovarian cancer** 9 studies (14 / 4658): 0.3% (CI NR) **Prevalence (95% CI) of germline PMS2 PV in women with ovarian cancer** 9 studies (7 / 3538): 0.2% (CI NR) **Prevalence (95% CI) of germline MLH1 PV in women with ovarian cancer** 9 studies (7 / 4658): 0.2% (CI NR) **Prevalence (95% CI) of germline MSH2 PV in women with ovarian cancer** 9 studies (7 / 4658): 0.2% (CI NR) **Prevalence (95% CI) of germline BRIP1, RAD51C, RAD51D, PALB2, or ATM PV in women with ovarian cancer**

	9 studies (NR): 3.3% (CI NR) **Prevalence (95% CI) of germline MMRd (MLH1, MSH2, MSH6 or PMS2) PV in women with ovarian cancer** 9 studies (NR): <1% (CI NR)

CI, confidence interval; MMRd: mismatch repair deficiency; NR: not reported; PV: pathological variants

Critical appraisal - NGA Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

Appendix E Forest plots

Forest plots for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F Modified GRADE tables

GRADE tables for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

Table 6: Evidence profile for prevalence of germline *BRCA1/2* pathogenic variants in ovarian cancer overall and by histological subtype, age and family history

No. of studies	Study design	N pathogenic variants / Sample size	Prevalence % (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of germline *BRCA1/2* PV in women with epithelial ovarian cancer (of any histological subtype)									
28 (SR; Witjes 2022)	Cross-sectional studies	2105/11351	16.8 (14.6 to 19.2); ranged from 6.5 (3.4 to 19.2) to 28.6 (25.5 to 31.8)[1]	Not serious	Very serious[1]	Not serious	Not serious	LOW	CRITICAL
9 (SR; Arts-de Jong 2016)		Not reported	12.7 (9.5 to 15.9)	Serious[2]	Serious[3]		Not serious[4]	LOW	
Prevalence of germline *BRCA1/2* PV in women with high grade serous ovarian cancer									
28 (SR; Witjes 2022)	Cross-sectional studies	1738/7914	22.2 (19.6 to 25.0)	Not serious	Very serious[1]	Not serious	Not serious	LOW	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with carcinosarcoma ovarian cancer									
10 (SR; Witjes 2022)	Cross-sectional studies	9/77	11.9 (5.8 to 22.6)	Not serious	Not serious	Not serious	Very serious[5]	LOW	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with endometrioid ovarian cancer									
27 (SR; Witjes 2022)	Cross-sectional studies	67/764	5.8 (3.3 to 9.9)	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with low-grade serous ovarian cancer									
23 (SR; Witjes 2022)	Cross-sectional studies	34/422	5.2 (2.3 to 11.3)	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with clear cell ovarian cancer									
27 (SR; Witjes 2022)	Cross-sectional studies	29/794	3.0 (1.6 to 5.6)	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with mucinous ovarian cancer									
17 (SR; Witjes 2022)	Cross-sectional studies	11/244	2.5 (0.6 to 9.6)	Not serious	Not serious	Not serious	Serious[6]	MODERATE	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with "other histological type" ovarian cancer									

No. of studies	Study design	N pathogenic variants / Sample size	Prevalence % (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
25 (SR; Witjes 2022)	Cross-sectional studies	19/272	7.0 (4.5 to 10.7)	Not serious	Not serious	Not serious	Serious[6]	MODERATE	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with epithelial ovarian cancer – age of onset ≤ 40 years									
8 (SR; Arts-de Jong 2016)	Cross-sectional studies	Not reported	10 (3.2 to 16.9)	Serious[2]	Serious[3]	Not serious	Not serious[4]	LOW	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with epithelial ovarian cancer – age of onset 40 to 50 years									
8 (SR; Arts-de Jong 2016)	Cross-sectional studies	Not reported	19.7 (15.1 to 24.3)	Serious[2]	Serious[3]	Not serious	Not serious[4]	LOW	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with epithelial ovarian cancer – age of onset 50 to 60 years									
9 (SR; Arts-de Jong 2016)	Cross-sectional studies	Not reported	14.8 (7.8 to 21.7)	Serious[2]	Serious[3]	Not serious	Not serious[4]	LOW	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with epithelial ovarian cancer – age of onset ≥ 60 years									
9 (SR; Arts-de Jong 2016)	Cross-sectional studies	Not reported	7.1 (4.4 to 10.0)	Serious[2]	Serious[3]	Not serious	Not serious[4]	LOW	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with epithelial ovarian cancer – positive family breast/ovarian cancer history (variously defined in studies from 1st to 3rd degree relatives)									
10 (SR; Arts-de Jong 2016)	Cross-sectional studies	Not reported	26.4 (20.5 to 32.3)	Serious[2]	Serious[3]	Serious[7]	Not serious[4]	VERY LOW	CRITICAL
Prevalence of germline *BRCA1/2* PV in women with epithelial ovarian cancer – negative family breast/ovarian cancer history (variously defined in studies from 1st to 3rd degree relatives)									
9 (SR; Arts-de Jong 2016)	Cross-sectional studies	Not reported	6.2 (3.2 to 9.1)	Serious[2]	Serious[3]	Serious[7]	Not serious[4]	VERY LOW	CRITICAL

