National Institute for Health and Care Excellence

Final

Ovarian cancer: identifying and managing familial and genetic risk

[F] Carrier probability – any person

NICE guideline NG241

Evidence reviews underpinning recommendations 1.3.1 and 1.4.1 to 1.4.4 in the NICE guideline

March 2024

Final

These evidence reviews were developed by NICE

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Review question

At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

Introduction

Those affected by an inherited predisposition to ovarian cancer may have a family history of cancer which suggests an underlying familial pathogenic variant. For example, those who carry a path_*BRCA1* may have a strong family history of breast and ovarian cancers which would indicate an underlying genetic risk. Ideally, these family histories would be similar between individual families who carry a pathogenic variant. If this was the case, those families with increased familial risk of ovarian cancer would be easy to identify and could be offered testing in a targeted and reliable way. Sadly, however, this is not the case.

Those who have a familial predisposition to ovarian cancer have family histories that are diverse. For example, one individual who carries a path_*BRCA1* may have many relatives who have been affected by ovarian and breast cancer whereas another individual who carries a path_*BRCA1* may have very few or no relatives who had ovarian or breast cancer. In addition, some may be adopted or have lost contact with their relatives which prevents them from getting an accurate family history.

This is important as family history is often used as a criterion by which genetic testing is offered. That is, germline testing is only offered for a familial predisposition to ovarian cancer to those women who meet a certain level of risk as defined by their family history. This increases the yield of positive results and helps with the interpretation of results. However, at what probability of carrying a pathogenic variant based on familial history should genetic testing be offered?

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	People with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes
Intervention	Germline pathogenic variant analysis only if carrier probability exceeds a threshold value
Comparator	Different threshold value

Outcomes	**Critical**
	• Cancer incidence
	• Number of people carrying pathogenic variants
	• Rates of uptake of risk reducing treatments:
	  ○ chemoprevention
	  ○ surgery
	  ○ surveillance
	
	Important
	• Rates of genetic testing for relatives

- Rates of dissemination of the genetic information within the family

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

A systematic review of the literature was conducted but no studies were identified which were applicable to this review question.

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

No studies were identified which were applicable to this review question (and so there are no evidence tables in Appendix D). No meta-analysis was conducted for this review (and so there are no forest plots in Appendix E).

Summary of the evidence

No studies were identified which were applicable to this review question (and so there are no GRADE tables in Appendix F).

Economic evidence

Included studies

Four economic studies were identified which were relevant to this review (Hoskins 2019, Kwon 2019, Muller 2019, NICE CG164 2013).

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 unaffected by cancer with a carrier risk ranging from 5% to 40%:

- One UK study which examined the cost-utility of *BRCA* genetic testing for two groups: (A) women unaffected by breast or ovarian cancer with an available affected relative for testing, and (B) women unaffected by breast or ovarian cancer without an available affected relative for testing. The carrier risks considered in the study ranged from 5% to 40% (NICE CG164 published 2013, last updated 2019).

Women unaffected by cancer with a carrier risk of ≥10%:

- One German study which examined the cost-utility of *BRCA* genetic testing for women unaffected by cancer with a carrier risk of ≥10% (Muller 2019).

Women unaffected by cancer but with first-degree relatives who have *BRCA*-related cancer:

- One Canadian study which examined the cost-utility of *BRCA* genetic testing for women unaffected by cancer but with a first-degree relative who have *BRCA*-related cancer (Kwon 2019).

Women unaffected by cancer but with first- and/or second-degree relatives who have *BRCA*-related cancer:

- One Canadian study which examined the cost-utility of *BRCA* genetic testing and management of first and second-degree relatives of women with ovarian cancer if index patient or first-degree relative were positive (Hoskins 2019).

See the economic evidence tables in appendix H. See Table 2 to Table 6 for the economic evidence profiles of the included studies as well as the de novo economic modelling conducted for this review question.

Table 2: Economic evidence profile for panel genetic testing in individuals unaffected by cancer with carrier risks ranging from 1% to 10% and including impact index cases themselves and on eligible first-degree relatives:

				Incremental			
Study	**Limitations**	**Applicability**	**Other comments**	**Costs**	**QALYs**	**Cost effectiveness (Cost/QALY)**	**Uncertainty**
Guideline de-novo economic analysis (2023) UK Cost-utility analysis	Minor [1]	Directly [2]	Modelling hybrid of decision tree and Markov Time horizon: 110 years Outcome: QALYs Cohort: 1,000 index cases and all eligible first-degree relatives	Males and females combined at carrier risk of 3%: £209,650	Males and females combined at carrier risk of 3%: 19.44	£10,782/QALY	-Probability of being cost-effective 0.72 at £20k/QALY and 0.82 at £30k/QALY. - The findings were sensitive to index cases' gender and age. Panel genetic testing was cost-effective at a carrier risk of 2% for females and 6% for males. However, these thresholds varied depending on the age of the index cases. - The ICER was sensitive to inputs such as age at risk-reducing surgery, uptake of genetic testing in relatives, end-of-life care cost, and relative risk of ovarian cancer for risk-reducing surgery. However, conclusions remained unchanged. That is, the ICER of genetic testing versus no testing stayed below £20k/QALY threshold.

Abbreviations: ICER: Incremental cost-effectiveness ratio; k: Thousands; QALY: Quality-Adjusted Life-Year
[1] In the analysis, ovarian and breast cancer mortality rates for individuals with pathogenic variants were assumed to be equivalent to those in the general ovarian and breast cancer population. However, the model did not show sensitivity to this input. Many inputs were based on individuals with BRCA mutations and were assumed to be applicable to individuals with other pathogenic variants such as RAD51C, RAD51D and BRIP1. The relative risk of ovarian cancer incidence for BRIP1 was derived from a study that had methodological issues and potentially underestimated the relative risk. Nonetheless, the model did not show sensitivity to this input.
[2] UK study, QALYs, NHS and PSS perspective

Table 3: Economic evidence profile for *BRCA1/2* genetic testing for women unaffected by cancer with carrier risks ranging from 5% to 40% (with and without available affected relative to test):

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	QALYs	Cost effectiveness (Cost/QALY)	
NICE Familial Breast Cancer Guideline CG164 2013 (Last updated: 2019) UK Cost-utility analysis ***An affected relative is available to test***	Minor [1]	Directly [2]	Modelling study (Markov) Time horizon: 50 years Outcome: QALYs Comments: - Base-case analysis includes index population only. There is a sensitivity analysis which also considers costs and outcomes to eligible first- and second-degree relatives. - The analysis stratified the results by age and whether relative with cancer is available to be tested.	**Relative available to test** For carrier risks of 5% and 40%: 20-29 years £1,275 and £690 30-39 years £1,179 and £605 40-49 years £1,176 and £657 50-59 years £1,273 and £873 60-69 years £1,403 and £1,104 70+ years	**Relative available to test** For carrier risks of 5% and 40%: 20-29 years 0.0627 and 0.1357 30-39 years 0.0880 and 0.1546 40-49 years 0.0863 and 0.1389 50-59 years 0.0611 and 0.0963 60-69 years 0.0352 and 0.0550 70+ years	**Relative available to test** 20-29 years £20,348/QALY – 5% carrier risk <£20k/QALY for carrier risks 10-40% 30-39 years <£20k/QALY for carrier risks 5-40% 40-49 years <£20k/QALY for carrier risks 5-40% 50-59 years £20,821/QALY - 5% carrier risk <£20k/QALY 10-40% carrier risks 60-69 years	Using £20k/QALY threshold, the probabilities of genetic testing being cost effective: - 20-29 years - 0.510 (no genetic testing preferred) for a carrier risk of 5%, 0.692 to 0.987 for carrier risks of 10% and 40% (genetic testing preferred), respectively - 30-39 years - 0.813 and 0.996 for carrier risks of 5% and 40%, respectively (genetic testing preferred) - 40-49 years - 0.80 and 0.99 for carrier risks of at 5% and 40%, respectively (genetic testing preferred) - 50-59 years - 0.48 for a carrier risk of 5% (no genetic testing preferred), and 0.58 and 0.95 for carrier risks of 10% and 40% respectively (genetic testing preferred) - 60-69 years - 0.03 and 0.50 for carrier risks of 5% and 40% respectively (no genetic testing preferred) - 70+ years - 0.000 and 0.001 for carrier risks of 5% and 40% respectively (no genetic testing preferred)

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	**QALYs**	**Cost effectiveness (Cost/QALY)**	
				£1,575 and £1,378	0.0139 and 0.0236	>£30k/QALY for carrier risks 5-20% £20-22k/QALY for carrier risks 30-40% 70+ years >£58k/QALY for all carrier risks	**Including costs and QALYs for eligible relatives:** - 30-39 years – for carrier risk 5% to 40% genetic testing was cost effective - 40-49 years - for carrier risk 5% to 40% genetic testing was cost effective - 50-59 years - for carrier risk 5% to 40% genetic testing was cost effective - 60-69 years - for carrier risk 5% and 10% genetic testing was unlikely to be cost effective, for carrier risk of 15% the ICER was £17,513 - £20,252/QALY gained, for carrier risks 20% to 40% genetic testing was cost-effective - 70+ years – at carrier risks 5% to 20% genetic testing was unlikely to be cost-effective, and at carrier risks of 30% to 40% genetic testing was cost-effective
NICE Familial Breast Cancer Guideline CG164 2013 (Last updated: 2019) UK	**Same as above**	**Same as above**	**Same as above**	**No relative available to test** For carrier risks of 5% and 40%: 20-29 years	**No relative available to test** For carrier risks of 5% and 40%: 20-29 years	**No relative available to test** 20-29 years Dominant for all carrier risks of 5-40%	Using £20k/QALY threshold, the probabilities of genetic testing being cost effective: - 20-29 years - 0.982 and 0.999 at carrier risks of 5% and 40% respectively (genetic testing preferred) - 30-39 years - 0.989 and 1.000 at carrier risks of 5% and 40%

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	QALYs	Cost effectiveness (Cost/QALY)	
Cost-utility analysis ***No affected relative is available to test***				-£212 and -£703 (favouring genetic testing) 30-39 years -£262 and -£702 (favouring genetic testing) 40-49 years -£217 and -£595 (favouring genetic testing) 50-59 years -£72 and -£341 (favouring genetic testing) 60-69 years £117 and -£58 (negative	0.0601 and 0.1170 30-39 years 0.0860 and 0.1362 40-49 years 0.0847 to 0.1232 50-59 years 0.0596 and 0.0849 60-69 years 0.0336 and 0.0477 70+ years 0.0122 and 0.0193	30-39 years Dominant for all carrier risks of 5-40% 40-49 years Dominant for all carrier risks of 5-40% 50-59 years Dominant for carrier risks of 5%, 10%, 30% and 40% <£1,500/QALY for carrier risks of 15% and 20% 60-69 years Dominant for carrier risks of 30% and 40% <£20k/QALY for carrier risks of 5%, 10%, 15%, and 20% 70+ years >£30k/QALY for carrier risks of	respectively (genetic testing preferred) - 40 to 49 years - 0.988 and 1.000 at carrier risks of 5% and 40% respectively (genetic testing preferred) - 50-59 years - 0.973 and 1.000 at carrier risks of 5% and 40% respectively (genetic testing preferred) - 60-69 years - 0.892 and 0.990 at carrier risks of 5% and 40% respectively (genetic testing preferred) - 70+ years - 0.349 to 0.213 for carrier risks of 5% to 20% (no genetic testing preferred), and 0.736 and 0.619 for carrier risks of 30% and 40%, respectively (genetic testing preferred) **Including costs and QALYs for eligible relatives:** - Genetic testing was cost effective across all carrier risks ranging from 5% to 40% and all age groups ranging from 20-29 years up to 70 + years

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	QALYs	Cost effectiveness (Cost/QALY)	
				difference favours genetic testing) 70+ years £366 and £300		5%, 10%, 15%, and 20% <£16k/QALY for carrier risks of 30% and 40%	

Abbreviations: QALY: Quality-Adjusted Life-Year
[1] There was a lack of cancer incidence data stratified by age and carrier risk
[2] UK study, QALYs

Table 4: Economic evidence profile for *BRCA1/2* genetic testing for women with a carrier risk ≥10% versus no genetic testing:

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
Müller 2019 Germany Cost-utility analysis	Minor [2]	Partially [3]	Modelling study (Markov) Time horizon: 65 years Outcome: QALYs	£6,650	0.42	£15,833/QALY	-Probability of being cost-effective: 36%, 92% and 99% at a willingness to pay of £9,165, £18,330 and £27,495/QALY -The ICER was most sensitive to the incidence of first breast cancer, the choice of prophylactic surgery, relative risks associated with prophylactic surgeries, the discount rate, and ranged from £19k-41k/QALY

Abbreviations: QALY: Quality-Adjusted Life-Year
[1] Costs were converted to UK pounds using OECD purchasing power parities (PPPs)
[2] Some data sources unclear, otherwise a well conducted study
[3] Non-UK study

Table 5: Economic evidence profile for *BRCA1/2* genetic testing for women unaffected by cancer but with first-degree relatives who have BRCA-related cancer versus no genetic testing and also risk reducing surgery for all first-degree relatives without genetic testing:

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
Kwon 2019 Canada Cost-utility analysis	Potentially serious [2]	Partially [3]	Modelling study (Markov) Time horizon: 50 years Outcome: QALYs	£889/QALY (*BRCA1/2* testing versus no testing)	0.21/QALY (*BRCA1/2* testing versus no testing)	£4,233/QALY (*BRCA1/2* testing versus no testing) Universal risk reducing surgery for all first-degree relatives without *BRCA1/2* testing was dominated	-Findings were robust to a wide range of costs and variables such as BRCA mutation rates, the proportion having risk reducing surgery - Compliance with hormone replacement therapy must be very high to mitigate the downstream consequences associated with premenopausal risk reducing surgery

Abbreviations: QALY: Quality-Adjusted Life-Year
[1] Costs were converted to UK pounds using OECD purchasing power parities (PPPs)
[2] Some data sources unclear, no probabilistic sensitivity analysis
[3] Non-UK study

Table 6: Economic evidence profile for *BRCA1/2* genetic testing for women unaffected by cancer but with first- and/or second-degree relatives who have *BRCA*-related cancer versus no genetic testing:

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
Hoskins 2019 Canada	Potentially serious [2]	Partially [3]	Modelling study (Patient-level simulation) Genetic test: *BRCA1/2* Time horizon: 50 years Outcome: QALYs	−£1,629,638	326	BRCA1/2 testing dominant (versus no testing)	- Probability of genetic testing (versus no testing) being cost-effectives: 100% at a threshold of £56k/QALY

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
Cost-utility analysis			Comment: Includes index population, N=2,786 people eligible for *BRCA1/2* testing) and their cancer-free family members (N=766 first-degree and N=207 second-degree eligible relatives)				- Genetic testing remained dominant at risk-reducing surgery uptake levels of ≥40% and resulted in an ICER > £20k/QALY at 20% and 30% uptake levels - Genetic testing remained dominant when the age of risk-reducing bilateral salpingo-oophorectomy was 35 and 50 years and resulted in an ICER of £12,758/QALY at 60 years (base-case: 40 years) - Genetic testing remained dominant when varying the ovarian cancer cost (without surgery) from £22k-45k (base-case: £19k) and at the cost of £11k genetic testing resulted in an ICER of £1,610/QALY

Abbreviations: k: Thousands; N: Number of people; QALY: Quality-Adjusted Life-Year
[1] Costs were converted to UK pounds using OECD purchasing power parities (PPPs)
[2] Breast cancer development was not included in the model, mortality was measured as all-cause mortality over a 50-year time horizon rather than epithelial ovarian cancer-specific mortality
[3] Non-UK study

Economic model

A decision-analytic model was developed to assess the relative cost-effectiveness of offering genetic testing to people with varying family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes. The objective of economic modelling, the methodology adopted, the results and the conclusions from this economic analysis are described in detail in appendix I. This section provides a summary of the methods employed and the key results of the economic analysis.

Overview of economic modelling methods

A hybrid decision-analytic model was developed to assess the cost-effectiveness of genetic testing for individuals with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes. The index population included males and females with varying carrier risks of pathogenic variants, ranging from 1% to 10%. The model considered the use of a panel including *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1*.

In cases of a true positive outcome in an index case, genetic testing for the same pathogenic variant in first-degree relatives, including mothers, fathers, siblings, and children was considered. The model focused only on the impact of pathogenic variants in terms of ovarian and breast cancer and outcomes for males themselves were not included.

The model structure consisted of a decision tree for genetic testing outcomes in index and eligible first-degree relatives, followed by a Markov model for states of being at risk (due to being a carrier), developing new cancer, being a cancer survivor and death. The time horizon was the lifetime of an individual, spanning up to 110 years to capture the impact on index cases' children who may also be carriers.

Carrier risks in first-degree relatives were estimated using The CanRisk tool, which uses BOADICEA, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm. Risk-reducing surgery included risk-reducing bilateral mastectomy and risk-reducing bilateral salpingo-oophorectomy in people with *BRCA1* and *BRCA2*, and risk-reducing bilateral salpingo-oophorectomy in people with *RAD51C*, *RAD51D*, and *BRIP1*. The effectiveness of risk-reducing surgery was obtained from a systematic review conducted for this guideline. All other model inputs were derived from various published sources.

The economic analysis used the number of Quality Adjusted Life Years (QALYs) gained as the measure of outcome. Utility data were obtained from various published sources, with priority given to utilities generated using EQ-5D-3L measurements and the UK population tariffs. The perspective of the analysis was that of NHS and Personal Social Services (PSS) and resource use was based on published literature, national guidance and expert opinion where evidence was lacking. National UK unit costs were used for the cost year of 2020/21.

A probabilistic analysis was conducted to synthesize the model input parameters, allowing for a more comprehensive consideration of uncertainty and non-linearity in the economic model structure. Also, a number of deterministic sensitivity analyses were carried out. The results were presented in the form of Net Monetary Benefits (NMBs) and Incremental Cost-Effectiveness Ratios (ICERs) for each carrier risk. The results of the probabilistic analysis were presented using the cost-effectiveness plane and by deriving the probabilities of genetic testing being cost-effective at NICE's lower and upper cost-effectiveness thresholds of £20,000 and £30,000/QALY gained, respectively.

Overview of economic modelling results and conclusions

The probabilistic results indicate that providing genetic testing to individuals with a carrier risk of 3% is potentially cost-effective when using the lower NICE cost-effectiveness threshold of £20,000/QALY gained. The ICER for genetic testing (versus no genetic testing) is

£10,782/QALY gained, with a 72% probability of being cost-effective at the NICE lower cost effectiveness threshold of £20,000/QALY.

The cost-effectiveness of genetic testing varied depending on the gender and age of index case. The cost-effectiveness of genetic testing was driven by the benefits to the index cases. Consequently, panel genetic testing was more cost-effective for female index cases, as they could benefit directly from preventive measures like risk-reducing surgery, resulting in reduced cancer risk. This means that for female index cases panel genetic testing could be offered at lower carrier risks.

For females aged 30-40, there was potential cost-effectiveness in offering genetic testing at a carrier risk threshold of approximately 2%. However, as the age increased, the carrier risk threshold also increased. For female cases aged 70, it was unlikely to be cost-effective to offer genetic testing at any carrier risk ranging from 1% to 10%.

Generally, the cost-effectiveness of panel genetic testing decreased as the index cases age increased. As the ages of index cases increased, the benefits to index cases themselves, their older mothers and female siblings of a similar age decreased. Therefore, in older index cases, the benefits were mainly derived from identifying younger children who might carry pathogenic variants in ovarian cancer predisposition genes. Consequently, for the benefits of panel genetic testing to outweigh the additional costs, the prevalence of pathogenic variants in the older age groups needs to be higher.