CI, confidence interval; EOC: epithelial ovarian cancer; NR: not reported; PV: pathological variants
1 Very serious heterogeneity not explained by subgroup analysis
2 Serious risk of bias per ROBIS
3 Heterogeneity not reported
4 Sample size not reported, but total sample size was 6218 women in 11 studies, so likely to be above N=400
5 Sample size < 200
6 Sample size < 400
7 Variable definition of family history in studies – negative in one study could be positive in another

Table 7: Evidence profile for prevalence of germline *MMR* deficient pathogenic variants in ovarian cancer

No. of studies	Study design	N pathogenic variants / Sample size	Prevalence % (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of germline *MMR* PV in women with ovarian cancer – unselected populations									
9 (SR; Atwal 2022)	Cross-sectional studies	57/7047	0.8 (0.52 to 1.3)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *MMR* PV in women with ovarian cancer – selected populations (based on predefined criteria such as histological type)									
3 (SR; Atwal 2022)	Cross-sectional studies	24/1904	2 (0.5 to 7.1); the individual study results were 6.9 (3.7 to 11.5), 0.5 (0.3 to 1), 2.6 (0.3 –9.1)[2]	Not serious	Very serious[2]	Not serious	Not serious	LOW	CRITICAL

CI, confidence interval; MMR: mismatch repair; NR: not reported; PV: pathological variants
1. Serious heterogeneity not explained by subgroup analysis
2 Very serious heterogeneity not explained by subgroup analysis

Table 8: Evidence profile for prevalence of germline *BRIP1, RAD51C, RAD51D, PALB2, ATM, MLH1, MSH2, MSH6, PMS2* pathological variants in ovarian cancer

No. of studies	Study design	N pathogenic variants / Sample size	Prevalence % (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of germline *BRIP1* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	42/4658	0.9 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *RAD51C* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	44/5257	0.8 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *RAD51D* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	34/5195	0.7 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *PALB2* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	27/4658	0.6 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *ATM* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	14/4658	0.3 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL

No. of studies	Study design	N pathogenic variants / Sample size	Prevalence % (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of germline *MSH6* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	14/4658	0.3 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *PMS2* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	7/3538	0.2 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *MLH1* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	7/4658	0.2 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *MSH2* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	7/4658	0.2 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *BRIP1, RAD51C, RAD51D, PALB2, or ATM* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	Not reported	3.3 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL
Prevalence of germline *MMRd (MLH1, MSH2, MSH6 or PMS2)* PV in women with ovarian cancer									
9 (Witjes 2022)	Cross-sectional studies	Not reported	<1 (not reported)	Not serious	Serious[1]	Not serious	Not serious	MODERATE	CRITICAL

CI, confidence interval; MMRd: mismatch repair deficiency; NR: not reported; PV: pathological variants
1.Heterogeneity not reported

Table 9: Evidence profile for prevalence of germline *BRCA1, BRCA2, RAD51C, RAD51D or BRIP1* pathological variants in ovarian cancer

No. of studies	Study design	N pathogenic variants / Sample size	Prevalence % (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of germline *BRCA1, BRCA2, RAD51C, RAD51D or BRIP1* PV in women with ovarian cancer									
1 (Chandrasekan 2021)	Cross-sectional study	54/303	17.8 (13.5 to 22.1)	Not serious	Not serious	Not serious	Serious[1]	MODERATE	CRITICAL
Prevalence of germline *BRCA1, BRCA2, RAD51C, RAD51D or BRIP1* PV in women with ovarian cancer and positive family history (1st or 2nd degree relative with breast or ovarian cancer)									
1 (Chandrasekan 2021)	Cross-sectional study	24/52	46.2 (32.6 to 59.7)	Not serious	Not serious	Not serious	Very serious[2]	LOW	CRITICAL
Prevalence of germline *BRCA1, BRCA2, RAD51C, RAD51D or BRIP1* PV in women with ovarian cancer and negative family history									
1 (Chandrasekan 2021)	Cross-sectional study	30/251	12.0 (7.9 to 16.0)	Not serious	Not serious	Not serious	Serious[1]	MODERATE	CRITICAL
Prevalence of germline *BRCA1, BRCA2, RAD51C, RAD51D or BRIP1* PV in women with high-grade serous ovarian cancer									
1 (Chandrasekan 2021)	Cross-sectional study	52/259	20.1 (15.2 to 25)	Not serious	Not serious	Not serious	Serious[1]	MODERATE	CRITICAL
Prevalence of germline *BRCA1, BRCA2, RAD51C, RAD51D or BRIP1* PV in women with early stage serous ovarian cancer									
1 (Chandrasekan 2021)	Cross-sectional study	10/67	14.9 (6.4 to 23.5)	Not serious	Not serious	Not serious	Very serious[2]	LOW	CRITICAL
Prevalence of germline *BRCA1, BRCA2, RAD51C, RAD51D or BRIP1* PV in women with advanced stage serous ovarian cancer									
1 (Chandrasekan 2021)	Cross-sectional study	44/236	18.6 (13.7 to 23.6)	Not serious	Not serious	Not serious	Serious[1]	MODERATE	CRITICAL

CI, confidence interval; EOC: epithelial ovarian cancer; MMR: mismatch repair; NR: not reported; PV: pathological variants
1.Sample size < 400
2 Sample size < 200

Appendix G Economic evidence study selection

Study selection for: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

One global search was undertaken – please see Supplement 2 for details on study selection.

Appendix H Economic evidence tables

Economic evidence tables for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

Table 10: Economic evidence table for *BRCA1/BRCA2* genetic testing in women with breast or ovarian cancer with carrier risks ranging from 5% to 40% (the impact on first- and second-degree relatives included only as part of sensitivity analyses):

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
NICE CG164, published 2013 (last updated in 2019) UK Cost-utility analysis Source of funding: The Department of Health and Social Care	Intervention Genetic Testing at different carrier probabilities ranging from 5-40% Comparator Genetic testing at a different threshold and no genetic testing	Women affected by breast or ovarian cancer Modelling study (Decision tree and Markov) Source of baseline data: Incidence data produced by BOADICEA, based on a 45-year-old affected index individual and her 20-year-old unaffected daughter from example families with carrier probabilities ranging from 5% to 40%; probability of death from cancer taken from cohort study and supplemented with assumptions where data was lacking.	Costs: Diagnostic genetic testing (counselling, genetic test), risk reducing surgery (mastectomy, bilateral salpingo-oophorectomy), surveillance (annual magnetic resonance imaging or mammography), breast and ovarian cancer treatment, palliative care 40-49 years Mean cost per participant (for 5% and 40% carrier risk): Genetic testing: £22,815 and £31,458 Control: £21,818 and £30,085 Difference: £997 and £1,373 50-59 years Mean cost per participant (for 5% and 40% carrier risk): Genetic testing: £23,966 and £32,577	ICERs: - 40-49 years - genetic testing for carrier probabilities 5-40% was cost effective at £20k/QALY threshold - 50-59 years - genetic testing for carrier probabilities 5-40% was cost effective at £30k/QALY threshold - 60-69 years - genetic testing for carrier probabilities 5-40% was not cost effective (all ICERs > £40k) - 70+ years - genetic testing for carrier probabilities 5-40% was not cost	Perspective: NHS Currency: UK£ Cost year: 2011 Time horizon: 50 years Discounting: 3.5% for costs and outcomes Applicability: Directly Limitations: Potentially serious Other comments: - Includes men within the population, however the incidence of breast cancer in men is very low and it is unlikely to impact cost effectiveness substantially - Annual ovarian cancer incidence was the same for different carrier