In the case of male index cases aged 30, it was cost-effective to offer genetic testing at carrier risks of approximately 6% and above. Similarly for male index cases aged 40, a higher carrier risk of 8% would be necessary to justify genetic testing. However, for index cases aged 50-70, it was unlikely to be cost-effective to offer genetic testing below a carrier risk of 10%. In male index cases, genetic testing aimed to identify relatives who might carry pathogenic variants in ovarian cancer predisposition genes. There were no direct benefits to males themselves. Therefore, panel genetic testing for males was considered cost-effective only at higher carrier risks where the prevalence of pathogenic variants in the population was high enough to offset the additional costs associated with genetic testing.

The analysis showed considerable uncertainty, as reflected in probabilistic results producing consistently higher ICERs. However, deterministic sensitivity analyses suggested overall robustness of the results in different scenarios explored. In some scenarios, such as optimal uptake of genetic testing in FDRs or optimal uptake of risk-reducing surgery, genetic testing was potentially cost-effective at lower carrier risks. The results were also sensitive to the age at which risk reducing surgery is initiated, with a slight decrease in cost-effectiveness as the age increases.

Evidence statements

Economic

Panel genetic testing (BRCA1, BRCA2, RAD51C, RAD51D, BRIP1) for people unaffected by cancer with carrier risks ranging from 1% to 10%

- Evidence from a cost-utility analysis based on modelling (guideline de-novo economic modelling) suggests that genetic testing for people with a carrier risk of 3% is potentially cost-effective, with an ICER of £10,782/QALY and a 72% probability of being cost-effective at this carrier risk. The results are sensitive to the gender and age of the index cases. For female index cases aged 30, genetic testing at a carrier risk of 2% is considered to be potentially cost-effective, with an ICER of £5,164/QALY gained. However, for male index cases aged 30, genetic testing is cost-effective only at a carrier risk of 6% and higher. In general, as the age of the index cases increases, the cost-effectiveness of panel genetic testing decreases. The study is directly applicable to the NICE decision-making context and has minor limitations.

BRCA genetic testing for women unaffected by cancer with carrier risks ranging from 5% to 40% and considering costs and QALYs for index people only:

- Evidence from a cost-utility analysis based on modelling (NICE CG164 2013) in the UK suggests that in women **unaffected by cancer but with a relative available for testing,** *BRCA* genetic testing is unlikely to be cost-effective for those aged 20-29 with a carrier risk of 5% but is cost-effective for carrier risks of 10% to 40%. For women aged 30-49, genetic testing is cost-effective for carrier risks of 5% to 40%. For women aged 50-59, genetic testing is unlikely to be cost-effective for a carrier risk of 5% but is cost-effective for carrier risks of 10% to 40%. For women aged 60-69 and 70+, genetic testing is unlikely to be cost-effective for carrier risks of 5% to 40%. The study is directly applicable to the NICE decision-making context and has minor limitations.
- Evidence from a cost-utility analysis based on modelling (NICE CG164 2013) in the UK suggests that in women **unaffected by cancer and with no relative available for testing,** *BRCA* genetic testing is likely to be cost-effective for those aged 20-69 with carrier risks ranging from 5% to 40%. However, for women aged 70+ genetic testing is unlikely to be cost-effective for carrier risks of 5% to 20% but may be potentially cost-effective for carrier risks of 30% to 40%. The study is directly applicable to the NICE decision-making context and has minor limitations.

BRCA genetic testing for women unaffected by cancer with carrier risks ranging from 5% to 40% and considering costs and QALYs for index people and all eligible relatives:

- Evidence from a cost-utility analysis based on modelling (NICE CG164 2013) suggests that in women **unaffected by cancer but with a relative available for testing,** *BRCA* genetic testing is likely to be cost-effective in those aged 30-59 with carrier risks ranging from 5% to 40%. For women aged 60-69, genetic testing is unlikely to be cost-effective for carrier risks of 5% and 10%. It is borderline cost-effective at a carrier risk of 15% (with the ICER of £17,513 - £20,252/QALY gained). However, genetic testing is likely to be cost-effective for carrier risks ranging from 20% to 40% in this age group. For women aged 70+, genetic testing is unlikely to be cost-effective for carrier risks of 5% to 20%. However, at carrier risks of 30% to 40%, genetic testing is likely to be 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 (NICE CG164 2013) suggests that in women **unaffected by cancer and who have no relative available for testing,** *BRCA* genetic testing is likely to be cost-effective for those aged 20 to 70+ with carrier risks ranging from 5% to 40%. The study is directly applicable to the NICE decision-making context and has minor limitations.

BRCA genetic testing for women with a carrier risk ≥10%

- Evidence from a cost-utility analysis based on modelling (Müller 2019) suggests that *BRCA1/2* genetic testing is likely to be cost-effective in women unaffected with cancer with a carrier risk ≥10% in Germany. The study is partially applicable to the NICE decision-making context and has minor limitations.

BRCA genetic testing for women unaffected by cancer but with first-degree relatives who have BRCA-related cancer (≥25%)

- Evidence from a cost-utility analysis based on modelling (Kwon 2019) suggests that *BRCA1/2* genetic testing is likely to be cost-effective compared with no genetic testing and also universal risk reducing surgery for all first-first degree relatives unaffected by cancer in Canada. The study is partially applicable to the NICE decision-making context and has potentially serious limitations.

BRCA genetic testing for women unaffected by cancer but with first- and/or second-degree relatives who have BRCA-related cancer

- Evidence from a cost-utility analysis based on modelling (Hoskins 2019) suggests that *BRCA1/2* genetic testing is likely to be cost-effective for eligible first- and second-degree relatives in Canada. The study is partially applicable to the NICE decision-making context and has minor limitations.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee were interested in cancer incidence and number of people carrying pathogenic variants associated with familial ovarian cancer and therefore chose them as critical outcomes. Identifying pathogenic variants associated with ovarian cancer has the potential to reduce cancer incidence through risk reducing treatments, but this will also depend on the rate of uptake of these treatments. Therefore, rates of uptake of risk reducing treatments such as chemoprevention, surgery and surveillance were also prioritised as critical outcomes.

Rates of genetic testing for relatives and rates of dissemination of the genetic information within the family were identified as important outcomes because the benefits of identification of pathogenic variants and risk reducing treatments can apply to blood relatives if the index case is found to carry a pathogenic variant.

The quality of the evidence

No studies were identified which were applicable to this review question.

Benefits and harms

No relevant clinical evidence for this review question was identified and so the recommendations are based on health economic evidence and modelling as well as the committee's clinical expertise and experience.

The committee decided that recommendations in the context of unaffected people would always be an economic decision rather than a clinical one, i.e. depending on how many people a health system could afford to test (for the related rationale see the 'cost effectiveness and resource use' section below). Testing anyone who wanted it would be too expensive so it has to be targeted at those who given the associated costs would most benefit from it. They also noted that it would not be necessary if someone had a low risk of having a pathogenic variant. The committee discussed that two groups of people would always be reaching a higher than 10% risk of having a pathogenic variant and should therefore be offered genetic testing (see section below with regards to the 10% threshold). These would be first-degree relatives of anyone with a pathogenic variant associated with ovarian cancer (cascade testing). They discussed that people who are blood relatives of a person with a known pathogenic variant and where no intervening blood relative (or their tissue) is available for genetic testing would also reach the 10% threshold and therefore should also be offered genetic testing.

They did not prioritise an effectiveness research recommendation because it would be unlikely to be carried out. There would be ethical considerations related to giving or not giving people a test when they have the same risk level.

Referral criteria

Based on information from the model the committee made a referral recommendation with a list of criteria for genetic counselling and genetic testing that healthcare professionals in primary care and secondary care can apply. These criteria include having any first-degree relative with a diagnosis of ovarian cancer or having a maternal or paternal second-degree

relative with a diagnosis of ovarian cancer (including people with an unaffected intervening blood relative). The committee noted that this is in line with the thresholds from the economic model. It also includes referral of people identified through cascade testing (which involves offering genetic testing to family members of individuals with known pathogenic variants).

Cost effectiveness and resource use

Evidence from the guideline de-novo economic analysis indicated that providing panel genetic testing to individuals with a carrier risk of 3% may be cost-effective when using the lower NICE cost-effectiveness threshold of £20,000/QALY gained. The ICER for genetic testing (versus no genetic testing) is £10,782/QALY gained, with a 72% probability of being cost-effective at the NICE lower cost effectiveness threshold of £20,000/QALY.

The committee noted that the cost-effectiveness of panel genetic testing differed based on the gender and age of index cases. As a result, they decided to recommend specific carrier risk thresholds for panel genetic testing in various populations. Evidence indicated that offering panel genetic testing to females was cost-effective at lower carrier risks, as they would directly benefit from the preventative measures, such as risk reducing surgery. For male index cases the benefits would arise from identifying carrier status in their female first-degree relatives. Therefore, there would be no direct benefits to male index cases themselves and the threshold for genetic testing would need to be higher in male index cases.

The committee additionally considered the finding that the cost-effectiveness of genetic testing diminishes with age, which is consistent with their expectations. This finding is also consistent with the economic modelling undertaken for the NICE guideline on familial breast cancer. Recognising the variations in the cost-effectiveness by gender and age of index cases, the committee acknowledged the need to capture these in their recommendations for the thresholds for genetic testing.

The committee acknowledged that the economic analysis has looked only at carrier risk ranging from 1% to 10% and the actual carrier risks at which it may be cost-effective to offer genetic testing could be higher for certain sub-groups, such as males aged 50 and above. Nevertheless, exploring carrier risks above 10% was beyond the economic analysis's scope as the committee ascertained that the current threshold used by services to offer genetic testing is 10%. Consequently, in sub-groups where genetic testing was unlikely to be cost-effective at the carrier risks explored in the economic analysis, the committee agreed to recommend the current practice threshold for genetic testing.

The committee further discussed that the sub-groups, specifically females aged 70 and above and males aged 50 and above, in which genetic testing is unlikely to be cost-effective at the carrier risks that were explored in de-novo modelling, would represent a small number of people. They explained that for females aged 70 and over who are at risk of familial ovarian cancer, it would be highly unusual for them to reach this age without having any relatives who have either undergone genetic testing or had cancer. Consequently, most of these people would likely have already been identified through cascade testing.

Eligibility criteria for genetic testing include having a relative diagnosed with breast or ovarian cancer. To provide the potential size of the population of women aged 70 and over, the average number of women in this age group in England and Wales was obtained, alongside the mean number of first- and second-degree relatives and their respective ages, as well as ovarian cancer incidence data. Based on this information, it was estimated that the cohort of relatives with ovarian cancer for women aged 70 and over would only represent approximately 13% of the entire cohort of relatives with ovarian cancer within a given year.

Also, currently very few males seek genetic testing and most eligible males would likely have been identified through cascade testing due to affected relatives. That is, it would be very rare for these males to have no affected first- or second-degree relatives.

The committee noted the consistency of the results with previous findings in populations at high risk of pathogenic variants linked to an increased ovarian cancer risk. Specifically, they referred to the evidence supporting the cost-effectiveness of genetic testing for *BRCA* in the Ashkenazi Jewish population, where the carrier risk is estimated to be around 2%.

The committee discussed the limitations of the economic analysis undertaken for this guideline. They acknowledged that the analysis focused on modelling the *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1* genes, due to the extensive scope of the question. Furthermore, the analysis considered the impact of pathogenic variants on ovarian and breast cancer risks. However, there are other genes included in the panel genetic test that are associated with an increased risk of ovarian cancer. It was recognised that this approach likely led to an underestimation of the cost-effectiveness of panel genetic testing. Therefore, there is greater confidence in the cost-effectiveness of genetic testing at the recommended carrier risks.

The committee discussed uncertainty in some model inputs used in the economic analysis. Specifically, the analysis approximated ovarian cancer mortality in individuals with pathogenic variants by using data from the general ovarian cancer population. The committee recognised that *BRCA* mutations might be associated with improved short-term survival but acknowledged that this evidence is uncertain. However, the sensitivity analysis indicated that varying this model input had minimal impact on the ICERs of genetic testing and did not change the conclusions.

There was also uncertainty in the uptake rate of genetic testing in first-degree relatives and the unit cost of genetic testing. Nevertheless, the committee referred to the sensitivity analyses, which demonstrated that the model's conclusions remained robust when varying these model inputs.

The committee also referred to the existing economic evidence, specifically five published studies on the cost-effectiveness of *BRCA* genetic testing in women unaffected by ovarian cancer.

They discussed the economic analysis conducted for the NICE guideline on familial breast cancer which was directly relevant to the decision-making context but had potentially serious methodological limitations. The committee noted that the analysis was outdated and used assumptions to approximate some of the cancer incidence data. They also noted that there is more recent effectiveness and cost data. Furthermore, the analysis incorporated the uptake rate of genetic testing in index cases, which the committee deemed irrelevant. Index individuals who do not take up genetic testing would receive no intervention and incur no intervention costs. Overall, the committee found it difficult to draw conclusions from this evidence.

Nonetheless, the findings of the economic analysis conducted for the NICE guideline on familial breast cancer aligned with the committee's expectations. Genetic testing for *BRCA* in women unaffected by cancer was cost-effective, even at lower carrier risks, when considering the impact on eligible relatives. Also, the cost-effectiveness of genetic testing decreased with age which is consistent with the economic modelling results conducted for this guideline.

The committee acknowledged other existing economic evaluations. However, all these studies were non-UK and were only partially applicable to the NICE decision-making context. The committee noted that none of the studies explicitly assessed the impact of offering genetic testing to women with different carrier risks. In many studies the population included people unaffected by cancer but with first and/or second-degree relatives who had cancer. This means that these unaffected women had higher pathogenic variant carrier risks than the current NHS threshold of 10%. Nevertheless, the committee found it encouraging that most of this evidence suggested that offering genetic testing to people unaffected by cancer may be a cost-effective use of healthcare resources.

The committee acknowledged that their recommendations may result in more unaffected people becoming eligible for genetic testing, requiring an expansion of services. Given the current capacity of genetic services and staffing issues, the committee noted that affected people or their tissues might be prioritised for testing. However, they also noted that unaffected individuals who may be at risk of familial ovarian cancer need to proactively seek testing, typically through their GP, or be identified in some other way by healthcare services.

The committee noted that, in the long term, services will need to increase their capacity to meet the increased demand for genetic testing in unaffected individuals. However, they also explained that any upfront costs associated with this expansion will be offset by improved identification of at-risk individuals who can then receive the necessary risk management.

Referral criteria

The committee explained that a family history of ovarian cancer in first- or second-degree relatives who have not had genetic testing is a standard criteria healthcare professionals use to refer individuals to genetic services. Such criteria are easy and efficient, particularly in primary care settings with limited consultation time. The committee noted that this recommendation would only apply to a small number of people, as most would have relatives with ovarian cancer who have already undergone genetic testing and would have accessed services via cascade testing.

The committee acknowledged that there could be an increase in historical referrals based on family history criteria, potentially creating additional demand for genetic services. For example, individuals not previously referred to genetic services due to the absence of the explicit criteria above may now be referred for genetic testing due to this recommendation.

The committee acknowledged that cascade testing is already current practice. Therefore, the implementation of this recommendation would not require additional resources.

Other factors the committee took into account

The committee noted the NICE guideline on familial breast cancer is relevant in the context of ovarian cancer because of pathogenic variants that predispose people to ovarian as well as breast cancer. They therefore cross-referred to it so that healthcare professionals can follow the recommendations for people with breast cancer.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.1, 1.4.1 to 1.4.4 in the guideline.

References

Economic

Hoskins 2019

Hoskins, P., Eccleston, A., Hurry, M., Dyer, M., Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. A Canadian model, Gynecologic Oncology, 153, 87-91, 2019

Kwon 2019

Kwon, J.S., Tinker, A.V., Hanley, G.E., Pansegrau, G., Sun, S., Carey, M.S., et al., BRCA mutation testing for first-degree relatives of women with high-grade serous ovarian cancer. Gynecologic Oncology, 152, 459-64, 2019

Müller 2019

Müller, D., Danner, M., Schmutzler, R., Engel, C., Wassermann, K., Stollenwerk, B., et al., Economic 24ffective of risk-adapted screen-and-treat strategies in women at high risk for breast or ovarian cancer, The European Journal of Health Economics, 20, 739-50, 2019

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

Appendices

Appendix A Review protocol

Review protocol for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

Table 7: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022351078
1.	Review title	Carrier probability at which genetic testing should be offered to people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes
2.	Review question	At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?
3.	Objective	To identify at what carrier probability threshold people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes 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 • 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**: people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes Exclusion: women with ovarian cancer (covered by I)
7.	Intervention	Germline pathogenic variant analysis only if carrier probability exceeds a threshold value
8.	Comparator	Different threshold values
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Systematic reviews/meta-analyses of RCTs In the absence of RCTs observational studies will be included
10.	Other exclusion criteria	**Inclusion**: • Full text papers • Comparative 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	The GC changed the review question from the scope as they thought the original question was too prescriptive in terms of the population by including only those with a family history of ovarian cancer. Family history of other cancers could also be linked to *BRCA1/2* or Lynch Syndrome.

		This question potentially updates CG 164 recommendations for people with no personal history of breast/ovarian cancer: 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] 1.5.12 Offer genetic testing in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more and an affected relative is unavailable for testing. [2013]

12.	Primary outcomes (critical outcomes)	• Cancer incidence
		• Number of people carrying pathogenic variants
		• Rates of uptake of risk reducing treatments:
		  ○ chemoprevention
		  ○ surgery
		  ○ surveillance

13.	Secondary outcomes (important outcomes)	• Rates of genetic testing for relatives • Rates of dissemination of the genetic information within the family
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI 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 quality assessed 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 I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 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: • Older studies vs newer studies (older sequencing methods vs next generation methods for germline pathogenic variant analysis) Evidence will be sub-grouped by the following only in the event that there is significant 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	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, Centre for Guidelines, National Institute for Health and Care Excellence (NICE) Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)		
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://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=351078	
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	

CENTRAL: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; INAHTA: International Health Technology Assessment; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; ROBs: risk of bias

Appendix B Literature search strategies

Literature search strategies for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

One literature search was performed for the review questions F and G.

Database: Ovid MEDLINE ALL

Date of last search: 25/01/2023

#	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*)).tw,kf.
3	or/1-2
4	exp Breast Neoplasms/
5	exp "Neoplasms, Ductal, Lobular, and Medullary"/
6	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
7	or/4-6
8	3 or 7
9	exp Genetic Predisposition to Disease/
10	Pedigree/
11	exp Neoplastic Syndromes, Hereditary/
12	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
13	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
14	HNPCC.tw,kf.
15	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
16	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
17	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
18	gardner* syndrome*.tw,kf.
19	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
20	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
21	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
22	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
23	risk factors/
24	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
25	((carrier* or gene*) adj3 mutat*).tw,kf.
26	exp Genes, Tumor Suppressor/
27	exp Tumor Suppressor Proteins/
28	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
29	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
30	exp Fanconi Anemia Complementation Group Proteins/
31	(Fanconi An?emia adj3 protein*).tw,kf.
32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.
33	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.