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of effectiveness data: Cohort studies and assumptions Source of resource use data: Expert opinion, published studies Source of unit cost data: National sources (BNF, NHS Reference Costs, Unit Costs of Health and Social Care)	Control: £22,920 and £31,108 Difference: £1,046 and £1,469 60-69 years Mean cost per participant (for 5% and 40% carrier risk): Genetic testing: £23,265 and £29,473 Control: £22,160 and £27,926 Difference: £1,105 and £1,547 70+ years Mean cost per participant (for 5% and 40% carrier risk): Genetic testing: £22,489 and £26,655 Control: £21,337 and £25,086 Difference: £1,152 and £1,569 Primary measure of outcome: QALYs 40-49 years Mean QALYs per participant (for 5% and 40% carrier risk): Genetic testing: 13.45 and 12.48 Control: 13.40 and 12.40 Difference: 0.0519 and 0.0780 50-59 years	effective (all ICERs > £80k) Using £20k/QALY threshold, the probabilities of genetic testing being cost effective: - 40-49 years - 0.501 and 0.594 for carrier probabilities of 5% and 40%, respectively - 50-59 years - 0.311 and 0.262 for carrier probabilities of 5% and 40%, respectively - 60-69 years - 0.076 and 0.043 for carrier probabilities of 5% and 40%, respectively - 70+ years - 0.006 and 0.000 for carrier probabilities of 5% and 40%, respectively Results including potential costs and benefits for family members of	probabilities, but was varied by age

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Mean QALYs per participant (for 5% and 40% carrier risk): Genetic testing: 11.43 and 10.59 Control: 11.39 and 10.54 Difference: 0.0400 and 0.0546 60-69 years Mean QALYs per participant (for 5% and 40% carrier risk): Genetic testing: 9.07 and 8.60 Control: 9.04 and 8.57 Difference: 0.0262 and 0.0346 70+ years Mean QALYs per participant (for 5% and 40% carrier risk): Genetic testing: 6.33 and 6.11 Control: 6.32 and 6.09 Difference: 0.0138 and 0.0180	individuals identified as BRCA-positive included - 40-49 years - genetic testing at all carrier probabilities from 5-40% was cost-effective - 50-59 years - genetic testing at all carrier probabilities from 10-40% was cost-effective (ICERs < £20k/QALY), at 5% carrier probability the ICER of genetic testing was £19-21k/QALY gained - 60-69 years - genetic testing was not cost effective at 5-10% carrier probabilities (ICERs > £30k/QALY), at 15% carrier probability the ICER of genetic testing was £18-21k/QALY, and 20-40% genetic testing was cost-effective - 70+ years – 5-15% genetic testing	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				was not cost effective, at 20% the ICER of genetic testing was £19-24k/QALY, and at 30-40% carrier risk genetic testing was cost effective (ICERs < £20k/QALY). The results were robust to changes in single parameter values including, genetic testing costs, palliative care cost, utilities associated with breast and ovarian cancer in treatment, decrement associated with genetic testing, and percent of eligible people who choose not to undergo genetic testing.	

1 *Abbreviations: BNF: British National Formulary; CG: Clinical Guideline; ICER: Incremental Cost-Effectiveness Ratio; k: Thousand; NA: Not applicable; NHS: National Health*
2 *Service; QALY: Quality-Adjusted Life-Year; UK: United Kingdom*

3

Table 11: Economic evidence tables for genetic testing in women with ovarian cancer versus no genetic testing or family history/clinical criteria for genetic testing, including impact on eligible first- and second-degree relatives (note: academic-in-confidence redaction for unpublished data related to Sun 2023):

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Sun 2023 (in publication) UK Cost-utility analysis Source of funding: The Barts Charity [grant ECMG1B6R].	Intervention Parallel BRCA1/BRCA2/RAD51C/RAD51D/BRIP1 panel-germline and somatic BRCA-testing of all ovarian cancer patients (+ PARP-i treatment) and their eligible first- and second-degree relatives (Strategy A) Comparator Family history/clinical-criteria-based BRCA1/BRCA2 germline-testing	Ovarian cancer patients and if patients had a BRCA1/BRCA2/RAD51C/RAD51D/BRIP1 pathogenic variants, their first-degree relatives were tested for the familial pathogenic variant, and the second-degree relatives were tested if the first-degree relative was detected to have a BRCA1/BRCA2/RAD51C/RAD51D/BRIP1 pathogenic variant Modelling study (Patient level simulation) Source of baseline data: Population-based registries Source of effectiveness data: Various published studies, including cohort studies for risk-reducing surgeries and RCT for the second progression-free survival	Costs: Germline-testing, somatic-testing, pre- and post-test genetic-counselling, treatment costs of breast cancer, ovarian cancer and excess coronary-heart-disease Mean cost per participant: Intervention: [redacted] Control: [redacted] Difference: [redacted] The primary measure of outcome: QALYs with health-related quality of life scores from various published sources Mean QALYs per participant: Intervention: [redacted] Control: [redacted] Difference: [redacted]	ICERs: Genetic testing (vs family history/clinical criteria based BRCA testing): [redacted] /QALY Probability of being cost-effective at: 18% at £30k/QALY threshold - unselected panel-germline testing and BRCA1/BRCA2 somatic testing for ovarian cancer patients incorporating PARP-i therapy - 99% at £30k/QALY - unselected panel-germline testing alone without PARP-i therapy Subgroup analysis: None. Sensitivity analysis: - Panel germline testing with no PARP-i - the ICER was [redacted] /QALY. - Strategy that includes panel germline testing and PARPi was extremely	Perspective: Healthcare Currency: UK£ Cost year: 2019 prices Time horizon: Lifetime time Discounting: 3.5% for costs and outcomes Applicability: Directly Limitations: Minor Other comments: - Also, reported results from a societal perspective and for the US.