#	Searches
34	Rad51 Recombinase/
35	Ataxia Telangiectasia Mutated Proteins/
36	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
37	Checkpoint Kinase 2/
38	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
39	Carcinoma, Small Cell/ge [Genetics]
40	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
42	exp Sertoli-Leydig Cell Tumor/
43	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
44	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
45	Epithelial Cell Adhesion Molecule/
46	Epithelial cell adhesion molecule*.tw,kf.
47	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
48	or/9-47
49	8 and 48
50	Germ-Line Mutation/
51	((germline* or germ line* or pathogenic) adj2 (carrier* or variant* or mutat*) adj3 (test* or analys?s or assess* or evaluat*)).ti,ab,kf.
52	(probabilit* adj2 threshold*).ti,ab,kf.
53	exp Genetic Testing/
54	(genetic adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)).ti,ab,kf.
55	exp Sequence Analysis/
56	((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.
57	((sanger or dna) adj2 (sequenc* or method* or technique* or technolog* or applicat*)).ti,ab,kf.
58	chain termination method*.ti,ab,kf.
59	((multi* adj3 probe amplification*) or MLPA).ti,ab,kf.
60	(next generation sequenc* or NGS).ti,ab,kf.
61	Precision Medicine/
62	((precision or predict* or individual* or personal*) adj2 medicine).ti,ab,kf.
63	(p health or phealth).ti,ab,kf.
64	exp Risk Assessment/ and ge.fs.
65	or/50-64
66	49 and 65
67	letter/
68	editorial/
69	news/
70	exp historical article/
71	Anecdotes as Topic/
72	comment/
73	case reports/
74	(letter or comment*).ti.
75	or/67-74
76	randomized controlled trial/ or random*.ti,ab.
77	75 not 76
78	animals/ not humans/
79	exp Animals, Laboratory/
80	exp Animal Experimentation/

#	Searches
81	exp Models, Animal/
82	exp Rodentia/
83	(rat or rats or mouse or mice or rodent*).ti.
84	or/77-83
85	66 not 84
86	limit 85 to English language
87	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.
88	drug therapy.fs.
89	(groups or placebo or randomi#ed or randomly or trial).ab.
90	Clinical Trials as Topic/
91	trial.ti.
92	or/87-91
93	Meta-Analysis/
94	Meta-Analysis as Topic/
95	(meta analy* or metanaly* or metaanaly*).ti,ab.
96	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
97	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
98	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
99	(search* adj4 literature).ab.
100	(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.
101	cochrane.jw.
102	or/93-101
103	86 and (92 or 102)
104	Observational Studies as Topic/
105	Observational Study/
106	Epidemiologic Studies/
107	exp Case-Control Studies/
108	exp Cohort Studies/
109	Cross-Sectional Studies/
110	Controlled Before-After Studies/
111	Historically Controlled Study/
112	Interrupted Time Series Analysis/
113	Comparative Study.pt.
114	case control$.tw.
115	case series.tw.
116	(cohort adj (study or studies)).tw.
117	cohort analy$.tw.
118	(follow up adj (study or studies)).tw.
119	(observational adj (study or studies)).tw.
120	longitudinal.tw.
121	prospective.tw.
122	retrospective.tw.
123	cross sectional.tw.
124	or/104-123
125	86 and 124

Database: Ovid Embase

Date of last search: 25/01/2023

#	Searches
1	exp ovary tumor/

#	Searches
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*)).tw,kf.
3	or/1-2
4	exp breast tumor/
5	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
6	or/4-5
7	3 or 6
8	exp genetic predisposition/
9	pedigree/
10	exp hereditary tumor syndrome/
11	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
12	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
13	HNPCC.tw,kf.
14	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
15	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
16	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
17	gardner* syndrome*.tw,kf.
18	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
19	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
20	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
21	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
22	risk factor/
23	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
24	((carrier* or gene*) adj3 mutat*).tw,kf.
25	tumor suppressor gene/
26	exp tumor suppressor protein/
27	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
28	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
29	Fanconi anemia protein/
30	(Fanconi An?emia adj3 protein*).tw,kf.
31	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.
32	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
33	Rad51 protein/
34	ATM protein/
35	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
36	checkpoint kinase 2/
37	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
38	small cell carcinoma/
39	genetics/
40	38 and 39
41	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
42	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
43	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/

#	Searches
44	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
45	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
46	epithelial cell adhesion molecule/
47	Epithelial cell adhesion molecule*.tw,kf.
48	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
49	or/8-37,40-48
50	7 and 49
51	germline mutation/
52	((germline* or germ line* or pathogenic) adj2 (carrier* or variant* or mutat*) adj3 (test* or analys?s or assess* or evaluat*)).ti,ab,kf.
53	(probabilit* adj2 threshold*).ti,ab,kf.
54	exp genetic screening/
55	(genetic adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)).ti,ab,kf.
56	exp sequence analysis/
57	((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.
58	((sanger or dna) adj2 (sequenc* or method* or technique* or technolog* or applicat*)).ti,ab,kf.
59	chain termination method*.ti,ab,kf.
60	((multi* adj3 probe amplification*) or MLPA).ti,ab,kf.
61	(next generation sequenc* or NGS).ti,ab,kf.
62	personalized medicine/
63	(next generation sequenc* or NGS).ti,ab,kf.
64	(p health or phealth).ti,ab,kf.
65	exp *risk assessment/
66	exp *genetics/
67	65 and 66
68	or/51-64,67
69	50 and 68
70	letter.pt. or letter/
71	note.pt.
72	editorial.pt.
73	case report/ or case study/
74	(letter or comment*).ti.
75	or/70-74
76	randomized controlled trial/ or random*.ti,ab.
77	75 not 76
78	animal/ not human/
79	nonhuman/
80	exp Animal Experiment/
81	exp Experimental Animal/
82	animal model/
83	exp Rodent/
84	(rat or rats or mouse or mice or rodent*).ti.
85	or/77-84
86	69 not 85
87	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
88	86 not 87
89	limit 88 to English language
90	random*.ti,ab.
91	factorial*.ti,ab.
92	(crossover* or cross over*).ti,ab.

#	Searches
93	((doubl* or singl*) adj blind*).ti,ab.
94	(assign* or allocat* or volunteer* or placebo*).ti,ab.
95	crossover procedure/
96	single blind procedure/
97	randomized controlled trial/
98	double blind procedure/
99	or/90-98
100	systematic review/
101	meta-analysis/
102	(meta analy* or metanaly* or metaanaly*).ti,ab.
103	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
104	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
105	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
106	(search* adj4 literature).ab.
107	(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.
108	((pool* or combined) adj2 (data or trials or studies or results)).ab.
109	cochrane.jw.
110	or/100-109
111	89 and (99 or 110)
112	Clinical study/
113	Case control study/
114	Family study/
115	Longitudinal study/
116	Retrospective study/
117	comparative study/
118	Prospective study/
119	Randomized controlled trials/
120	118 not 119
121	Cohort analysis/
122	cohort analy$.tw.
123	(Cohort adj (study or studies)).tw.
124	(Case control$ adj (study or studies)).tw.
125	(follow up adj (study or studies)).tw.
126	(observational adj (study or studies)).tw.
127	(epidemiologic$ adj (study or studies)).tw.
128	(cross sectional adj (study or studies)).tw.
129	case series.tw.
130	prospective.tw.
131	retrospective.tw.
132	or/112-117,120-131
133	89 and 132

Database: Cochrane Database of Systematic Reviews Issue 1 of 12, January 2023 2022; Cochrane Central Register of Controlled Trials Issue 1 of 12, January 2023

Date of last search: 25/01/2023

#	Searches
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2	(ovar* NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Breast Neoplasms] explode all trees

#	Searches
#5	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#6	((breast* or mammary) NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)):ti,ab,kw
#7	{OR #4-#6}
#8	#3 OR #7
#9	MeSH descriptor: [Genetic Predisposition to Disease] explode all trees
#10	MeSH descriptor: [Pedigree] this term only
#11	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees
#12	((hereditary or inherit* or familial) NEAR/3 (nonpolyposis or "non polyposis") NEAR/3 (colon or colorectal or bowel) NEAR/3 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#13	((lynch or "Muir Torre") NEAR/2 (syndrome* or cancer*)):ti,ab,kw
#14	HNPCC:ti,ab,kw
#15	(peutz* or intestin* NEXT polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* NEAR/1 lentigino*)):ti,ab,kw
#16	((hamartoma* or "polyps and spots" or cowden*) NEAR/2 (syndrome* or polyp*)):ti,ab,kw
#17	((hereditary or inherit* or familial or adenomato* or attenuated) NEAR/3 polyp* NEAR/3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)):ti,ab,kw
#18	gardner* NEXT syndrome*:ti,ab,kw
#19	(MUTYH or MYH or FAP or AFAP or APC):ti,ab,kw
#20	((familial or inherit* or heredit* or predispos* or pre NEXT dispos* or susceptib* or ancestr* or genealog* or descent) NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#21	("hereditary breast and ovarian cancer" or HBOC or "Li Fraumeni syndrome" or SBLA or LFS):ti,ab,kw
#22	(famil* NEAR/2 histor* NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#23	MeSH descriptor: [Risk Factors] this term only
#24	((risk* or probabil*) NEAR/3 (high* or increas* or factor* or rais*) NEAR/3 (mutat* or malignan* or gene* or variant*)):ti,ab,kw
#25	((carrier* or gene*) NEAR/3 mutat*):ti,ab,kw
#26	MeSH descriptor: [Genes, Tumor Suppressor] explode all trees
#27	MeSH descriptor: [Tumor Suppressor Proteins] explode all trees
#28	((tumor* or tumour* or cancer* or metastasis or metastases or growth*) NEAR/2 (suppress* NEAR/1 (gene* or protein*))):ti,ab,kw
#29	(anti NEXT oncogene* or antioncogene* or onco NEXT suppressor* or oncosuppressor*):ti,ab,kw
#30	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#31	((Fanconi NEXT Anemia or fanconi NEXT anaemia) NEAR/3 protein*):ti,ab,kw
#32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2):ti,ab,kw
#33	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw
#34	MeSH descriptor: [Rad51 Recombinase] this term only
#35	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only
#36	(("Ataxia telangiectasia" NEAR/1 mutated NEAR/1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1):ti,ab,kw
#37	MeSH descriptor: [Checkpoint Kinase 2] this term only
#38	(((checkpoint or "check point" or "serine threonine") NEAR/2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2):ti,ab,kw
#39	MeSH descriptor: [Carcinoma, Small Cell] this term only and with qualifier(s): [genetics - GE]
#40	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or "SNF2 beta"):ti,ab,kw
#42	MeSH descriptor: [Sertoli-Leydig Cell Tumor] explode all trees
#43	(((Sertoli or leydig) NEAR/3 (tumor* or tumour* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or androblastoma* or andreoblastoma* or SLCT or gynandroblastoma*):ti,ab,kw
#44	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H48 LIKE"):ti,ab,kw
#45	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only

#	Searches
#46	Epithelial NEXT cell NEXT adhesion NEXT molecule*:ti,ab,kw
#47	(EPCAM* or "EP CAM" or ESA or KSA or M4S1 or "MK 1" or DIAR5 or EGP* or Ly74 or gp40 or CD326 or GA733* or GA 733 or KS14 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or "MOC 31" or "Ber Ep4" or TACSTD1):ti,ab,kw
#48	{OR #9-#47}
#49	#8 AND #48
#50	MeSH descriptor: [Germ-Line Mutation] this term only
#51	((germline* or germ NEXT line* or pathogenic) NEAR/2 (carrier* or variant* or mutat*) NEAR/3 (test* or analysis or analyses or assess* or evaluat*)):ti,ab,kw
#52	(probabilit* NEAR/2 threshold*):ti,ab,kw
#53	MeSH descriptor: [Genetic Testing] explode all trees
#54	(genetic NEAR/2 (test* or screen* or analysis or analyses or assess* or evaluat* or detect* or incidence* or method*)):ti,ab,kw
#55	MeSH descriptor: [Sequence Analysis] explode all trees
#56	(("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
#57	((sanger or dna) NEAR/2 (sequenc* or method* or technique* or technolog* or applicat*)):ti,ab,kw
#58	chain termination method*:ti,ab,kw
#59	((multi* NEAR/3 probe amplification*) or MLPA):ti,ab,kw
#60	("next generation sequence" or "next generation sequencing" or NGS):ti,ab,kw
#61	MeSH descriptor: [Precision Medicine] this term only
#62	((precision or predict* or individual* or personal*) NEAR/2 medicine):ti,ab,kw
#63	("p health" or phealth):ti,ab,kw
#64	MeSH descriptor: [Risk Assessment] explode all trees
#65	MeSH descriptor: [Genetics] explode all trees
#66	#64 and #65
#67	{OR #50-#63, #66}
#68	#49 and #67
#69	conference:pt or (clinicaltrials or trialsearch):so
#70	#68 NOT #69

Database: Epistemonikos

Date of last search: 25/01/2023

#	Searches
1	(advanced_title_en:((advanced_title_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer)) OR advanced_abstract_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer))))
2	(advanced_title_en:((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

Database: INAHTA International HTA Database

Date of last search: 25/01/2023

#	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	"Breast Neoplasms"[mhe]
5	"Neoplasms, Ductal, Lobular, and Medullary"[mhe]

#	Searches
6	(((breast* or mammary) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[Title] OR (((breast* or mammary) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[abs]
7	#6 OR #5 OR #4
8	#7 OR #3
9	(((((hereditary or inherit* or familial) AND (nonpolyposis or non polyposis) AND (colon or colorectal or bowel) AND cancer*)))[Title] OR ((((hereditary or inherit* or familial) AND (nonpolyposis or non polyposis) AND (colon or colorectal or bowel) AND cancer*)))[abs]
10	((peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1))[Title] OR ((peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1))[abs]
11	(((hereditary or inherit* or familial or adenomato* or attenuated) AND polyp* AND (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)))[Title] OR (((hereditary or inherit* or familial or adenomato* or attenuated) AND polyp* AND (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)))[abs]
12	((MUTYH or MYH or FAP or AFAP or APC))[Title] OR ((MUTYH or MYH or FAP or AFAP or APC))[abs]
13	(((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib*) 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 (((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib*) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
14	(("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS))[Title] OR (("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS))[abs]
15	((famil* AND histor* 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 ((famil* AND histor* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
16	(((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[Title] OR (((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[abs]
17	(((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[Title] OR (((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[abs]
18	(((carrier* or gene*) AND mutat*))[Title] OR (((carrier* or gene*) AND mutat*))[abs]
19	((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2))[Title] OR ((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2))[abs]
20	#19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
21	#8 AND #20
22	"Germ-Line Mutation"[mh]
23	(((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]
24	((probabilit* AND threshold*))[Title] OR ((probabilit* AND threshold*))[abs]
25	"Genetic Testing"[mhe]
26	((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]
27	"Sequence Analysis"[mhe]
28	(((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]
29	(((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]
30	("chain termination method*")[Title] OR ("chain termination method*")[abs]
31	((multi* AND probe amplification*))[Title] OR ((multi* AND probe amplification*))[abs]
32	(MLPA)[Title] OR (MLPA)[abs]
33	(("next generation sequenc*" or NGS))[Title] OR (("next generation sequenc*" or NGS))[abs]
34	"Precision Medicine"[mh]
35	(((precision or predict* or individual* or personal*) AND medicine))[Title] OR (((precision or predict* or individual* or personal*) AND medicine))[abs]

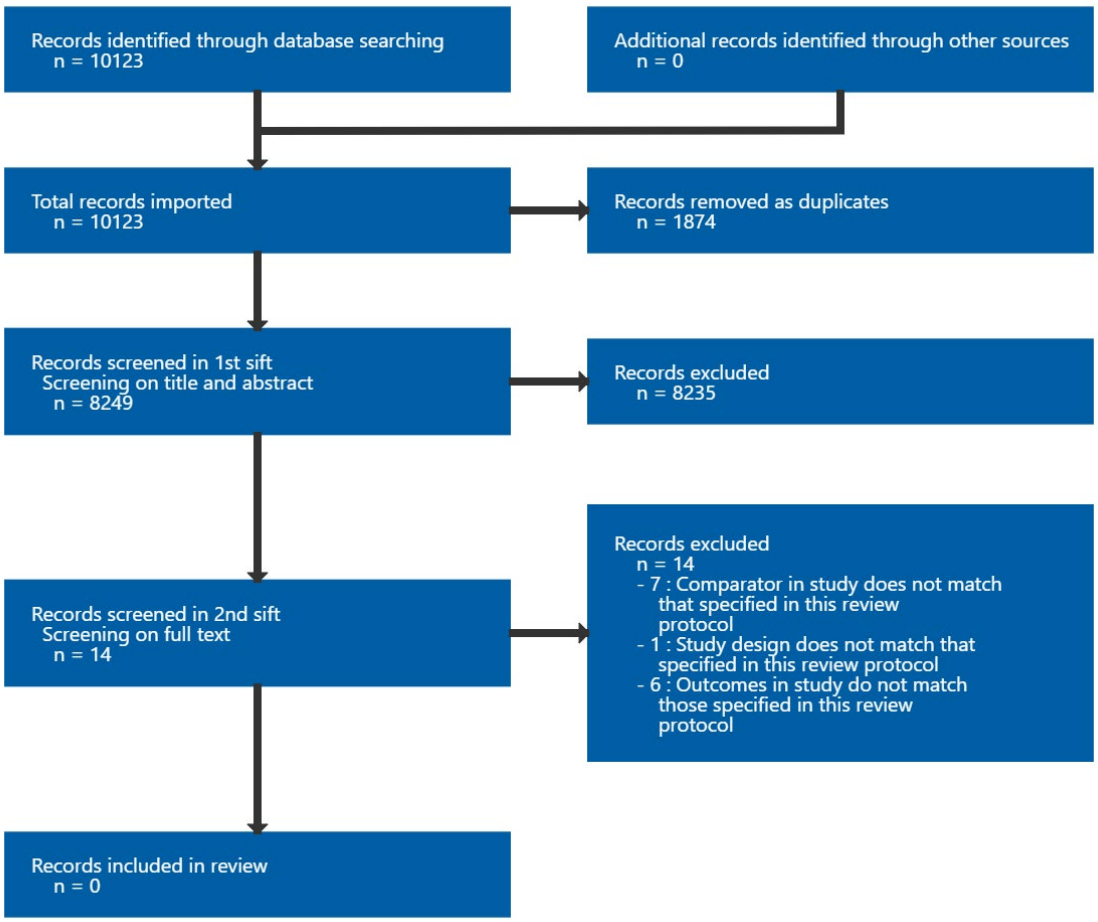
#	Searches
36	((p health or phealth))[Title] OR ((p health or phealth))[abs]
37	#36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22
38	#21 AND #37

Appendix C Effectiveness evidence study selection

Study selection for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

One literature search was performed for the review questions F and G.

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

No evidence was identified which was applicable to this review question.

Appendix E Forest plots

Forest plots for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

No evidence was identified which was applicable to this review question.

Appendix F GRADE tables

GRADE tables for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

No evidence was identified which was applicable to this review question.

Appendix G Economic evidence study selection

Study selection for: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes 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 people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

Table 8: Economic evidence tables for *BRCA1/2* genetic testing for women unaffected by cancer with carrier risks ranging from 5% to 40% (with and without available affected relative to test)

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
NICE Familial Breast Cancer Guideline CG164 2013 (Last updated: 2019) UK Cost-utility analysis Source of funding: The Department of Health and Social Care ***An affected relative is available to test***	Intervention Genetic testing at carrier risks ranging from 5% to 40% Comparator No genetic testing	Women unaffected by cancer with an affected relative available to test 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 of 5%, 10%, 15%, 20%, 30% and 40% -Probability of death from cancer 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 Mean cost per participant (for carrier probabilities of 5% and 40%): 20-29 years Genetic testing: £9,081 and £19,137	ICERs: - 20-29 years – genetic testing for a carrier risk of 5% was cost effective at £30k/QALY threshold (ICER £20,348/QALY); genetic testing for carrier risk of 10-40% was cost effective at £20k/QALY threshold - 30-39 years – genetic testing for carrier risks of 5-40% was cost effective at £20k/QALY threshold (ICER<£13k/QALY) - 40-49 years – genetic testing for carrier risks of 5-40% was cost effective at £20k/QALY threshold (ICER<£14k/QALY)	Perspective: NHS Currency: UK£ Cost year: 2011 Time horizon: 50 years Discounting: 3.5% for costs and outcomes Applicability: Directly Limitations: Minor

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 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: £7,805 and £18,447 Difference: £1,275 and £690 30-39 years Genetic testing: £11,458 and £24,432 Control: £10,279 and £23,827 Difference: £1,179 and £605 40-49 years Genetic testing: £13,062 and £27,587 Control: £11,886 and £26,930 Difference: £1,176 and £657 50-59 years Genetic testing: £12,773 and £25,082 Control: £11,500 and £24,209 Difference: £1,273 and £873 60-69 years Genetic testing: £11,541 and £20,889	- 50-59 years – genetic testing for a carrier risk of 5% was cost effective at £30k/QALY threshold (ICER of £20,821/QALY), and for carrier risks of 10-40% was cost effective at £20k/QALY threshold (ICER <£19k/QALY) - 60-69 years – genetic testing for carrier risks of 5-20% was unlikely to be cost effective at £30k/QALY threshold (ICERs>£30k/QALY), and genetic testing for 30-40% carrier risks was cost effective at £30k/QALY threshold (ICERs <£20-22k/QALY) - 70+ years – genetic testing for any carrier risk of 5%-40% was unlikely to be cost-effective (ICERs>£58k/QALY) Using £20k/QALY threshold, the probabilities of genetic testing being cost effective:	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Control: £10,138 and £19,785 Difference: £1,403 and £1,104 70+ years Genetic testing: £9,762 and £16,161 Control: £8,187 and £14,783 Difference: £1,575 and £1,378 Primary outcome measure: QALYs with health-related quality of life scores from various published studies Mean QALYs per participant (for carrier probabilities of 5% and 40%): 0-29 years Genetic testing: 20.39 and 18.81 Control: 20.32 and 18.67 Difference: 0.0627 and 0.1357	- 20-29 years – 0.510 (no genetic testing preferred) for a carrier risk of 5%, 0.692 to 0.987 for carrier risks of 10% and 40% (genetic testing preferred), respectively - 30-39 years – 0.813 and 0.996 for carrier risks of 5% and 40%, respectively (genetic testing preferred) - 40-49 years – 0.80 and 0.99 for carrier risks of 5% and 40%, respectively (genetic testing preferred) - 50-59 years – 0.48 for a carrier risk of 5% (no genetic testing preferred), and 0.58 and 0.95 for carrier risks of 10% and 40% respectively (genetic testing preferred) - 60-69 years – 0.03 and 0.50 for carrier risks of 5% and 40% respectively (no genetic testing preferred) - 70+ years – 0.000 and 0.001 for carrier risks of 5% and 40%	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			30 to 39 years Genetic testing: 19.20 and 17.15 Control: 19.11 and 16.99 Difference: 0.0880 and 0.1546 40 to 49 years Genetic testing: 17.39 and 15.29 Control: 17.31 and 15.16 Difference: 0.0863 and 0.1389 50 to 59 years Genetic testing: 15.03 and 13.51 Control: 14.97 and 13.41 Difference: 0.0611 and 0.0963 60 to 69 years Genetic testing: 12.09 and 11.21 Control: 12.05 and 11.15 Difference: 0.0352 and 0.0550	respectively (no genetic testing preferred) Subgroup analysis: NA Sensitivity analysis: 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. **Including costs and QALYs for eligible relatives:** - 30-39 years – for carrier risks of 5% to 40% genetic testing was cost effective - 40-49 years – for carrier risks 5% to 40% genetic testing was cost effective	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			70+ years Genetic testing: 8.57 and 8.16 Control: 8.56 and 8.14 Difference: 0.0139 and 0.0236	- 50-59 years – for carrier risks 5% to 40% genetic testing was cost effective - 60-69 years – for carrier risks 5% and 10% genetic testing was unlikely to be cost effective, at a carrier risk of 15% the ICER was £17,513 - £20,252/QALY gained, and for carrier risks of 20% to 40% genetic testing was cost-effective - 70+ years – at carrier risks 5% to 20% genetic testing was unlikely to be cost-effective, and at carrier risks of 30% to 40% genetic testing was cost-effective	
NICE Familial Breast Cancer Guideline CG164 2013 (Last updated: 2019) UK Cost-utility analysis	**Intervention and comparator are the same as outlined above.**	Women unaffected by cancer without an affected relative available to test ***All data sources are the same as outlined above.***	**Costs includes are the same as outlined above.** Mean cost per participant (for carrier risk of 5% and 40%): 20-29 years	- 20-29 years – genetic testing for carrier risks ranging from 5-40% was dominant - 30-39 years – genetic testing for carrier risks ranging from 5-40% was dominant - 40-49 years – genetic testing for carrier risks	***All methods are the same as outlined above.***

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Source of funding: The Department of Health and Social Care ***An affected relative is not available to test***			Genetic testing: £7,515 and £16,667 Control: £7,727 and £17,370 Difference: -£212 and -£703 (favouring genetic testing) 30-39 years Genetic testing: £9,930 and £21,739 Control: £10,192 and £22,441 Difference: -£262 and -£702 (favouring genetic testing) 40-49 years Genetic testing: £11,579 and £24,731 Control: £11,796 and £25,325 Difference: -£217 and -£595 (favouring genetic testing) 50-59 years Genetic testing: £11,373 and £22,514 Control: £11,444 and £22,855	ranging from 5-40% was dominant - 50-59 years – genetic testing for carrier risks of 5%, 10%, 30% and 40% was dominant, and for carrier risks of 15% and 20% genetic testing was cost effective at £20k/QALY threshold (ICERs <£1,500/QALY) - 60-69 years – genetic testing for carrier risks of 5%, 10%, 15%, and 20% was cost-effective using £20k/QALY threshold, and for carrier risks of 30% and 40% genetic testing was dominant - 70+ years – genetic testing for carrier risks of 5%, 10%, 15%, and 20% was unlikely to be cost-effective at £30k/QALY threshold (ICERs >£30k/QALY), and for carrier risks of 30% and 40% genetic testing was cost-effective at £20k/QALY threshold (ICERs <16k/QALY)	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Difference: -£72 and -£341 (favouring genetic testing) 60-69 years Genetic testing: £10,227 and £18,688 Control: £10,110 and £18,747 Difference: £117 and -£58 (negative difference favours genetic testing) 70+ years Genetic testing: £8,538 and £14,352 Control: £8,171 and £14,052 Difference: £366 and £300 Primary outcome measure: QALYs with health-related quality of life scores from various published studies. Mean QALYs per participant (for carrier risks of 5% and 40%): 0-29 years	Using £20k/QALY threshold, the probabilities of genetic testing being cost effective: - 20-29 years – 0.982 and 0.999 at 5% and 40% carrier risks respectively (genetic testing preferred) - 30-39 years – 0.989 and 1.000 at 5% and 40% carrier risks respectively (genetic testing preferred) - 40 to 49 years – 0.988 and 1.000 at 5% and 40% carrier risks respectively (genetic testing preferred) - 50-59 years – 0.973 and 1.000 at 5% and 40% carrier risks respectively (genetic testing preferred) - 60-69 years – 0.892 and 0.990 at 5% and 40% carrier probability respectively (genetic testing preferred) - 70+ years – 0.349 to 0.213 for carrier risks of 5% to 20% (no genetic testing preferred), and	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Genetic testing: 20.40 and 18.96 Control: 20.34 and 18.84 Difference: 0.0601 and 0.1170 30-39 years Genetic testing: 19.21 and 17.34 Control: 19.13 and 17.21 Difference: 0.0860 and 0.1362 40-49 years Genetic testing: 17.41 to 15.50 Control: 17.32 to 15.38 Difference: 0.0847 to 0.1232 50-59 years Genetic testing: 15.04 and 13.66 Control: 14.98 and 13.57 Difference: 0.0596 and 0.0849 60-69 years	0.736 and 0.619 for carrier risks of 30% and 40%, respectively (genetic testing preferred) ***Results of sensitivity analyses same as above.*** **Including costs and QALYs for eligible relatives:** - Genetic testing was cost effective across all carrier risks ranging from 5% to 40% and all age groups ranging from 20-29 years up to 70 + years.	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Genetic testing: 12.09 and 11.30 Control: 12.06 and 11.25 Difference: 0.0336 and 0.0477 70+ years Genetic testing: 8.57 and 8.20 Control: 8.56 and 8.18 Difference: 0.0122 and 0.0193		

BNF: British National Formulary; BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; CG: Clinical Guideline; ICER: Incremental cost-effectiveness ratio; k: thousand; NA: Not applicable; NHS: National Health Service; QALY: Quality-adjusted life years; UK: United Kingdom

Table 9: Economic evidence table for *BRCA1/2* genetic testing for women unaffected by cancer but with first-degree relatives who have *BRCA*-related cancer

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Kwon 2019 Canada Cost-utility analysis Source of funding: UBC Division of Gynecologic	Intervention *BRCA1/2* mutation testing for all first-degree relatives followed by risk-reducing surgery (bilateral salpingo-oophorectomy, with or without mastectomy and reconstruction) for confirmed mutation carriers Comparator	A hypothetical cohort of unaffected female first-degree relatives, aged 40 years, of women with ovarian, fallopian tube or peritoneal high-grade serous carcinoma Modelling study (Markov)	Costs: *BRCA* mutation testing, genetic counselling, breast and ovarian cancer first line treatment, ovarian cancer first line treatment, outpatient laparoscopic risk reducing bilateral sapingo-oophorectomy, prophylactic	Universal risk reducing surgery was dominated by other options *BRCA1/2* testing (versus no testing): $7,888/QALY gained Probability of being cost-effective: NR	Perspective: Healthcare Currency: CAD Cost year: 2018 Time horizon: 50 years Discounting: 3% for costs and benefits Applicability: Partially Limitations: Potentially serious Other comments:

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Oncology Research Award. One of the authors has received funding from Astra Zeneca to conduct research relating to ovarian cancer detection.	No genetic testing for first-degree relatives Risk-reducing bilateral salpingo-oophorectomy for all first-degree relatives, without *BRCA* testing (this was as an alternative due to some first-degree relatives being referred for preventative surgery without genetic testing which may be unwarranted and may lead to increased risk of adverse effects such as early menopause)	Source of baseline data: Cancer risks, National US registries, and meta-analyses of cancer risks in people with *BRCA* Source of effectiveness data: Risk reducing surgery – unclear Source of resource use data: Various sources including national patient cost estimators, payment schedules, and reports Source of unit cost data: Unclear but seems to be National sources (Canadian Institute for Health Information, Breast Cancer Medical Services Plan schedule, Physician fee schedule)	mastectomy with reconstruction, annual cost of hormone replacement therapy Mean cost per participant: No *BRCA* testing: $8,524 BRCA testing all first-degree relatives: $10,135 All first-degree relatives receive risk reducing bilateral sapingo-oophorectomy without *BRCA* testing: $14,231 Primary measure of outcome: QALYs (with health-related quality of life scores from various published studies) Mean QALYs per participant: No *BRCA* testing: 18.99 *BRCA* testing all first-degree relatives: 19.20 All first-degree relatives receive risk reducing bilateral salpingo-	Subgroup analysis: NR Sensitivity analysis: -Findings robust to a wide range of costs, and variables such as *BRCA* mutation rates, and the proportion having risk reducing surgery in the context of a known *BRCA* mutation - Compliance with hormone replacement therapy must be very high to mitigate the downstream consequences associated with premenopausal risk reducing surgery. For example, the proportion using hormone replacement therapy must be higher than 79.3% for universal risk reducing bilateral salpingo-oophorectomy to be a more effective strategy than *BRCA* mutation testing first. Similarly, the utility for	- Lifetime risk ovarian cancer with *BRCA* mutation based on 22 studies involving 8,139 index case patients unselected for family history. Breast and ovarian cancer incidence rates for mutation carriers were estimated using a modified segregation analysis, based on the occurrence of these cancers in the relatives of mutation-carrying index case patients.

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			oophorectomy without *BRCA* testing: 18.52.	premenopausal risk reducing bilateral salpingo-oophorectomy must be greater than 0.956, for the universal risk reducing bilateral salpingo-oophorectomy (without *BRCA* mutation testing) to be preferred to *BRCA* mutation testing.	

Table 10: Economic evidence table for *BRCA1/BRAC2* genetic testing for women unaffected by cancer with a carrier risk ≥10% versus no genetic testing

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Müller 2019 Germany Cost-utility analysis Source of funding: Federal Ministry of Education and Research	Intervention *BRCA1/2* testing for women with a mutation probability of ≥10% Comparator No genetic testing	A cohort of 35-year-old women with an increased familial cancer risk but without a history of breast or ovarian cancer Modelling study (Markov) Source of baseline data: Unclear but for breast cancer risk includes prospective cohort	Costs: Genetic testing, ongoing intensified surveillance, prophylactic mastectomy, prophylactic oophorectomy, prophylactic mastectomy plus oophorectomy, breast conserving surgery (in case of breast cancer), oophorectomy in case of breast cancer, mastectomy in case of ovarian cancer, mastectomy in case of	ICERs: *BRCA1/2* testing (versus no testing): €17,027/QALY Probability of being cost-effective: 36%, 92% and 99% at a willingness to pay of €10k, €20k and €30k/QALY Subgroup analysis: NR Sensitivity analysis: - The ICER of genetic testing (versus no	Perspective: Healthcare Currency: Euro € Cost year: Likely 2018 Time horizon: 65 years Discounting: 3% for costs and benefits Applicability: Partially Limitations: Minor

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: Risk reducing surgery – cohort studies Source of resource use data: Data from specialized university hospitals across Germany and various other published studies Source of unit cost data: Unclear but seems to include National sources (National costing tool), university hospitals across Germany, and local sources (University Breast Centre for Franconia)	breast cancer, chemotherapy, end-of-life treatment Mean cost per participant: *BRCA* testing: €22,253 No testing: €14,997 Difference: €7,256 Primary measure of outcome: QALYs (with health-related quality of life scores from various published studies that used a mixture of measurement and valuation methods) Mean QALYs per participant: *BRCA* testing: 17.49 No testing: 17.07 Difference: 0.42.	testing) was most sensitive to the incidence of the first breast cancer, the choice of prophylactic surgery, relative risks associated with prophylactic surgeries, the discount rate, and ranged from €21k-45k/QALY. - In all other sensitivity analyses the ICER of genetic testing (versus no testing) remained below €20k/QALY including changes to the proportion mutation carriers, costs of prophylactic surgeries, costs of chemotherapy for women with breast cancer, costs of palliative care, first-year costs of treatment for women with ovarian cancer, screening and monitoring costs, utilities, genetic testing at the age of 40 years, and assumed risk reduction for breast cancer due to oophorectomy, and doubling the probability	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				of ipsilateral recurrent breast cancer	

Table 11: Economic evidence table for *BRCA1/BRAC2* genetic testing for women unaffected by cancer but with first- and/or second-degree relatives who have BRCA-related cancer

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Hoskins 2019 Canada Cost-utility analysis Source of funding: Not reported. Most of the authors have involvement with AstraZeneca.	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* testing and people were treated only if epithelial ovarian cancer developed.	A cohort of people of first-degree (N=766) and second-degree (N=207) female relatives of women with epithelial ovarian cancer Modelling study (Patient level simulation) Source of baseline data: Unclear Source of effectiveness data: Hazard ratios for risk-reducing surgeries from various published sources, unclear whether systematic review/meta-analysis, most estimates are likely from cohort studies Source of resource use data: Various published	Costs: *BRCA* test, genetic counselling (one pre-test session and one post-test session if a mutation was found), bilateral salpingo-oophorectomy, ovarian cancer treatment with/without surgery, chemotherapy, palliative care Total cost for a cohort of 3,759 people: Intervention: $133,862,700 Control: $136,767,186 Difference: −$2,904,486 The primary measure of outcome: QALYs with health-related quality of life scores from various published studies	ICERs: *BRCA* testing (vs no testing) dominant Probability of being cost-effective: 100% using a threshold of $100k/QALY Subgroup analysis: NR Sensitivity analysis: - Varying the proportion of people receiving risk-reducing surgery from 10% to 90% (base-case: 100%), genetic testing was dominant at risk-reducing surgery uptake levels of ≥40% and cost-effective (ICER < $50k/QALY) at 20% and 30% uptake levels	Perspective: Healthcare Currency: Canadian dollars Cost year: 2016 Time horizon: 50 years Discounting: 1.5% for costs and outcomes Applicability: Partially Limitations: Minor - Does not include the outcomes of the index patients, either in terms of their ovarian cancer or subsequent development of breast cancer - Breast cancer development was not included in the model, the inclusion of which may have resulted in higher testing costs and risk-reducing surgery costs, but greater QALY

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		sources and assumptions Source of unit cost data: National sources and published studies	Total QALYs for a cohort of 3,759 people: Intervention: 9951 Control: 9626 Difference: 325.65	- Genetic testing remained dominant when the age of risk-reducing bilateral salpingo-oophorectomy was 35 and 50 years and resulted in an ICER of $22,738/QALY at 60 years (base-case: 40 years) - Genetic testing remained dominant when changing the mean age of index case to 40 and 60 years (base-case: 50 years) - Genetic testing remained dominant when varying the ovarian cancer cost (without surgery) from $40,000-80,000, and at the cost of $20,000, genetic testing resulted in an ICER of $2,869/QALY (base-case: $34,412) - Genetic testing remained dominant when varying *BRCA* test costs from $250-1,600 (base-case: $675)	gains due to the avoidance of breast cancer - Base case assumes 100% risk-reducing surgery uptake. However, sensitivity analyses were undertaken. - Adverse events due to the risk-reducing surgery not included, such as menopause - Mortality was measured as all-cause mortality over a 50-year time horizon rather than epithelial ovarian cancer-specific mortality, which may have underestimated the cost-effectiveness (that is, survival optimistic, meaning that the impact of risk-reducing surgery was underestimated) - A 50% overall mortality rate with epithelial ovarian cancer was used. The estimate was from the Canadian Cancer Society

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
					Advisory Committee on Cancer Statistics.

Appendix I Economic model

Economic model for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

Introduction – objective of economic modelling

Identification of individuals with an increased risk of ovarian cancer, allows for early detection, empowers individuals to make informed decisions about their health, including the option of risk-reducing surgeries (RRS).

Currently, it is recommended that genetic testing be offered to those with a 10% combined pathogenic variant probability. However, with panel testing costs reducing, the threshold for testing has fallen, albeit inconsistently across centres.

Therefore, the aim of this economic evaluation was to assess at which carrier risk panel genetic testing should be offered to people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes, where there is no living affected relative available to test.

This type of genetic testing can also identify other relatives who may be susceptible to the mutation and allow for proactive measures to prevent the onset of cancer. Consequently, the economic analysis considered the potential impact of genetic testing on first-degree relatives (FDRs) as well.

Model structure

The model was constructed in two stages.

Stage 1

A decision tree was used to reflect key events in the clinical pathway from diagnostic genetic testing through to RRS and cancer progression (stage 2).

In the decision tree for each carrier risk ranging from 1% to 10% people (index population) were offered panel genetic testing.