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of resource use data: NICE guidelines, various published sources and assumptions Source of unit cost data: National sources for the UK, including NHS-reference costs, PSSRU, and BNF for the UK; published literature for the US		sensitive to both PARP-i cost and overall survival associated with PARP-i treatment. For example, the hazard ratio for ovarian cancer survival would need to be (base-case: 0.46) for this strategy to be cost-effective. - The annual PARP-i treatment costs would need to fall by [redacted] to [redacted] (base-case: £60,462) for panel germline testing to be cost-effective - Two-way sensitivity analyses showed that annual PARP-i costs would need to fall to [redacted] (base-case: £60,462) if the overall survival hazard rises to [redacted] (base-case: 0.46) - Individual model inputs such as pathogenic variant prevalence, costs, utility scores, and transition probabilities had minimal impact on the cost-effectiveness of unselected panel-germline testing - Assuming half the rate of hormone replacement adherence (40%), with PARP-i - the ICER was	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				[redacted] /QALY - Assuming half the rate of hormone replacement adherence (40%), panel germline testing with no PARP-i - the ICER was [redacted] /QALY - Parallel testing in ovarian cancer patients <70 years and sequential somatic testing followed by germline testing in patients >70 years - the ICER was [redacted] /QALY	
Eccleston 2017 UK Cost-utility analysis Source of funding: Astra Zeneca UK Ltd, the Wellcome Trust (098518/Z/12/Z, and the Royal Marsden/Institute of Cancer Research National Institute for	Intervention BRCA mutation testing for all women with epithelial ovarian cancer and the subsequent testing and management of their first and second-degree relatives if index patient or first-degree relative were positive. Comparator No BRCA testing	Adult patients with epithelial ovarian cancer (index population, N=7,284 people eligible for BRCA testing) and their cancer-free family members (N=3,768 first-degree and N=935 second-degree family members eligible for testing) Modelling study (Patient-level simulation) Source of baseline data: Unclear Source of effectiveness data: Diagnostic	Costs: BRCA testing, genetic counselling (one post-test session for index patients with a BRCA mutation, one pre-test genetic session for all relatives, and one additional post-test session for relatives found to have a BRCA mutation, cancer surveillance (magnetic resonance imaging and mammography), risk-reducing surgery, hormone replacement therapy, cancer treatment, and palliative care Total discounted costs for the cohort of N=11,987: Intervention: £99,894,892 Control: £96,833,471 Difference: £3,061,420	ICERs: Genetic testing (vs no testing): £5,282/QALY (95% CI £1,593–£11,764) Probability of being cost-effective: 99.9% at £20,000/QALY Subgroup analysis: NR Sensitivity analysis: The findings were robust and the ICER remained under £20,000/QALY in all deterministic sensitivity analyses, including: - Changing the probability of having a BRCA mutation to	Perspective: NHS Currency: UK£ Cost year: 2014/15 Time horizon: 50 years Discounting: 3.5% to costs and outcomes Applicability: Directly Limitations: Minor Other comments: None