Given high sensitivity and specificity associated with panel genetic testing, the likelihood of obtaining a false positive or false negative result was very small and the model considered only true positive cases (see section on Accuracy of genetic testing). Also, true negative result means that no genetic mutations were found in the individual being tested and these individuals would not incur any additional healthcare costs beyond the genetic test itself. While there is a possibility that individuals with a negative genetic test result, but a confirmed family history of ovarian cancer may still be offered RRS, this scenario is rare and to simplify the modelling process was not considered.

The decision tree included an extra step, whereby genetic testing was offered to FDRs (unaffected individuals) if the index individual's genetic test yielded a positive result.

Stage 2

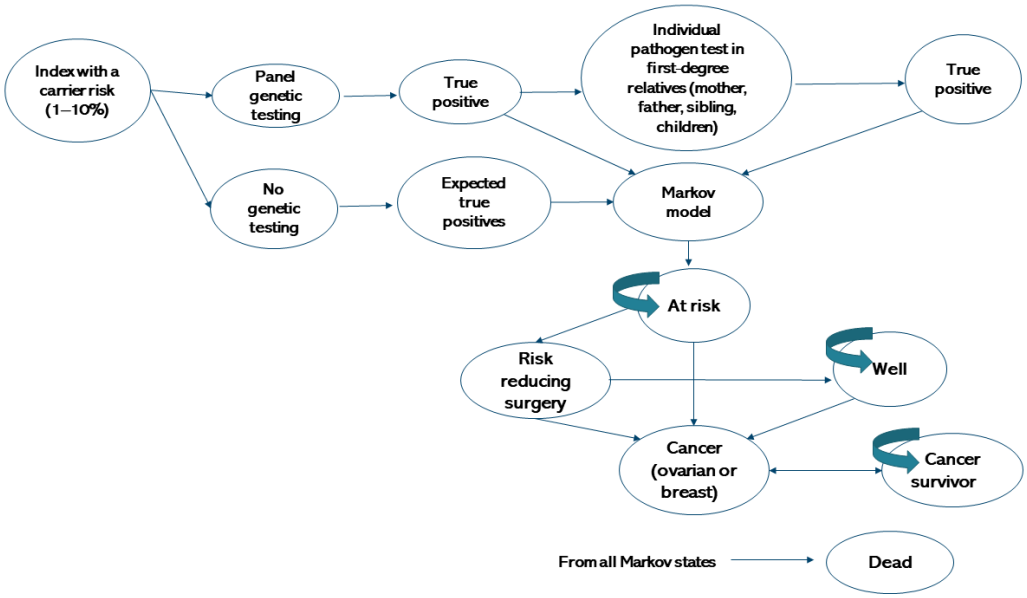
A Markov model was constructed to model long-term costs and outcomes of genetic testing or the absence of genetic testing.

The model incorporated various health states to simulate the take up of RRS, occurrence of new ovarian and breast cancers, survival and mortality, encompassing both cancer-related deaths and all-cause mortality.

Annual transitions between health states were evaluated over a model time horizon.

Please refer to Figure 2 for an illustration of the model structure and see section on Population for a more detailed explanation of how the model considered various populations and transitions.

Figure 2: Model overview. Upper part: decision tree model pathway. Lower part: Simplified illustration of the Markov model's health states with key transitions.



Note: Expected true positives following no genetic testing were equal to true positives cases following panel genetic testing. People following no genetic testing had zero probability of progressing to the 'Risk reducing surgery' state but followed the same Markov pathway. In the model from 'At risk' health state each year people could have opted to undergo RRS, enter a state of new ovarian or new breast cancer or die. Following RRS people could remain well or develop cancer. A circling arrow denotes recurrent health states where individuals could reside for multiple consecutive years. Once in cancer state individuals could reside in it for 10 years, included as tunnel states, after which survivors progressed to 'Cancer survivor' state. Cancer survivors could develop different type of cancer and progress through cancer-related states. The single arrow entering the 'Dead' state illustrates the possibility of transitioning there from all Markov health states and includes all-cause mortality and cancer-related mortality.

Intervention

The model considered offering panel genetic testing to people with initial carrier risks of pathogenic variants ranging from 1% to 10%. The model considered the panel genetic testing consisting of *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1*.

There are many more genes included in a panel of genetic testing. However, to simplify the modelling the committee prioritised the above 5 genes which are most

prevalent and have the substantial impact on ovarian cancer risk in pathogenic variant carriers.

The committee recognized that there are other Lynch syndrome-related mutations that raise the risk of ovarian cancer to the same level or even higher than *RAD51C*, *RAD51D* and *BRIP1* mutations. However, accounting for the full impact of Lynch syndrome-related mutations would require considering a broader range of cancers. Therefore, to narrow the scope of the analysis, the committee agreed to concentrate on *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* and their effect on ovarian and breast cancer.

It was further modelled that eligible FDRs will be offered genetic testing only for a variant that was identified in an index case. For example, if an index case was found to be a carrier of *BRCA1* pathogen variant using a panel genetic test, it was modelled that their eligible FDRs would be tested only for *BRCA1* pathogen variant.

Population

Both women and men were included in the decision tree component of the model, but men were solely modelled to identify eligible FDRs who may carry pathogenic variants in ovarian cancer predisposition genes. Thus, they were only considered in the decision tree and were not included in the Markov model.

Following the identification of a pathogenic variant in women they all progressed to the Markov model to allow the estimation of long-term costs and benefits associated with genetic testing.

The model assumed that women with a pathogenic variant would start in a state of no cancer but would be at an increased risk of ovarian and breast cancer (‘At risk’ health state).

From ‘At risk’ health state each year they could have opted to undergo RRS, enter a state of new ovarian or new breast cancer or die. RRS included Risk Reducing Bilateral Mastectomy (RRBM) or Risk Reducing Bilateral Salpingo-Oophorectomy (RRBSO).

According to the committee, individuals with *BRCA1* and *BRCA2* pathogenic variants have substantially higher risks for both ovarian and breast cancer. Therefore, the model assumed that *BRCA1* and *BRCA2* mutation carriers who opted for RRS would undergo both RRBM and RRBSO. To simplify the modelling, it was assumed that RRBM would always be the first procedure done in their treatment pathway.

The committee further explained that women with *RAD51C*, *RAD51D* and *BRIP1* pathogenic variants do not have significantly elevated breast cancer risks and were modelled to only undergo RRBSO. However, these individuals were still eligible for breast screening as outlined in the NICE Familial Breast Cancer Clinical Guideline [CG164].

Women who entered ovarian or breast cancer states transitioned through 10 cancer sub-states. These sub-states allowed the application of costs, quality of life and survival rates specific to time since cancer diagnosis.

It was agreed by the committee that while the detection of breast and ovarian cancers may occur simultaneously/within a short time, this was uncommon and was not to be considered in the model.

The committee also discussed how these people would be identified. It was clarified that these people would initiate contact with services themselves due to concerns about their family's cancer history. For example, they may undergo a family history assessment with their general practitioner and if deemed at increased risk they would be referred to specialist services like genetics or gynaecological services for further evaluation and genetic testing.

Generating eligible FDRs for genetic testing

In the model, if an index case was found to have a pathogenic variant, their FDRs were simulated and tested for the same variant. The age of the simulated relatives was determined based on their relationship to the index case and those under 18 years old were tested once they turned 25 years (Eccleston 2017).

The average number of FDRs, their ages relative to the index case and their gender were obtained from a recent economic evaluation (Sun 2023 – in publication).

The probability of eligible relatives being alive at the beginning of the model was estimated using the National Life Tables for the UK, which were based on data collected from 2018-20. Details on the parameters utilised to construct FDR cohort are outlined in Table 12.

Table 12: Parameters for generating first-degree relative cohort.

	Mother	Father	Siblings	Children	Source
Number, mean and SD	1	1	0.91 (SD: 0.5)	1.91 (SD: 0.5)	Sun 2023
Age relative to index case, mean and SD	30 (SD: 5)	32 (SD: 5)	0 (SD: 5)	-30 (SD: 5)	Sun 2023
Sex, probability female	100%	0%	56%	56%	ONS 2019

Abbreviations: ONS: Office for National Statistics; SD: Standard deviation

Perspective

A UK NHS and Personal Social Services (PSS) perspective was adopted in the analysis, in line with NICE methodological recommendations.

Outcomes

Health outcomes were expressed in terms of quality-adjusted life years (QALYs). The analysis undertaken was a cost-utility analysis producing cost per QALY results expressed as incremental cost effectiveness ratios (ICERs).

Time horizon

The model was designed to evaluate the long-term benefits of diagnostic genetic testing and had a time horizon of up to 80 years for each individual.

To account for the lifetime costs and benefits for all FDRs, the time horizon extended up to 110 years until all FDRs reached the age of 80.

The upper limit of 80 years was selected based on the availability of data, such as cancer incidence data for some genes of interest which were not available beyond 80 years.

The cost-effectiveness model was developed in Microsoft® Excel® for Microsoft 365 MSO (Version 2303 Build 16.0.16227.20202).

Cost effectiveness model: Inputs

The cost-effectiveness analysis required relevant clinical evidence, health-related preferences (utilities), healthcare resource use and costs.

A considerable challenge was presented when no relevant clinical evidence was identified under the PICO for this topic. Therefore, searches had to be undertaken for all relevant parameters and, where published evidence was limited, the expert opinion of the committee was used to estimate relevant parameters.

Clinical data

Uptake of genetic testing

The uptake rate of genetic testing was not considered in the index population. This is because the intervention cost to people who do not take up genetic testing would be zero and they would not be relevant to the decision problem.

However, the model did consider the uptake of genetic testing among FDR relatives, as not all of them may choose to undergo testing. This uptake rate can have an impact on the cost-effectiveness of testing, as lower uptake rates may result in fewer people being identified and receiving RRS.

In a recent UK study (Martin 2021), hospital data from the Merseyside and Cheshire Regional Genetic Service was used to examine the uptake of predictive *BRCA* testing in individuals aged 18 and above who underwent testing between 2010-17. The study reported that in 83.4% of index cases predictive testing was received by relatives. While the study found that being male was associated with higher odds of *BRCA* testing for a family variant in *BRCA*-positive probands, this result was not statistically significant.

Similarly, an older study in Norway (Bodd 2003) within a consecutive series, identified 75 *BRCA1* mutation carriers. The study registered information transmission and uptake of genetic testing 6 months or more after the index mutation carriers had been informed about their mutation status. Forty-four out of 54 (81.5%) of females over 30 had opted for genetic testing. The testing rate among all relatives was 43%. At any age, 63% of the females underwent genetic testing compared with 24% of the males (p-value <0.05).

However, several international studies have reported lower uptake rates among first- and second-degree relatives. For example, in Israel, only 48% of healthy Ashkenazi Jews who were first- or second-degree relatives of *BRCA1* and *BRCA2* carriers underwent cascade testing (Landsbergen 2005). Similarly, a study done in South Korea (Jeong 2021) found a low uptake rate of predictive BRCA mutation testing among first- and second-degree relatives of patients with peritoneal, ovarian, or fallopian tube cancer with confirmed *BRCA1* or *BRCA2* germline mutations. The study found that only 30.5% of first-degree living relatives and 53.5% of the overall family unit underwent family-specific mutation testing.

After a discussion with the committee, it was decided that the findings from the UK study (Martin 2021) would be utilised in the base-case analysis, while the alternative lower uptake rates from the international studies would be incorporated into the sensitivity analysis. To simplify the modelling the same rate was used for males and females since this UK study did not find statistically significant differences between the two.

The model assumed that in the no testing arm none of the individuals or their FDRs would be tested for genetic mutations and hence their status would remain unknown for the duration of the model.

Accuracy of genetic testing

The committee explained that genetic testing is highly sensitive and specific, making it a reliable and accurate method for identifying pathogenic variants with very low rates of false positive and false negative results. Also, considering the wide scope of the analysis, the committee decided to focus on the impact of true positive results only.

Favourable diagnostic accuracy of next generation sequencing-based tests for hereditary cancer risk assessment is supported by recent research (Chan 2020). For example, a 35-gene hereditary cancer panel designed to identify germline cancer-causing mutations for 8 different cancers including breast, ovarian, prostate, uterine, colorectal, pancreatic, stomach cancers and melanoma, showed high sensitivity (99.9%) and specificity (100%) across 4,820 variants.

To simplify the modelling, a consistent methodology was employed when estimating the outcomes of individual gene testing in FDRs of an index case with a confirmed pathogenic variant. This also involved focusing on true positive results only.

Variant of unknown significance (VUS)

The committee discussed VUS a genetic change or mutation that has been identified through genetic testing. However, its clinical significance is unclear and it does not provide clear information about an individual's risk, for example, for ovarian cancer. The committee was particularly concerned that as more genes are included in a genetic testing panel, the likelihood of identifying VUS also increases.

According to an economic evaluation by Sun (2023 – in publication), the estimated prevalence of *BRCA1* and *BRCA2* VUS in individuals with ovarian cancer was 0.0486 and the prevalence of *RAD51C*, *RAD51D* and *BRIP1* VUS was 0.0393. The combined prevalence of these VUS was used in the model, resulting in an estimated VUS rate of 9% for a panel consisting of *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1*.

Additionally, Sun (2023 – in publication) determined a reclassification rate of VUS as 0.0869 (95% CI: 0.0755 to 0.0999), which was incorporated into the model to approximate the number of VUS results that would be reclassified as pathogenic variants.

It was modelled that all FDRs would undergo individual pathogenic variant testing for the variant identified in an index case. For those FDRs who were tested for the single variant only, the VUS rate was approximated using the average prevalence of 2% for the 5 genes as reported in the above economic evaluation (Sun 2023). The

reclassification rate for VUS was assumed to be the same as that for the panel genetic test.

Mutation frequencies

A US study (Norquist 2016) was used to model the distribution of germline mutations following panel genetic testing for individuals who tested positive. This study aimed to determine the frequency of germline mutations in ovarian cancer-associated genes. The study population consisted of 1,915 women with ovarian cancer and available germline DNA. These women were identified from the University of Washington (UW) gynaecologic tissue bank (N=570) and from Gynecologic Oncology Group (GOG) phase III clinical trials 218 (N=788) and 262 (N=557).

The women's germline DNA was sequenced using a targeted capture and multiplex sequencing assay. Of the 1,915 individuals, 182 (9.5%) had mutations in *BRCA1*, 98 (5.12%) in *BRCA2*, 26 (1.36%) in *BRIP1*, 11 (0.57%) in *RAD51C* and 11 (0.57%) in *RAD51D*. These mutation frequencies were utilised in the model to estimate the number of positive cases for each pathogenic variant.

The committee expressed the view that, even though the target population was people unaffected by ovarian cancer, these people had a family history suggestive of pathogenic variants in ovarian cancer predisposition genes. Consequently, it would be more appropriate to use the distribution of ovarian cancer-associated genes seen in people diagnosed with ovarian cancer. However, overall, it would be generally expected that the distribution of ovarian cancer-associated genes would be similar in people with ovarian cancer and unaffected people with a familial risk of ovarian cancer.

Carrier risks for pathogenic variants

Carrier risks modelled in an index population ranged from 1% to 10%. This was the model's assumption. Pathogenic variant carrier risks in FDRs, conditional on an index case, having a pathogenic variant were estimated using CanRisk tool. The CanRisk tool is a web interface to BOADICEA, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (Lee 2019, Carver 2020, Archer 2020). This risk prediction model is used to calculate future breast and ovarian cancer risks.

The model utilises mutation screening data, personal lifestyle and reproductive factors, family history and mammographic density (in the case of breast cancer) to predict risks. The CanRisk tool can also estimate the probability of being a mutation carrier in breast and ovarian cancer susceptibility genes based on pre-specified criteria such as family history. It was used to estimate the likelihood of pathogenic variant carrier status among FDRs.

Multiple scenarios were created to determine the carrier risks of FDRs of the index case. These relatives included the mother, father, siblings and children.

These scenarios accounted for the possibility of:

- both female and male siblings and children,
- the index case being either male or female,
- the index case carrying one of the genes of interest, including *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1*.

To further populate the CanRisk tool, the age distribution of all first-degree relatives in relation to the index case was obtained from the published literature (Sun 2023). See section on Generating Eligible FDRs for genetic testing.

The above inputs were used to create scenarios that allowed for the estimation of carrier risks for *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1*, assuming that the index case carried the same pathogenic variant. For example, if the index case was a 30-year-old female who tested positive for *BRCA1*, the CanRisk tool was populated with this information to estimate the probability of, for example, the index case's 60-year-old mother also having the *BRCA1* pathogenic variant.

The committee acknowledged that the risk of carrying a pathogenic variant can be complex and influenced by several factors, such as: detailed family history, ethnicity and lifestyle factors. Nevertheless, the approach outlined above is expected to provide a reliable approximation of carrier risks in FDRs. The carriers risks that were used in the model are summarised in appendix 2 (Carrier risks in FDRs).

Cancer incidence

BRCA1 and BRCA2

The age-specific risks of ovarian and breast cancer for individuals with *BRCA1* and *BRCA2* pathogenic variants were obtained from a prospective cohort study (Kuchenbaecker 2017). This study included 6,036 *BRCA1* and 3820 *BRCA2* female carriers, 5,046 of whom were unaffected and 4,810 who had breast or ovarian cancer, or both, at baseline. Participants were recruited between 1997-2011 through the International *BRCA1/2* Carrier Cohort Study, the Breast Cancer Family Registry and the Kathleen Cuningham foundation Consortium for Research into Familial Breast Cancer and included people from large national studies in the United Kingdom (EMBRACE), the Netherlands (HEBON), and France (GENEPSO).

The reported ovarian and breast cancer incidence rates for individuals with *BRCA1* and *BRCA2* pathogenic variants are summarised in Table 14.

BRIP1

A case-control study (Ramus 2015) was used to obtain the relative risk of ovarian cancer for individuals with *BRIP1* pathogenic. This study included 3,374 case patients and 3,487 control patients from eight ovarian cancer case-control studies, one familial ovarian cancer registry from the US and one case series. In addition, 2,167 unaffected women from the UK Familial Ovarian Cancer Screening Study (UKFOCSS) were also considered. The analysis estimated that the average relative risks in *BRIP1* mutation carriers compared to the general population was 3.41 (95% CI = 2.12 to 5.54).

To estimate the age-specific risks of ovarian cancer in people with *BRIP1* pathogenic variants the age-specific risks of ovarian cancer (based on 2016-18 data) in the general population were obtained from the Cancer Research UK (2021). These age-specific risks of ovarian cancer in the general population were multiplied by the average relative risks in *BRIP1* mutation carriers compared to the general population (Ramus 2015).

The committee explained that the risk of breast cancer is not increased for individuals with *BRIP1*. This is supported by research which showed that the odds ratio of *BRIP1* for breast cancer risk was 1.24, however, this finding was not significant (95% CI:

0.93 to 1.66) (Kurian 2015). Therefore, in the model individuals with *BRIP1* were assumed to have the same breast cancer risk as the general population.

RAD51C and RAD51D

The risks of ovarian and breast cancer for individuals with *RAD51C* and *RAD51D* pathogenic variants were estimated from a retrospective cohort study (Yang 2020).

This analysis included 215 women with *RAD51C* pathogenic variants from 125 families and 92 women with *RAD51D* pathogenic variants from 60 families. The families were enrolled in the study between 1996-2017 through 28 study centres from 12 countries in Europe and North America.

The results suggested that for both *RAD51C* and *RAD51D*, the risks of breast and ovarian cancer increased with age until around 60 years and then decreased thereafter. The age-specific ovarian and breast cancer risks stratified by the pathogenic variant and for the general population that were used in the model are summarised in Table 14.

Surveillance and associated outcomes

According to the guideline systematic review, ovarian cancer surveillance may lead to downstaging of ovarian cancer. However, the effect of downstaging on final outcomes, such as mortality, remains uncertain and there is a lack of data on stage-specific outcomes. Therefore, the committee agreed to exclude ovarian cancer surveillance from the model.

Breast cancer surveillance for individuals with *BRCA1* or *BRCA2* mutations was included in the model based on the recommendations outlined in the NICE Familial Breast Cancer Clinical Guideline [CG164]. The guideline recommends annual mammographic surveillance for women aged 40 to 69 with a confirmed *BRCA1* or *BRCA2* mutation and annual MRI surveillance for women aged 30 to 49 with a confirmed *BRCA1* or *BRCA2* mutation. Breast cancer surveillance was only modelled until RRBM was undertaken.

Breast cancer surveillance can help with early detection in people with pathogenic variants, which can lead to earlier treatment and potentially improve outcomes. The committee explained that breast cancer surveillance does not reduce breast cancer risk itself but is associated with a reduction in breast cancer mortality.

For example, in a recent study (Evans 2021) women with an increased lifetime breast cancer risk were offered enhanced screening with annual mammography starting at age 35 or at 5-years younger than the youngest affected relative, with an upper age limit of 50 for moderate and 60 for high-risk.

Overall, of those invasive breast cancers which occurred while on enhanced screening, most were lymph-node negative (72.9%) and stage-1 (61.4%). The reported breast cancer specific 10-year survival was 91.8% and 95.0%, in people with *BRCA1* and *BRCA2*, respectively.

These rates were annualised and applied each year in the model in people eligible for breast cancer surveillance, that is, those with *BRCA1* and *BRCA2* and who eventually developed breast cancer and did not have RRS.

While individuals with pathogenic variants in *RAD51D* and *RAD51C* do not have increased breast cancer risk justifying RRBM, they would still be eligible for breast

cancer surveillance. Their moderate risk level would make them eligible for annual mammographic surveillance between the ages of 40 to 69 (NICE Familial Breast Cancer Clinical Guideline, CG164).

A single-arm cohort study (Duffy 2013) was used to obtain the mortality outcomes associated with mammographic surveillance. The study aimed to evaluate the benefit of mammographic surveillance in women aged 40 to 49 with a moderate family history of breast cancer. The study included 6,710 women from 74 surveillance centres in England, Wales, Scotland and Northern Ireland, with a family history of breast cancer.

In the study, regression modelling was used to predict an average 10-year survival rate of 84% (95% CI: 81% to 87%). This rate was annualised and applied each year in the model for individuals with *RAD51C* and *RAD51D* pathogenic variants who progressed to the breast cancer state and did not have RRS.

The breast cancer risk for individuals with *BRIP1* pathogenic variants is not significant enough for them to undergo more intensive breast cancer surveillance than the general population (or have RRBM). Accordingly, the age-specific survival data for the general population was utilised in the model in people with *BRIP1*. For more information, please see section on Mortality (cancer-related specific).

Risk-reducing surgery and associated outcomes

People with *BRCA1* and *BRCA2* pathogenic variants were modelled to receive both RRBM and RRBSO. It was modelled that RRBM would always be the first procedure done in their treatment pathway.

People with *RAD51C*, *RAD51D* and *BRIP1* pathogenic variants were modelled to receive only RRBSO, because breast cancer risk is not increased sufficiently to offer RRBM in these people.

Uptake of risk-reducing surgery

The uptake rates of RRS were obtained from UK-based observational study (Evans 2009). The study examined the uptake of RRS, including RRBM and RRBSO, in individuals with *BRCA1* and *BRCA2* pathogenic variants (N=211) in the northwest of England up to 7 years after genetic testing.

The study stratified RRS uptake rates by age (<36, 36-45 and >45) and these rates were used in the model to estimate RRS uptake in an index population and all eligible FDRs who entered model at different ages. To simplify modelling, a one-off age-specific uptake rate was applied in the year of surgery initiation, which aligns with the research showing that most of the uptake tends to occur within the first 2 years after gene testing (Evans 2009).

The reported uptake rates in *BRCA1* and *BRCA2* individuals were also used to approximate RRBSO uptake in individuals with *RAD51C*, *RAD51D* and *BRIP1* pathogenic variants.

Age at risk-reducing surgery

The committee recognised that recommending RRS for individuals with pathogenic variants is a complex and personalised decision which depends on several factors, including family history of cancer and whether people have completed their family

planning. Based on the committee's expert opinion and the UK Cancer Genetics Group guidance the committee recommended that individuals with *BRCA1* could consider undergoing the RRBSO at age 35, those with *BRCA2* at age 40 and those with *RAD51C*, *RAD51D* and *BRIP1* at age 45. As a result, these ages were utilised in the base-case analysis of the model.

The committee further explained that individuals with *BRCA1* and *BRCA2* pathogenic variants may consider undergoing RRBM at age 30. However, since the index case's initial age was 30 and the model structure had two stages, individuals would not enter the Markov model until the following year (that is, age 31). Thus, age 31 was considered the earliest possible age for RRBM uptake and was incorporated into the base-case analysis of the model.

The committee explained that the recommended ages for RRS reflect the ages at which the incidence of cancer begins to increase in individuals with these pathogenic variants. The impact of varying ages at which RRS is initiated will be assessed in sensitivity analyses.

Effectiveness of risk-reducing surgery

RRS was shown to significantly decrease breast and ovarian cancer incidence and cancer-related mortality.

RRBSO and ovarian cancer incidence

The meta-analysis done for the guideline systematic review found a 90% reduction in ovarian cancer incidence resulting from RRBSO. That is, the risk ratio of RRBSO (versus surveillance) on ovarian cancer incidence was 0.10 (95% CI: 0.03 to 0.34). This was applied to the age-specific baseline ovarian cancer risks for individuals with *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1* who chose to undergo RRBSO.

RRBSO and ovarian cancer-related mortality

The systematic review also found that RRBSO reduces ovarian cancer-related mortality when compared with no surveillance/no RRBSO, with a risk ratio of 0.36 (95% CI: 0.21 to 0.60). Thus, in the model, this risk ratio was applied to the baseline ovarian cancer mortality of individuals with *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* and *BRIP1* who had undergone RRBSO and developed ovarian cancer. For the details on the baseline ovarian cancer mortality see section on Mortality (cancer-related specific).

RRBM and breast cancer risk

To determine the effectiveness of RRBM for reducing breast cancer risk in women with *BRCA1* and *BRCA2* pathogenic variants, a cohort study (Rebbeck 2004) was used in the model because of the lack of more recent evidence.

The study aimed to estimate the extent of breast cancer risk reduction after surgery in women with *BRCA* mutations (N=483). The cases were mutation carriers who underwent RRBM and controls were *BRCA* carriers with no history of RRBM.

The study reported that in people with prior or concurrent bilateral prophylactic oophorectomy, RRBM reduced the risk of breast cancer by approximately 95% (HR 0.05, 95% CI: 0.01 to 0.22). In women with intact ovaries, the risk reduction was approximately 90% (HR 0.09, 95% CI: 0.02 to 0.38). Because the model assumed that RRBM would always be the first procedure done in their treatment pathway and

to simplify the modelling, the HR associated with RRBM (that is, the risk reduction of 90%) was used in the model.

RRBM and breast cancer-related mortality

Overall, the evidence regarding the effect of RRBM on breast cancer mortality is not conclusive (De Felice 2015). However, there has been a recent Dutch multicentre cohort study (Heemskerk-Gerritsen 2019) in healthy *BRCA* mutation carriers (N=2,857).

This study found that during a mean follow-up of 10.3 years, RRBM was associated with a HR of 0.06 (95% CI 0.01 to 0.46) for breast cancer-specific mortality in people with *BRCA1* pathogenic variant (when compared with breast cancer surveillance). However, for people with *BRCA2* pathogenic variant, the study concluded that RRBM may lead to similar breast cancer-specific survival as surveillance. As a result, in the model the above reduction in breast cancer mortality associated with RRBM was applied only in breast cancer affected *BRCA1* carriers.

Individuals carrying *BRCA2* pathogenic variants, irrespective of whether they undergo RRBM, and *BRCA1* carriers until they choose to undergo RRBM were modelled to experience breast cancer specific mortality reduction associated with breast cancer surveillance (Evans 2021).

The effectiveness and details of breast cancer surveillance are outlined in the section on Surveillance and associated outcomes.

RRBSO and breast cancer outcomes

The impact of RRBSO on breast cancer outcomes is unclear because of conflicting evidence. For example, a retrospective study, in 676 women with *BRCA1* or *BRCA2* mutations and stage I or II breast cancer monitored women for up to 20 years after being diagnosed between 1975-2008 (Metcalfe 2015). The study found that oophorectomy affected the survival of people with *BRCA*-associated breast cancer. That is, oophorectomy was linked to a 54% decrease in breast cancer-specific mortality (HR 0.46, 95% CI: 0.27 to 0.79, p-value = 0.005).

However, a recent systematic review concluded differently (Gaba 2023). It was found that RRBSO did not significantly reduce the risk of primary breast cancer (RR = 0.84, 95% CI: 0.59 to 1.21) or contralateral breast cancer (RR = 0.95, 95% CI: 0.65 to 1.39) in *BRCA1* and *BRCA2* carriers combined. Further subgroup analyses showed that RRBSO did not reduce the risk of primary breast cancer (RR = 0.89, 95% CI: 0.68 to 1.17) or contralateral breast cancer (RR = 0.85, 95% CI: 0.59 to 1.24) in *BRCA1* carriers. However, RRBSO was associated with a reduced BC-specific mortality in BC-affected *BRCA1* carriers (RR = 0.46, 95%CI: 0.30 to 0.70).

It was further found that RRBSO was associated with a reduced risk of primary breast cancer (RR = 0.63, 95% CI: 0.41 to 0.97) but not contralateral breast cancer risk in *BRCA2* carriers (RR = 0.35, 95% CI: 0.07 to 1.74).

Although RRBSO was found to lower the risk of primary breast cancer in *BRCA2* carriers, the risk reduction observed with RRBM was more significant (HR 0.09, 95% CI: 0.02 to 0.38) (Rebbeck 2004). As individuals were modelled to receive RRBM first along their pathway, the breast cancer risk reduction associated with RRBM was used in the model.

In people with *BRCA1* pathogenic variants there is no evidence that RRBSO reduces breast cancer risk. Hence, the breast cancer risk reduction associated with RRBM (HR 0.09, 95% CI: 0.02 to 0.38) was also used in the model (Rebbeck 2004).

Concerning RRBSO and decreased breast cancer mortality in *BRCA1* carriers affected by breast cancer, individuals were always modelled to undergo RRBM earlier in the pathway. As RRBM (versus surveillance) was found to have a greater reduction in breast cancer mortality (HR = 0.06 versus RR = 0.46, for RRBM and RRBSO, respectively), the mortality reduction associated with RRBM was used in the model in people with *BRCA1* pathogenic variants.

The additional impact of RRBSO on breast cancer mortality in individuals with *BRCA1* who had undergone RRBM is likely to be modest and the adopted modelling approach would result a slightly more conservative estimate.

Since there was the lack of data on RRBSO and the effect on breast-cancer specific mortality in people with BRCA2 (Gaba 2023) and RRBM had a similar breast cancer-specific survival as surveillance (Heemskerk-Gerritsen 2019) the breast cancer mortality reduction associated with breast cancer surveillance was used in the model (Evans 2021) in people who progressed to breast cancer health state.

The results regarding the impact of RRBSO on breast cancer outcomes were specific to individuals with *BRCA1* or *BRCA2* pathogenic variants. As a result, the impact of RRBSO on breast cancer risk and mortality was not considered in the model for individuals with *RAD51C*, *RAD51D*, or *BRIP1* pathogenic variants.

Table 13 provides a summary of the evidence for breast cancer surveillance, RRBSO, RRBM and their respective impact on breast cancer outcomes. The table also specifies which evidence was utilised in the modelling.

The model assumed that in the no testing arm, individuals would not be tested for genetic mutations and hence their status would remain unknown. Consequently, they would not have access to risk-reducing care and there would be no improvement in their outcomes due to surveillance or RRS.

Table 13: A summary of the evidence for breast cancer surveillance, RRBSO, RRBM and their respective impact on breast cancer outcomes. The table also shows which evidence was utilised in the modelling for each outcome (cells with an asterisk).

	BRCA1	***BRCA1***	***BRCA2***	***BRCA2***	***RAD51C*, *RAD51D***	***RAD51C*, *RAD51D***	***BRIP1***	***BRIP1***
	BC mortality	BC incidence	BC mortality	BC incidence	BC mortality	BC incidence	BC mortality	BC incidence
Breast cancer surveillance	10-year survival was 91.8%, Evans 2021 (used up to the time of RRBM) *	NA	10-year survival was 95.0%, Evans 2021 (used up to the time of RRBM) *	NA	10-year survival was 84% (95% CI: 81 to 87), Duffy 2013*	NA (general population)	NA (general population)	NA (general population)
RRBM	Reduced mortality HR = 0.06, 95% CI: 0.01 to 0.46 (vs surveillance), Heemskerk-Gerritsen 2019 *	HR 0.09, (95% CI: 0.02 to 0.38), Rebbeck 2004 *	Similar breast cancer-specific survival as surveillance, Heemskerk-Gerritsen 2019	HR 0.09 (95% CI: 0.02 to 0.38), Rebbeck 2004 *	NA	NA	NA	NA
RRBSO	Reduced mortality, RR = 0.46, (95% CI: 0.30 to 0.70), Gaba 2023	No effect, Gaba 2023	No effect, Gaba 2023	Reduced risk of primary breast cancer, RR = 0.63, (95% CI: 0.41 to 0.97), Gaba 2023	NA	NA	NA	NA

Mortality (cancer-related specific)

The impact of germline mutations, such as those in *BRCA1* and *BRCA2*, on mortality in ovarian cancer patients remains uncertain.

Evidence from a population-based case-control study (Alsop 2012) suggests that individuals with germline mutations may have better rates of progression-free and overall survival. Another study (Candido-dos-Reis 2015), which analysed data from multiple cohorts, found that the presence of *BRCA1* or *BRCA2* mutations was initially linked to improved short-term survival. However, this advantage diminishes over time and is eventually reversed in *BRCA1* carriers.

As a result, the age-specific ten-year survival rate of 35% for ovarian cancer in England during 2013-17 among adults aged 15-99 was used in the model for people with *BRCA1*, *BRCA1*, *RAD51C*, *RAD51D* and *BRIP1* pathogenic variants who progress to ovarian cancer health state (Cancer Research 2020) and did not undergo RRBSO or those in the no genetic testing arm. For those who have undergone RRBSO relative risk reduction was applied as outlined in the section on the Effectiveness of risk-reducing surgery.

The overall survival data from 2013-17 for England indicates that 75.9% of females are expected to survive breast cancer for ten years or more (Cancer Research 2020). This rate was applied to individuals who were not eligible for intensified breast cancer surveillance, such as those with *BRIP1* pathogenic variants, as well as those in the no genetic testing arm. The impact of the national breast cancer screening programme has not been explicitly considered in the model. However, the national breast cancer survival data would be expected to account for some of the effects of the national breast cancer screening programme.

Mortality (non-disease specific)

In order to quantify the benefits of genetic testing and potential outcomes such as better survival, it was necessary to consider non-disease specific mortality. To do this, gender-specific life tables were used to estimate all-cause mortality events and the annual probability of death for female individuals at each age using interim life tables for 2018-20 (ONS 2021). This non-disease specific probability of death was then applied annually in the model. For the sensitivity analysis, pre-COVID data from 2017-19 was used.

The non-disease-specific mortality rates were also utilised to calculate the number of eligible FDRs who were alive at the time of genetic testing where an index case was found to have a pathogenic variant.

Utility data

The model calculated the cost of genetic testing per QALY gained. This means that the analysis considers a change in quality of life as well as any additional life years which result from genetic testing. It was therefore necessary to estimate QALYs associated with various health states and events, such as cancer treatment and RRS.

Baseline utility

The baseline utility of an individual who is not suffering from ovarian or breast cancer was assumed to be the same as the average person in the general population. The utilities for the general population were obtained from a cross-sectional study (Janssen 2021). This study obtained EQ-5D-3L values for the five largest European

economies, including the UK, through a general population-based survey done in 2014 using the Health Survey for England. Country-specific time trade-off (TTO)-based value sets were utilised to calculate utility values in the study. The study reported age and gender-specific utilities which were subsequently applied to individuals who were in an 'At risk' health state and did not have ovarian or breast cancer (including the no genetic testing arm), as well as those who were well after RRS, in the model. Also, when calculating utilities the multiplicative method was used to apply a constant proportional decrement relative to the age-related baseline utility values (NICE DSU 2011).

Utility decrement associated with genetic testing

The committee discussed that the impact of genetic testing on health-related quality of life (HRQoL) can vary depending on several factors, including the reason for testing and the individual's personal circumstances. In some cases, genetic testing can provide individuals with valuable information about their risk of developing ovarian cancer. This knowledge can empower individuals to make informed decisions about their health, such as taking preventative measures, for example, RRS.

However, it was discussed that genetic testing can also have a negative effect on HRQoL, particularly if the results are uncertain or if they reveal a high risk of developing ovarian cancer. In these cases, individuals may experience heightened anxiety and other negative emotions, which can negatively impact their HRQoL.

Previous economic analyses, such as the analysis done for the NICE Familial Breast Cancer Clinical guideline [CG164] and an economic evaluation on panel genetic testing in Norway (Asphaug 2019), have included a utility decrement associated with a positive genetic testing result. Thus, following the discussion with the committee for the base case analysis, a one-off utility decrement of 0.05, consistent with the NICE Familial Breast Cancer Clinical guideline [CG164] was applied to individuals with a positive genetic testing result.

Utility decrement associated with risk-reducing surgery

The committee explained that the impact of RRS on HRQoL in people with pathogenic variants can be complex and varies depending on a number of factors. For example, RRS such as RRBSO can reduce the risk of ovarian cancer in people with *BRCA* mutations. This can lead to improved HRQoL, as individuals may feel more in control of their health and less anxious about the possibility of developing ovarian cancer.

However, it was explained that RRS can also have negative effects on HRQoL, particularly in the short term after surgery. For example, removal of the ovaries can lead to menopausal symptoms such as hot flushes, mood changes, and vaginal dryness, which can negatively impact HRQoL.

Utility values associated with RRS were obtained from an economic analysis conducted for the Familial Breast Cancer Guideline [CG164]. A utility decrement of 0.03 for RRBM and 0.08 for RRBSO were applied only during the cycle in which RRS occurred. No utility decrement was applied in subsequent years, following the committee's advice.

Utility during cancer treatment

Ovarian cancer

The utility values used for individuals undergoing treatment for ovarian cancer were taken from the NICE Familial Breast Cancer Clinical Guideline [CG164] cost-effectiveness model, which relied on a published study (Havrilesky 2009) and breast cancer committee expert opinion.

Havrilesky (2009) provided utility values for a range of health states that represented different experiences relating to ovarian cancer, including diagnostic testing and natural history such as early-stage and progressive cancer. Individual interviews were done with 13 ovarian cancer patients and 37 female members of the general public using TTO method to obtain a valuation for each health state.

The NICE Familial Breast Cancer Clinical Guideline [CG164] committee assumed a steady improvement in quality of life over the years. However, this utility was never assumed to return to the baseline general population norms.

Table 14 summarises the utility values which were assigned to ovarian cancer health sates in the model.

Breast cancer

The utility scores for early, advanced, recurrent, remittent and end-stage breast cancer were reported to be 0.71, 0.65, 0.45, 0.81 and 0.16, respectively (NICE Clinical Guideline on Advanced Breast Cancer [CG81], NICE Familial Breast Cancer Clinical Guideline [CG164] and Peasgood 2010).