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Health Research Specialist Biomedical Research Centre for Cancer		accuracy from the Royal Marsden empirical data and published literature; hazard ratios for ovarian and breast cancer risk associated with risk-reducing surgery from the meta-analysis of cohort studies Source of resource use data: NICE Clinical Guidelines, care model at the Royal Marsden, published sources supplemented with assumptions Source of unit cost data: Royal Marsden centre and various national sources (BNF, NHS reference costs)	The primary measure of outcome: QALYs with health-related quality of life scores from various published sources Total discounted QALYs for the cohort of N=11,987: Intervention: 22,296 Control: 21,591 Difference: 706	10% and 16% (base case 13%) - Lowering the risk-reducing bilateral salpingo-oophorectomy uptake rate to 75% (base-case: 88%) - Increasing the risk-reducing mastectomy uptake rate to 50% (base-case: 34%) - Varying the mean age of the index population from 40 to 60 years (base-case: 50 years) - Using the 95% CIs of 0.09–0.26 for the hazard rate for developing ovarian cancer after risk-reducing bilateral salpingo-oophorectomy (base-case: 0.16) - Using the 95% CIs of 0.03–0.31 for the hazard rate for developing breast cancer after risk-reducing mastectomy (base-case: 0.10) - Increasing/decreasing the survival rates for breast cancer/ovarian cancer (these vary by age and too many to report) - Including two pre-test genetic counselling sessions for relatives of the index	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				population (base-case: one session) - Applying a disutility associated with BRCA testing of 0.13 (base-case: no disutility).	
Hurry 2020 Canada Cost-utility analysis Source of funding: Astra Zeneca Canada	BRCA mutation testing in all women with epithelial ovarian cancer or breast cancer, along with subsequent testing and management of their first and second-degree relatives if the index patient or first-degree relative tests positive. Comparator: No BRCA testing and treatment upon cancer development	Adult patients with epithelial ovarian cancer (index population, N=2,786 individuals with EOC) and those with breast cancer (N=26,316), along with their cancer-free family members (N=6,136 first-degree relatives and N=1,052 second-degree relatives). Modelling study (Patient-level simulation) Source of baseline data: Cohort studies and registry data Source of effectiveness data: Cohort studies Source of resource use data: Published studies supplemented with authors' assumptions	Costs: BRCA testing, genetic counselling, cancer treatment, RRBM and RRBSO, palliative care Total discounted costs for the cohort of N=36,290: No BRCA testing: CAD 296,941k BRCA testing: CAD 285,163k Difference: CAD 11,777k The primary measure of outcome: QALYs with health-related quality of life scores from various published sources including NICE familial BC guideline Total discounted QALYs for the cohort of N=36,290: No BRCA testing: 49,996 BRCA testing: 50,784 Difference: 788	ICERs: CAD 14,942/QALY Probability of being cost-effective: 96% at WTP of CAD 50,000 per QALY gained Subgroup analysis: NR Sensitivity analyses: The results remained robust in various sensitivity analyses, which included variations in the age of RRBM and RRBSO, uptake rates of RRS, age of index cases, germline sensitivity, cost estimates for OC and BC, considering OC or BC index cases, genetic testing costs and BRCA testing rate. In all these sensitivity analyses, the ICER of genetic testing remained below CAD 100k/per quality-adjusted life year QALY.	Perspective: Healthcare payer Currency: Canadian dollars (CAD) Cost year: 2016 Time horizon: 50 years Discounting: 1.5% to costs and outcomes Applicability: Partially Limitations: Minor Other comments: None

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of unit cost data: Various published studies			
Moya-Alarcón 2019 Spain Cost-utility analysis Source of funding: AstraZeneca Farmaceutica Spain.	Intervention BRCA testing (index patient BRCA tested and the first and second-degree relatives tested if index patient or first-degree relative respectively were positive) Comparator No BRCA genetic testing, that is, cancer management for the index population and their relatives that developed breast cancer and/or epithelial ovarian cancer.	Women with incident non-mucinous high-grade epithelial ovarian cancer without a family history of ovarian or breast cancer, aged 51 years (N=130), their first-degree (N=104) and second-degree relatives were also tested (N=19). Modelling study (Patient level simulation) Source of baseline data: Unclear Source of effectiveness data: Unclear Source of resource use data: Published sources, including Spanish national guidelines Source of unit cost data: National sources and published studies	Costs: Genetic counselling (one visit and a germline BRCA test), risk-reducing surgery, surveillance (annual magnetic resonance imaging and annual mammography, along with one biannual transvaginal ultrasound and one biannual CA125 test), cancer management (treatment, hospitalisations, emergency visits and follow-up tests), palliative care. Total cost for a cohort of 205 people: Intervention: €13,437,897 Control: €12,053,291 Difference: €1,384,606 The primary measure of outcome: QALYs with health-related quality of life scores from various published studies Total QALYs for a cohort of 205 people: Intervention: 2,109 Control: 2,064 Difference: 44	ICERs: BRCA screening (vs no screening): €31,621/QALY Probability of being cost-effective: 52.52% at €35k/QALY threshold, 60.56% at €37k/QALY, and 89.12% €50k/QALY Subgroup analysis: None reported. Sensitivity analysis: The findings were robust to various sensitivity analyses explored, including varying patients' age (±10%), cancer risk in BRCA carriers (±25%), preventive surgery uptake (±25%), costs of tests and cancer management (±10%), cancer risk after preventive surgery (±25%), and cancer utilities (±10%). The ICERs ranged from €14,692/QALY to €37,597/QALY.	Perspective: Healthcare Currency: Euros € Cost year: 2017 Time horizon: 50 years Discounting: 3% for costs Applicability: Partially applicable Limitations: Potentially serious Other comments: - Included large gene rearrangements (10% of the initial population and 10% of their relatives) - Considered the cost of breast cancer management only in the first year after the diagnosis; however, this is likely to have underestimated cost-effectiveness - Adverse events due to the cancer treatment were not considered -QALYs not discounted