Breast cancer surveillance for individuals with pathogenic variants, including *BRCA1*, *BRCA2*, *RAD51C* and *RAD51D*, is more intensive than for the general population. This surveillance is more likely to detect breast cancers at earlier stages. Annual breast cancer utilities were therefore calculated to capture this benefit for those who undergo surveillance when compared to those who do not.

To achieve this, the staging data at diagnosis for individuals undergoing breast cancer surveillance was obtained from Evans (2021). The staging data at diagnosis for individuals who do not undergo genetic testing and consequently are not under breast cancer surveillance was estimated using breast cancer staging data for the general population (Cancer Research 2021, NHS Digital & NDRS 2023).

To simplify the modelling process, recurrence and progression have not been explicitly included in the model structure. However, this has been accounted for in the cost estimates (Wei 2024). A similar approach was adopted to account for relapse, recurrence and progression rates when estimating breast cancer-related utilities.

Stage-specific recurrence and progression rates were obtained from various published sources. Those with non-invasive breast cancers (DCIS) were found to have 12.5% relapse rate both for non-invasive and for invasive stages (NICE Early and locally advanced breast cancer [NG101]). These rates were annualised and when calculating utilities, it was modelled that a proportion of the initial cohort of people with DCIS breast cancer would experience relapse to the same stage, while some people would relapse to early and locally advanced breast cancers every year.

It is reported that approximately 35% of early and locally advanced invasive breast cancers progress to advanced disease (Advanced breast cancer [CG81]). This rate

was annualised and when calculating utilities, it was modelled that each year, individuals with early and locally advanced breast cancers would progress at this rate to advanced breast cancer.

The composite recurrence rate for the same stage breast cancer for early and locally advanced breast cancer was estimated to be 12.5% (Sun 2023). This estimate used the recurrence rates for early and locally advanced breast cancer of 15.9% for node-positive disease and 11% for node-negative disease (Anderson 2009), with weights of 31% for node-positive and 69% for node-negative breast cancers. Similarly, these rates were annualised and when calculating utilities it was modelled that each year individuals with early and locally advanced breast cancers would experience same stage breast cancer recurrence at this rate.

The reported recurrence rate for advanced breast cancer is 66% (Gennari 2005). In the model this rate was annualised and when calculating utilities it was assumed that each year individuals with advanced breast cancer would experience a recurrence at this rate.

Using the relapse, progression and recurrence rates outlined above, the average annual breast cancer utilities were estimated for a 10-year period that individuals were modelled to transition through after developing breast cancer.

Breast cancer utilities were estimated using a similar approach for individuals who don't undergo genetic testing and surveillance. These individuals were assigned an initial distribution of breast cancer stages based on less favourable staging data at diagnosis in the general breast cancer population (Cancer Research 2021, NHS Digital & NDRS 2023). This is because they don't benefit from early detection through genetic testing and breast cancer surveillance.

Individuals with *BRIP1* pathogenic variants are not eligible for breast cancer surveillance. However, people at risk of ovarian cancer who have not undergone RRS are likely to have regular annual review visits with a clinician. These reviews may have broader benefits in detecting and managing other cancers, including breast cancer. Therefore, the model assumed that the staging of breast cancer at diagnosis in people with *BRIP1* would be similar to those who undergo breast cancer surveillance. However, the number of individuals with *BRIP1* pathogenic variants is very small and any impact on the cost-effectiveness is likely to be insignificant, if any.

Table 14 summarises the utility values which were used in the model.

Resource use and cost data

The costs considered in this analysis were those relevant to the UK NHS setting and included the cost of diagnostic genetic testing, treatment (including expected in-patient and out-patient costs) and surveillance.

Costs of diagnostic genetic testing and variants of unknown significance (VUS)

The committee discussed the unit costs provided by genetics laboratory services and agreed to use the unit cost of £493 for a panel genetic test in the base case analysis. This was NHSE cost using 2022-23 tariff for a small panel.

The committee discussed the challenges associated with identifying VUS, which may need additional testing and laboratory studies to further clarify the clinical significance of the result, adding time and cost to the genetic testing process. The unit cost of £750 reported by one of the genetics laboratory services included the additional

laboratory work related to VUS and overheads. This higher cost of genetic panel test was used in people with a VUS result.

For a genetic test for a single pathogenic variant, the committee agreed to use the unit cost of £189, which includes overheads and any additional costs associated with VUS. This was also based on costings provided by a genetics laboratory service. The cost of a single pathogenic variant without additional work related to the VUS was estimated based on the proportionate differential in the panel genetic test unit costs with and without VUS. This resulted in the unit cost of £124 for a single pathogen genetic test without VUS.

Based on the committee expert opinion the costings assumed that all individuals would receive one pre-test counselling session before undergoing genetic testing to discuss the risks and benefits of the test. Additionally, individuals with a positive result and VUS would receive one post-test counselling session to understand the implications of the results and discuss options for risk management and follow-up care. People with VUS who get re-classified to a positive result would also receive an additional post-test genetic counselling session.

The cost of counselling was obtained from an economic evaluation by Sun (2023). The unit cost included 20 minutes of administrator time, 20 minutes of counsellor preparation and 20 minutes of counselling time. The reported 2019 cost was inflated to 2020-21 prices using the NHS cost inflation index, HCHS/NHS inflators all sectors (Jones & Burns 2021).

Table 14 summarises the costs of diagnostic genetic testing and VUS which were used in the model.

Costs of risk-reducing surgery and related costs

The cost estimate for RRBSO includes the procedure cost for RRBSO, which was estimated at £4,254 based on the NHS Reference Costs 2020-21 for HRG MA09B Intermediate, Laparoscopic or Endoscopic, Upper Genital Tract Procedures, with CC Score 0-1 (Wei 2024).

Additionally, the cost estimate included the resources associated with bone health because RRBSO can have a negative impact on bone health and increase the risk of osteoporosis and fractures, particularly in pre-menopausal women who undergo surgery before natural menopause. The bone health costs included three DEXA scans at a total cost of £311 and additional osteo-protection with calcium and vitamin-D3 of £511.

After undergoing pre-menopausal RRBSO, individuals will experience a decrease in oestrogen production which can lead to surgical menopause and related symptoms. As oestrogen is believed to provide protection against coronary heart disease (CHD), individuals who undergo RRBSO may be also at a higher risk of developing CHD because of the loss of this protective effect. To address these symptoms, it was assumed in the model that individuals who undergo pre-menopausal RRBSO would receive hormone replacement therapy (HRT) following surgery.

To simplify modelling, it was assumed that all individuals would comply with HRT treatment and not experience an increased risk of CHD. Additionally, the increased risk is generally modest, with an estimated annual excess risk of developing CHD after RRBSO of 0.0072 (Sun 2023 – in publication) and is unlikely to have a significant impact on the cost-effectiveness of genetic testing.

The cost of HRT, which includes the management of adverse outcomes such as bleeding, treatment of breast cancer and treatment of venous thromboembolism, was obtained from an economic model undertaken for the NICE guideline [NG23], Menopause: diagnosis and management. The reported cost was for oral oestradiol and progestogen and was uprated to 2020-21 prices using the NHS cost inflation index, HCHS/NHS inflators all sectors (Jones & Burns 2021). It was modelled that HRT is given from the age of RRBSO to the average age of menopause of 51 years (Local Government Association 2023).

The cost of RRBM was obtained from an economic evaluation (Wei 2024), which used the procedure cost from the NHS Reference Costs 2020-21, HRG code JA21B for Bilateral Major Breast Procedures with CC Score 0. The study considered the proportion of individuals opting for breast reconstruction (HRG code JA33Z for Bilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction).

Additionally, the study accounted for the rate of minor and major complications after RRBM (with reconstruction). The adjusted total cost of RRBM was estimated to be £11,768 and this cost estimate was used in the economic model.

Costs of surveillance

Individuals who opt not to undergo RRS would receive annual breast cancer surveillance only, but not ovarian cancer surveillance, for the reasons explained in previous sections.

Unaffected individuals with *BRCA1* or *BRCA2* pathogenic variants would be offered annual mammographic surveillance between the ages of 40 and 69 and annual MRI surveillance between the ages of 30 and 49 (as per NICE Familial Breast Cancer Clinical Guideline [CG164]). As individuals with *RAD51C* and *RAD51D* pathogenic variants generally have a lower breast cancer risk than those with *BRCA1* and *BRCA2* pathogenic variants, they would only be eligible for annual mammographic breast cancer surveillance between the ages of 40 and 69.

The NHS cost of a mammogram was not available, so it was estimated to be £190 based on the fee charged by a private provider (Genesis Care 2023). Given the uncertainty in this estimate, it will be varied in the sensitivity analysis.

The cost of an MRI (£178) was obtained from the NHS References costs 2020-21 HRG code RD01A Magnetic Resonance Imaging Scan of One Area, without Contrast, aged 19 and over.

The breast cancer surveillance costs outlined above were applied to all at-risk individuals until they choose to have RRBM.

Cost of cancer

The cancer costs were obtained from an existing economic evaluation (Wei 2024). The cost estimates were reviewed by the committee sub-groups responsible for the review questions on the effectiveness of RRS and the carrier risk for genetic testing. These cost inputs were ensured to be representative of current NHS practice.

Ovarian cancer

The ovarian cancer diagnosis cost was estimated to be £1,304, which included pelvic examination, CA125 test, transvaginal ultrasound, CT scan, abdominal ultrasound with biopsy, histopathology assessment and cytology assessment.

The initial ovarian cancer treatment cost was estimated to be £24,250, which included the cost of the surgical procedure (HRG code MA26A Complex, Open or Laparoscopic, Upper or Lower Genital Tract Procedures for Malignancy, with CC Score 5+, NHS Reference costs 2020-21), histological assessment of surgical specimen, surgical follow-up, appointment for planning chemotherapy per cycle, blood test for tumour marker, carboplatin and paclitaxel per cycle, administration costs of carboplatin and paclitaxel per cycle and CT in the middle and at the end of treatment. This cost estimate was based on six cycles of chemotherapy.

The annual ovarian cancer follow-up costs were estimated to be £18,568 in years 1 to 2 and £1,560 in years 3 to 10. These cost estimates include follow-up consultant visits, CA125 and CT scans and account for recurrence and associated costs, which include treatment with chemotherapy and secondary surgery.

The same annual ovarian cancer diagnosis, initial treatment, and follow-up costs were modelled for the 'No genetic testing' arm. The committee explained that although some people may have ovarian cancer surveillance and, as a result, more favourable staging data at diagnosis, the impact on final outcomes and costs is unclear. Due to this uncertainty, using the same ovarian cancer costs would result in more conservative cost-effectiveness estimates for genetic testing.

Breast cancer

The breast cancer costs included the diagnosis and initial treatment of breast cancer, as well as the costs of the annual treatment and follow-up for up to 10 years (Wei 2024).

The diagnosis and initial treatment costs comprised of clinical assessment, mammography, ultrasound-guided core needle biopsy of breast lesions, and additional investigations for lymph node involvement, such as ultrasound-guided needle sampling of the axilla, sentinel lymph node biopsy and axillary lymph node dissection for lymph node-positive cases.

The cost estimate also included surgical management including breast-conserving surgery and mastectomy (with or without reconstruction) and the associated complications.

Chemotherapy costs were also accounted for, including chemotherapy with docetaxel-capecitabine or docetaxel-capecitabine-vinorelbine, as well as treatment with radiotherapy.

The costs also included endocrine therapy (ER test, tamoxifen, or anastrozole), targeted therapy (HER2 test, trastuzumab), and treatment for bone metastases (MRI scan, oral sodium clodronate, oral ibandronic acid, zoledronic acid (IV), pamidronate disodium (IV), bisphosphonates) as well as mammograms and clinician visits.

The costs were weighted based on the stage distribution at diagnosis and were stratified by pathogenic variant. However, there was little difference in costs by pathogenic variant. To simplify the modelling, the cost associated with *BRCA1* of £18,378 was used for all pathogenic variants.

The annual follow-up costs included clinical appointments every four months during the initial two years, every six months from the third to the fifth year and annually from the sixth to the tenth year. Additionally, annual mammography for the duration of 10 years was included. The follow-up costs also accounted for stage specific relapse, recurrence and progression rates.

The total average annual follow-up cost for *BRCA1* was estimated to be £758. As the follow up costs were similar for other pathogenic variants, the cost associated with *BRCA1* was used for all pathogenic variants to simplify the modelling.

Breast cancer costs in the no genetic testing arm

In the economic evaluation of RRS for people with pathogenic variants breast cancer treatment costs were stratified by stage (Wei 2024). The estimated costs were £9,167 for DCIS, £19,959 for stage 1, £21,951 for stage 2 and £28,399 for stage 3+. In this study, the distribution of cancer stages was based on breast cancers identified under surveillance, with approximately 20% accounted for DCIS, 54% stage 1, 25% stage 2, and 1% stage 3+ (Evans 2021).

Breast cancer surveillance detects breast cancer earlier than waiting for symptoms to develop. Therefore, in the non-genetic testing arm, breast cancer costs were modified to reflect potentially more breast cancers being detected in advanced stages.

Breast cancer stages were estimated using reported new breast cancer cases stratified by stage in the general population. The number of DCIS cases was obtained from Cancer Research UK (2021), using average cases between 2016-18 in England. The number of people diagnosed by stage in England in 2019 was obtained from the National Disease Registration Services and the NHS Digital population-based cancer registry for England (CancerData 2023).

Based on this data, it was estimated that approximately 15% of cases were DCIS, 38% were stage 1, 34% stage 2, 8% stage 3, and 4% stage 4.

Using the above staging data in the general population and the cost data by stage (Wei 2024), the cost of diagnosis and initial treatment of breast cancer was estimated to be £20,025 in people who do not undergo genetic testing. The same approach was taken to estimate annual follow-up breast cancer costs in people who do not undergo genetic testing. These costs were slightly higher at £774 when compared with follow-up costs in people who undergo genetic testing and are under surveillance or have RRS (£758).

End of life care

The estimated cost of end of life care for ovarian cancer, as reported in published economic evaluation in the UK (Sun 2023). The estimate was derived from the total NHS and social care cost for end of life care to cancer patients in the 12 months leading up to their death in 2006-07. This cost only includes care that was funded by the NHS. The reported estimate was uprated to 2020-21 prices using the NHS cost inflation index, HCHS/NHS inflators all sectors (Jones & Amanda 2021). The final estimated cost for end of life ovarian cancer care was £19,224.

The end of life care cost for breast cancer was derived from a modelling study done by Round (2015) which utilised data from literature and publicly available datasets to estimate the direct and indirect healthcare costs for lung, breast, colorectal, and prostate cancer patients at the end of their lives in England and Wales.

The costs were categorised by resource type, including healthcare, social care, charity and informal care. However, charity care services do not fall under NHS care in England and were excluded from the cost estimate. In addition, NICE typically does not include the costs of unpaid or informal care in cost-effectiveness analyses for healthcare interventions and thus these costs were also excluded from the estimate.

The reported costs for healthcare and social care were adjusted to 2020-21 prices using the NHS cost inflation index, HCHS/NHS inflators all sectors (Jones & Amanda 2021). The final estimated cost for end of life breast cancer care, including only NHS and PSS costs, was £8,203.

These end of life care costs were applied to the model for individuals who had died because of ovarian or breast cancer.

Table 14 summarises the resource use and cost data which were used in the model.

Discounting

Discounting was used to adjust future costs and QALYs to reflect the fact that costs and QALYs are valued less in the future than they are in the present. The annual rate of 3.5% was used to discount both future costs and QALYs as recommended by NICE (2014).

Presentation of the results

For various carrier risks the total genetic testing costs and QALY loss associated with genetic testing in an initial cohort of index individuals and their eligible FDRs were estimated.

For different carrier risks and a resulting cohort of true positive index and first-degree female relatives identified as having pathogenic variants, total long-term costs and QALYs were estimated assuming they are known carriers and will receive risk-reducing care. An alternative scenario estimated costs and QALYs for the same cohort, assuming they would not undergo genetic testing, their status would be unknown and no risk-reducing care would be available to them.

Based on the above genetic testing and long-term care costs and QALYs, the incremental costs and QALYs associated with genetic testing were estimated for each carrier risk, as compared to no genetic testing alternative. The incremental cost-effectiveness ratios (ICERs) were used to determine the relative cost-effectiveness between genetic testing and no genetic testing for each carrier risk.

The ICERs were calculated using the following formula:

$$ICER = \Delta C / \Delta E$$

where ΔC is the difference in total costs between the genetic testing and no genetic testing option and ΔE the difference in their effectiveness (QALYs). The ICER expresses the extra cost per extra unit of benefit (QALY) associated with genetic testing relative to the no genetic testing comparator.

Calculating the ICER allowed for the evaluation of whether the additional benefits of genetic testing for a particular carrier risk were worth the additional costs compared to the no genetic testing option.

Generally, interventions with an ICER of less than £20,000/QALY gained are considered cost-effective. However, if the ICER is above £20,000/QALY gained, other factors such as the degree of certainty around the ICER, whether the change in the quality of life has been adequately captured, and the innovative nature of the technology must be considered when determining the acceptability of the intervention as an effective use of NHS resources (NICE 2014).

For each alternative the Net Monetary Benefit (NMB) was also estimated using the following formula:

$NMB = E \bullet \lambda - C$

where E and C are the effects (QALYs) and total costs, respectively, of genetic testing at each carrier risk and λ represents the monetised value of each QALY, set at the NICE lower cost-effectiveness threshold of £20,000/QALY (NICE 2014). The option with the highest NMB is the most cost-effective option (Fenwick 2001).

Handling uncertainty

Probabilistic sensitivity analysis

Model input parameters were synthesised in a probabilistic analysis. This means that the input parameters were assigned probability distributions (rather than being expressed as point estimates). This approach allowed more comprehensive consideration of the uncertainty characterising the input parameters. Subsequently, for each carrier risk 1,000 iterations were done, each drawing random values out of the distributions fitted onto the model input parameters.

For example, risk ratios were given a log-normal distribution, costs were sampled from gamma distributions and utilities from beta distributions. When data was unavailable, generally a standard error of the mean of 20% of the mean was assumed, or obtained from confidence intervals if they were available. For cost data from the NHS References Costs a smaller standard error of the mean of 5% was used since nationally collected data is likely to have less uncertainty as it is based on a larger and more representative population. For gamma and beta distributions, the alpha and beta parameters for sampling were obtained from the mean and standard error.

Table 14 reports the mean values of all input parameters which were used in the economic model and provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

Results (mean costs and QALYs for each alternative) were averaged across the 1000 iterations for each carrier risk. This exercise provides more accurate estimates than those derived from a deterministic analysis (which utilises the mean value of each input parameter ignoring any uncertainty around the mean), by capturing the non-linearity characterising the economic model structure (Briggs 2006).

The incremental mean costs and QALYs of genetic testing versus no genetic testing were presented in the form of cost effectiveness plane. Results of probabilistic analyses were also used to estimate for each carrier risk the probability of genetic testing being the most cost effective option (when compared with no genetic testing) at upper and lower NICE cost-effectiveness thresholds of £20,000/QALY and £30,000/QALY gained, respectively.

Deterministic sensitivity analyses

One-way sensitivity analyses were undertaken to assess the impact of all key parameters on the ICER. However, because of the wide range of carrier risks examined in the analysis, these analyses were only done for the carrier risk at which it was deemed cost-effective to offer genetic testing, that is, for a carrier risk at which the ICER of genetic testing (versus no genetic testing) was below the lower NICE cost-effectiveness threshold of £20,000/QALY gained.