Abbreviations: BC: Breast cancer; BNF: British National Formulary; CAD: Canadian Dollars; CI: Confidence interval; EOC: Epithelial ovarian cancer; ICER: Incremental cost-effectiveness ratio; k: Thousand; N: Number of people; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: Not reported; OC: Ovarian cancer; PARP-i: Poly(ADP-ribose) polymerase inhibitor; PSSRU: Personal Social Services Research Unit; QALY: Quality-adjusted life-year; RRBM: Risk reducing bilateral mastectomy; RRBSO: Risk reducing bilateral salpingo-oophorectomy; RRS: Risk reducing surgery; UK: United Kingdom; US: United States; WTP: Willingness-to-pay

Appendix I Economic model

Economic model for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

Excluded effectiveness studies

Table 12: Excluded studies and reasons for their exclusion

Study	Exclusion reason
Benusiglio, Patrick R, Korenbaum, Clement, Vibert, Roseline et al. (2020) Utility of a mainstreamed genetic testing pathway in breast and ovarian cancer patients during the COVID-19 pandemic. European journal of medical genetics 63(12): 104098	- Comparator in study does not match that specified in this review protocol
D'Andrea, E., Marzuillo, C., De Vito, C. et al. (2016) Which BRCA genetic testing programs are ready for implementation in health care? A systematic review of economic evaluations. Genetics in Medicine 18(12): 1171-1180	- Study design does not match that specified in this review protocol *– Review of health economics evaluations*
Delahunty, R., Nguyen, L., Craig, S. et al. (2022) TRACEBACK: Testing of Historical Tubo-Ovarian Cancer Patients for Hereditary Risk Genes as a Cancer Prevention Strategy in Family Members. Journal of Clinical Oncology 40(18): 2036-2047	- Comparator in study does not match that specified in this review protocol
Eccles, D.M., Balmana, J., Clune, J. et al. (2016) Selecting Patients with Ovarian Cancer for Germline BRCA Mutation Testing: Findings from Guidelines and a Systematic Literature Review. Advances in Therapy 33(2): 129-150	- Study reported is included systematic review *Overlap of studies included in this review with Arts-de Jong 2016 systematic review. Outcomes are reported in a way that more closely matches our review protocol in the Arts-de Jong 2016 review*
Hodan, R., Kingham, K., Cotter, K. et al. (2021) Prevalence of Lynch syndrome in women with mismatch repair-deficient ovarian cancer. Cancer Medicine 10(3): 1012-1017	- Study reported is included systematic review *Included in Atwal 2022 systematic review*
Ip, E., Young, A.L., Scheinberg, T. et al. (2022) Evaluation of a mainstream genetic testing program for women with ovarian or breast cancer. Asia-Pacific Journal of Clinical Oncology 18(5): e414-e419	- Comparator in study does not match that specified in this review protocol
Jeong, G.W., Shin, W., Lee, D.O. et al. (2021) Uptake of family-specific mutation genetic testing among relatives of patients with ovarian cancer with BRCA1 or BRCA2 mutation. Cancer Research and Treatment 53(1): 207-211	- Outcomes in study do not match those specified in this review protocol
Kansu, B., Gardner, J., Price-Tate, R. et al. (2021) BRCA gene testing in women with high-grade serous ovarian carcinoma. Journal of Obstetrics and Gynaecology 41(6): 962-965	- Comparator in study does not match that specified in this review protocol
Kemp, Z., Turnbull, A., Yost, S. et al. (2019) Evaluation of cancer-based criteria for use in mainstream BRCA1 and BRCA2 genetic testing in patients with breast cancer. JAMA Network Open 2(5): e194428	- Population in study does not match that specified in this review protocol *– Not women with a personal history of ovarian cancer*

Study	Exclusion reason
Kim, S.R., Tone, A., Kim, R.H. et al. (2020) Performance characteristics of screening strategies to identify Lynch syndrome in women with ovarian cancer. Cancer 126(22): 4886-4894	- Study reported is included systematic review *Included in Atwal 2022 systematic review*
Konstantinopoulos, P.A., Norquist, B., Lacchetti, C. et al. (2020) Germline and somatic tumor testing in epithelial ovarian cancer: ASCO guideline. Journal of Clinical Oncology 38(11): 1222-1245	- Comparator in study does not match that specified in this review protocol
Lin, J., Sharaf, R.N., Saganty, R. et al. (2021) Achieving universal genetic assessment for women with ovarian cancer: Are we there yet? A systematic review and meta-analysis. Gynecologic Oncology 162(2): 506-516	- Comparator in study does not match that specified in this review protocol
Lindsay, Colin R, Shaw, Emily C, Blackhall, Fiona et al. (2018) Somatic cancer genetics in the UK: real-world data from phase I of the Cancer Research UK Stratified Medicine Programme. ESMO open 3(6): e000408	- Intervention in study does not match that specified in this review protocol
Menko, F.H., Jeanson, K.N., Bleiker, E.M.A. et al. (2020) The uptake of predictive DNA testing in 40 families with a pathogenic BRCA1/BRCA2 variant. An evaluation of the proband-mediated procedure. European Journal of Human Genetics 28(8): 1020-1027	- Outcomes in study do not match those specified in this review protocol
Mohyuddin, G.R., Aziz, M., Britt, A. et al. (2020) Similar response rates and survival with PARP inhibitors for patients with solid tumors harboring somatic versus Germline BRCA mutations: A Meta-analysis and systematic review. BMC Cancer 20(1): 507	- Comparator in study does not match that specified in this review protocol
Moya-Alarcon, Carlota, Gonzalez-Dominguez, Almudena, Simon, Susana et al. (2019) Cost-utility analysis of germline BRCA1/2 testing in women with high-grade epithelial ovarian cancer in Spain. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 21(8): 1076-1084	- Study design does not match that specified in this review protocol *Health economics evaluation*
Nelson, H.D., Pappas, M., Cantor, A. et al. (2019) Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA- Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA - Journal of the American Medical Association 322(7): 666-685	- Population in study does not match that specified in this review protocol *Not women with a personal history of ovarian cancer*
Nelson, Heidi D., Pappas, Miranda, Cantor, Amy et al. (2019) Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA1/2-Related Cancer in Women: A Systematic Review for the U.S. Preventive Services Task Force.	- Population in study does not match that specified in this review protocol *Not women with a personal history of ovarian cancer*
Saam, Jennifer, Moyes, Kelsey, Landon, Michelle et al. (2015) Hereditary cancer-associated mutations in women diagnosed with two primary cancers: an opportunity to identify hereditary cancer syndromes after the first cancer diagnosis. Oncology 88(4): 226-33	- Comparator in study does not match that specified in this review protocol
Scheinberg, T., Young, A., Woo, H. et al. (2021) Mainstream consent programs for genetic counseling in cancer patients: A systematic review. Asia-Pacific Journal of Clinical Oncology 17(3): 163-177	- Intervention in study does not match that specified in this review protocol

Study	Exclusion reason
Trainer, A.H., Meiser, B., Watts, K. et al. (2010) Moving toward personalized medicine: Treatment-focused genetic testing of women newly diagnosed with ovarian cancer. International Journal of Gynecological Cancer 20(5): 704-716	- Population in study does not match that specified in this review protocol *Predates WHO 2014 histology classification system for OC*
Yap, T.A., Ashok, A., Stoll, J. et al. (2022) Prevalence of Germline Findings among Tumors from Cancer Types Lacking Hereditary Testing Guidelines. JAMA Network Open 5(5): e2213070	- Population in study does not match that specified in this review protocol *Focus is on other tumour types*

OC: ovarian cancer

Excluded economic studies

See Supplement 2 for the list of excluded studies across all reviews.

Appendix K Research recommendations

Research recommendations for review question: At what carrier probability should women with ovarian cancer (with or without breast cancer) be offered genetic testing?

No research recommendations were made for this review question.