One-way sensitivity analyses were summarised using tornado diagram, which shows the possible range of ICER values obtained by varying each parameter within their predefined ranges. The parameters are positioned in order of importance, with the most influential parameters located at the top of the diagram and the least influential parameters at the bottom. In general, the upper and lower values to be tested were determined by the 95% confidence intervals if available. However, if information on the variability and uncertainty of a model input was absent, plausible ranges were established by reviewing previous studies that had done sensitivity analyses on similar parameters or using the committee expert opinion.

Because the model investigated multiple carrier risks, two-way sensitivity analyses were beneficial. These analyses enabled simultaneous variation of carrier risks and another model input, facilitating examination of their combined effect on the ICER. The following two-way sensitivity analyses were carried out:

- Varying carrier risks and the cost of panel genetic testing,
- Varying carrier risk and the take up of genetic testing in first-degree relatives,
- Varying carrier risks and the take up of risk-reducing surgery.

In addition, the following scenario analyses were explored:

- All people take up RRS,
- All first-degree relatives take up genetic testing,
- Modelling that all FDRs take up genetic testing and everyone take up RRS,
- Index population comprises of males or females only,
- Index population comprises of males or females and stratified by index cases' age.

Validation of the economic model

The economic model (including the conceptual model and the identification and selection of input parameters) was developed by the health economist in collaboration with a topic sub-group formed by members of the committee. The validity of the model structure, assumptions and input parameters were confirmed by the committee. As part of the model validation, all inputs and model formulae were systematically checked; the model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The base-case results and results of sensitivity analyses were discussed with the committee to confirm their plausibility. In addition, the economic model (excel spreadsheet) and this appendix were checked for their validity and accuracy by a health economist that was external to the guideline development team.

Table 14: Input parameters (deterministic values and probability distributions) that informed the economic model of genetic testing in people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes

Input parameter	Deterministic value	Probability distribution	Source of data – comments
Age of an index case (years)	30	No distribution	Model assumption based on the committee expert opinion
Probability being female	0.56		ONS 2019, at age 30 years
Variant of uncertain significance (VUS) results			
VUS rate associated with panel genetic test	0.09	Normal, SE=0.05*mean	Sun 2023
VUS rate associated with individual pathogenic variant test	0.02	Normal, SE=0.05*mean	Derived using the VUS rate associated with the panel genetic test reported in Sun 2023
The rate of VUS reclassified as positive	0.09	Normal, SE= 0.006	Sun 2023, distribution calculated using 95% CI
Uptake of genetic testing in first-degree relatives	0.83	Beta, α=387; β=77	Martin 2021, the distribution calculated using the number of events and sample size
Mutation distribution in positive cases			
BRCA1 *BRCA2* *RAD51C* *RAD51D* *BRIP1*	0.55 0.30 0.03 0.03 0.08	Based on below (residual) Beta, α=98; β=230 Beta, α=11; β=317 Beta, α=11; β=317 Beta, α=26; β=302	Norquist 2016, the distribution based assuming SE = mean x 0.20. For *BRCA1* distribution based on the residual of those with *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*.
Characteristics of FDRs			
Number of FDR Mother Father	 1 1	 No distribution No distribution	Sun 2023

Input parameter	Deterministic value	Probability distribution	Source of data – comments
Siblings	0.91	Normal, SD=0.50	
Children	1.91	Normal, SD=0.50	
Age FDR (years)			Sun 2023
Mother	60.00	Normal, SD=5	
Father	62.00	Normal, SD=5	
Sibling	30.00	Normal, SD=5	
Children	0.00	Log-Normal, SD=5	
Risk reducing surgery and cancer risks			
RR for ovarian cancer incidence for RRBSO in people with *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*	0.10	Log-Normal, SE: 0.08	Guideline systematic review on risk reducing surgery, distribution based on 95% CI
RR for breast cancer incidence for RRBM in people with *BRCA1*, *BRCA2*	0.09	Log-Normal, SE: 0.09	Rebbeck 2004, distribution based on 95% CI
Cancer risks			
Annual breast cancer incidence in the general female population aged:	Per 100,000 people	No distribution	Cancer Research 2021, data for 2016-18
30-34	31.2		
35-39	65.8		
40-44	124.6		
45-49	214.8		
50-54	279.8		
55-59	285.5		
60-64	337.9		
65-69	412.3		
70-74	372.7		
75-79	403		
80-84	430.4		
Annual ovarian cancer incidence in the general female population aged:	Per 100,000 people	No distribution	Cancer Research 2021, data for 2016-18

Input parameter	Deterministic value	Probability distribution	Source of data – comments
30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84	6.9 9.1 13.2 19.4 27.1 34.8 41.6 52.3 60.8 73.8 66.9		
Annual breast cancer incidence in females with *BRCA1* pathogenic variants aged: 31-40 41-50 51-60 61-70 71-80	Per 1,000 persons per year 23.5 28.3 25.7 25.0 16.5	Beta α=86.26; β=3584.38 α=88.84; β=3050.48 α=46.36; β=1757.7 α=17.37; β=677.52 α=2.88; β=171.57	Kuchenbaecker 2017, distribution calculated using 95% CI
Annual ovarian cancer incidence in females with *BRCA1* pathogenic variants aged: 31-40 41-50 51-60 61-70 71-80	Per 1,000 persons per year 1.8 7.0 13.8 29.4 5.7	Beta α=8.63; β=4783.73 α=23.01; β=3263.52 α=22.59; β=1614.21 α=22.17; β=731.8 α=1.08; β=188.09	Kuchenbaecker 2017, distribution calculated using 95% CI
Annual breast cancer incidence in females with *BRCA2* pathogenic variants aged: 31-40 41-50	Per 1,000 persons per year 10.8 27.5	Beta α=21.88; β=2003.85 α=61.98; β=2191.92	Kuchenbaecker 2017, distribution calculated using 95% CI

Input parameter	Deterministic value	Probability distribution	Source of data – comments
51-60 61-70 71-80	30.6 22.9 21.9	α=41.62; β=1318.49 α=12.47; β=532.28 α=4.77; β=212.88	
Annual ovarian cancer incidence in females with *BRCA2* pathogenic variants aged: 31-40 41-50 51-60 61-70 71-80	Per 1,000 persons per year 0.3 0 6.5 10.3 2.3	Beta α=0.26; β=869.92 NA α=10.6; β=1619.44 α=8.71; β=837.19 α=0.31; β=136.43	Kuchenbaecker 2017, distribution calculated using 95% CI. Between ages 41-50 the incidence and SE was 0.000, as a result the SD was imputed using the average of the SDs at the other ages
Annual breast cancer incidence in females with *RAD51C* pathogenic variants aged: 31-40 41-50 51-60 61-70 71-80 80+	Per 1,000 persons per year 0.4 2 5 6 7 8	Beta α=27.31; β=68239.49 α=15.33; β=7651.5 α=42.47; β=8450.74 α=21.99; β=3642.82 α=29.9; β=4241.57	Yang 2020, distribution calculated using 95% CI
Annual ovarian cancer incidence in females with *RAD51C* pathogenic variants aged: 31-40 41-50 51-60 61-70 71-80 80+	Per 1,000 persons per year 0.05 0.3 2 7 3 1	Beta α=1.06; β=21279.97 α=3.84; β=12796.65 α=15.33; β=7651.5 α=15.25; β=2163.58 α=2.81; β=934.17	Yang 2020, distribution calculated using 95% CI
Annual breast cancer incidence in people with *RAD51D* pathogenic variants aged: 31-40	Per 1,000 persons per year 0.3	Beta α=15.36; β=51189.61	Yang 2020, distribution calculated using 95% CI

Input parameter	Deterministic value	Probability distribution	Source of data – comments
41-50 51-60 61-70 71-80 80+	2 4 6 7 7	α=61.34; β=30608.99 α=27.2; β=6773.99 α=21.99; β=3642.82 α=20.76; β=2945.23	
Annual ovarian cancer incidence in people with *RAD51D* pathogenic variants aged: 31-40 41-50 51-60 61-70 71-80 80+	Per 1,000 persons per year 0.03 0.3 2 6 5 3	Beta α=1.6; β=53295.84 α=3.84; β=12796.65 α=15.33; β=7651.5 α=34.36; β=5692.46 α=7.8; β=1551.36	Yang 2020, distributions calculated using 95% CIs
RR for ovarian cancer associated with *BRIP1* pathogenic variant	3.41	Log-Normal, SE: 0.872	Ramus 2015, distribution calculated using 95%
RR risk for breast cancer associated with *BRIP1* pathogenic variant	1.00	No distribution	Committee expert opinion
Cancer mortality			
10-year breast cancer mortality in *BRCA1*-positive individuals undergoing enhanced screening	0.082	Beta (applied to annualised rate) α=2.37; β=274.88	Evans 2021 reported mortality for individuals receiving enhanced surveillance with mammography and MRI. The 10-year survival rate was converted to an annualised mortality rate. Distribution calculated using 95% confidence intervals. Confidence intervals were not available at 10 years. However, these were approximated using data reported at 20 years.

Input parameter	Deterministic value	Probability distribution	Source of data – comments
10-year breast cancer mortality in *BRCA2*-positive individuals undergoing enhanced screening	0.05	Beta (applied to annualised rate) α=0.36; β=69.40	Evans 2021 reported mortality for individuals receiving enhanced surveillance with mammography and MRI. The 10-year survival rate was converted to an annualised mortality rate. Distribution calculated using 95% confidence intervals. Confidence intervals were not available at 10 years. However, these were approximated using data reported at 20 years.
10-year breast cancer mortality in *RAD51C* and *RAD51D* positive individuals	0.160	Beta (applied to annualised rate) α=89.87; β=5064.39	Duffy 2013 reported mortality for individuals receiving surveillance with mammography. The 10-year survival rate was converted to an annualised mortality rate. Distribution calculated using 95% confidence intervals.
10-year breast cancer mortality in *BRIP1*-positive individuals	0.241	Beta (to annualised rates) α=1486.02; β=52403.3	*BRIP1* individuals' mortality was modelled to be equivalent to the general population. The 10-year survival rate from Cancer Research UK 2020, which used 2013-17 data, was converted to mortality, and the annualised rate was applied in the model, with the distribution calculated using 95% confidence intervals.
10-year ovarian cancer mortality in individuals with *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* or *BRIP1* mutation	0.647	Beta (applied to annualised rate) α=2556.05; β=21991	Mortality in individuals with *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* was modelled to be equivalent to the general population. The 10-year survival rate from Cancer Research UK 2020, which used 2013-17 data, was converted to mortality, and the

Input parameter	Deterministic value	Probability distribution	Source of data – comments
			annualised rate was applied in the model, with the distribution calculated using 95% confidence intervals.
RR of RRBSO (versus surveillance) for ovarian cancer mortality	0.36	Log-Normal, SE: 0.099	Guideline systematic review examining the effectiveness of risk reducing surgery
RR of RRBM (versus surveillance) for breast cancer mortality in people with *BRCA1*	0.06	Log-Normal, SE: 0.115	Heemskerk-Gerritsen 2019
RR of RRBSO (versus no RRBSO) for breast cancer mortality associated win people with *BRCA1*	0.46	Log-Normal, SE: 0.102	Gaba 2023
Genetic testing and associated costs			
Genetic panel test including processing VUS Panel genetic test Individual pathogen genetic test including processing VUS Individual pathogen genetic test	£750.00 £492.58 £189.00 £124.13	Gamma α=25; β=30 α=25; β=20 α=25; β=8 α=25; β=5	Expert opinion of the committee informed by laboratory cost data provided by a member of the committee. Distributions were based assuming SE = mean x 0.20.
Counselling session cost	£23.67	Gamma, α=25; β=1	Sun 2023. The distribution based assuming SE = mean x 0.20.
Number of pre-counselling sessions	1	Custom	Expert opinion of the committee. The custom distribution assumed that 80% of individuals would have one session, while the remaining 20% could have up to three sessions.
Number of post-counselling sessions	1	Custom	Expert opinion of the committee. The custom distribution assumed that 80% of individuals would have one session, while the remaining 20% could have up to three sessions.
Breast cancer surveillance costs			

Input parameter	Deterministic value	Probability distribution	Source of data – comments
Mammogram	£190	Gamma, α=25; β=8	Genesis Care private provider 2023. The distribution based assuming SE = mean x 0.20.
Magnetic Resonance Imaging	£178	Gamma, α=400; β=0.45	NHS Reference Costs 2020-21, HRG: RD01A Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over. The distribution based assuming SE = mean x 0.05.
Risk reducing surgery and associated costs			
RRBSO cost	£5,098	Gamma, α=400; β=10.64	This estimate comprises the costs of the procedure and bone health support. The procedure cost was obtained from the NHS Reference Costs 2020-21, HRG: MA09B Intermediate, Laparoscopic or Endoscopic, Upper Genital Tract Procedures, with CC Score 0-1. For bone health, individuals were modelled to undergo 3 Dexa Scans (Sun 2023) with a unit cost obtained from the NHS Reference Costs 2020-21, HRG: RD50Z Dexa Scan. The costs of osteoprotection included calcium and vitamin-D3 (Manchanda 2016). All reported costs were adjusted to 2020/2021 prices using HCHS/NHS inflators (PSSRU 2021). The distributions were based on the assumption of SE = mean x 0.20.
HRT cost in people undergoing RRBSO before menopause (per annum)	£88	Gamma, α=25; β=4	Based on the costings in the NICE Guideline NG23 for Menopause Diagnosis and Management. The cost includes oral oestradiol and

Input parameter	Deterministic value	Probability distribution	Source of data – comments
			progestogen and the management of associated adverse events. The reported cost was updated to 2020/2021 prices using HCHS/NHS inflators (PSSRU 2021). The distribution was based on the assumption that SE = mean x 0.20.
RRBM cost	£11,768	Gamma, α=400; β=29	Wei 2024. The estimate utilised the NHS Reference Costs 2020-21 HRG code JA21B for Bilateral Major Breast Procedures with CC (Complications and Comorbidities) Score 0 and JA33Z for Bilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction. The estimate also considered the rate of complications. A distribution was applied based on the assumption that the standard error (SE) was equal to the mean multiplied by 0.20.
Cancer diagnosis, treatment and follow-up costs			
Breast cancer diagnosis and initial treatment costs – genetic testing arm	£18,378	Gamma, α=25; β=735	Wei 2024. The estimate included clinical assessment, imaging (mammography, ultrasound-guided core needle biopsy), lymph node evaluation, surgical management (breast-conserving surgery and mastectomy with or without reconstruction), associated complications, chemotherapy (docetaxel-capecitabine or docetaxel-capecitabine-vinorelbine), and radiotherapy. The same cost was

Input parameter	Deterministic value	Probability distribution	Source of data – comments
			used for all pathogenic variants and a distribution was based assuming SE = mean x 0.20.
Breast cancer annual follow-up costs – genetic testing arm	£758	Gamma, α=25; β=30	Wei 2024. The estimate included endocrine therapy (ER testing, tamoxifen, or anastrozole), targeted therapy (HER2 testing, trastuzumab), treatment for bone metastases (MRI scan, oral sodium clodronate, oral ibandronic acid, zoledronic acid (IV), pamidronate disodium (IV), bisphosphonates), and follow-up costs such as mammograms and clinician visits. The follow-up costs accounted for stage-specific relapse, recurrence, and progression rates. The same cost was used for all pathogenic variants and a distribution was based assuming SE = mean x 0.20.
Breast cancer diagnosis and initial treatment costs – no genetic testing arm Breast cancer annual follow-up costs – no genetic testing arm	£20,025 £774	Gamma, α=25; β=801 Gamma, α=25; β=31	Based on the stage specific costings of breast cancer management (Wei 2024) and breast cancer staging data at the time of diagnosis in the general female population with breast cancer. The staging data in the general population was derived from various sources, including Cancer Research UK 2021, the National Disease Registration Services and the NHS Digital population-based cancer registry for England (CancerData 2023). The same cost was used for all pathogenic variants and distributions

Input parameter	Deterministic value	Probability distribution	Source of data – comments
			were based assuming SE = mean x 0.20.
Ovarian cancer diagnosis and initial treatment costs	£25,554	Gamma, α=25; β=1022	Wei 2024. The estimate included diagnosis (pelvic examination, CA125 test, transvaginal ultrasound, CT scan, abdominal ultrasound with biopsy, histopathology assessment and cytology assessment), initial treatment (surgical procedure, HRG code MA26A Complex, Open or Laparoscopic, Upper or Lower Genital Tract Procedures for Malignancy, with CC Score 5+, NHS Reference costs 2020-21), histological assessment of surgical specimen, surgical follow-up, appointment for planning chemotherapy per cycle, blood test for tumour marker, carboplatin and paclitaxel per cycle, administration costs of carboplatin and paclitaxel per cycle and CT in the middle and at the end of treatment. The cost estimate was based on six cycles of chemotherapy. The same cost was used for all pathogenic variants and a distribution was based assuming SE = mean x 0.20.
Ovarian cancer annual follow-up costs Years 1 and 2 (per annum) Years 3 to 10 (per annum)	 £18,568 £1,560	Gamma α=25; β=743 α=25; β=62	Wei 2024. These cost estimates include follow-up consultant visits, CA125 and CT scans and account for recurrence and associated costs, which include treatment with chemotherapy and secondary surgery. The same cost was used for all

Input parameter	Deterministic value	Probability distribution	Source of data – comments
			pathogenic variants and distributions were based assuming SE = mean x 0.20.
End of life care costs			
Ovarian cancer	£19,224	Gamma, α=25; β=769	Sun 2022. Includes NHS and social care services funded by the NHS only. The reported cost was adjusted to 2020-21 prices using HCHS/NHS inflators (PSSRU 2021). Distribution based assuming SE = mean x 0.20.
Breast cancer	£8,203	Gamma, α=25; β=328	Round 2015. Reports costs from a wider perspective. However, these were stratified so only NHS funded care was included. The reported cost was adjusted to 2020-21 prices using HCHS/NHS inflators (PSSRU 2021). Distribution based assuming SE = mean x 0.20.
Uptake of RRS			
Uptake of RRBSO in people with *BRCA1* or *BRCA2* (same uptake rate was modelled for *RAD51C*, *RAD51D*, *BRIP1*)	<36 years: 0.23 36-45 years: 0.76 >45 years: 0.5	Beta α=18.98; β=62.99 α=5.23; β=1.65 α=12.03; β=12.09	Evans 2009. The uptake rates for RRBSO, stratified by age, in individuals (N=211) with *BRCA* pathogenic variants. The same uptake rates were modelled for individuals with other pathogenic variants. Distributions based assuming SE = mean x 0.20.
Uptake of RRBM in people with *BRCA1* or *BRCA2*	<36 years: 0.86 36-45 years: 0.57 >45 years: 0.20	Beta α=2.55; β=0.4 α=10.21; β=7.73 α=19.81; β=79.52	Evans 2009. The uptake rates for RRBM, stratified by age, in individuals (N=211) with *BRCA* pathogenic variants. Distributions based assuming SE = mean x 0.20.

Input parameter	Deterministic value	Probability distribution	Source of data – comments
Age for RRS RRBM in *BRCA1* RRBM in *BRCA2* RRBSO in *BRCA1* RRBSO in *BRCA2* RRBSO in *RAD51C, RAD51D, BRIP1*	 31 31 35 40 45	Fixed	Expert opinion of the committee. The committee advised RRBM could be initiated around age 30. The earliest possible age for RRS in the model was 31 since people entered the decision tree part of the model at age 30.
Utility values			
Ovarian cancer Year 1 Year 2 Year 3 Year 4 Year 5 Year 6 onwards Advanced disease	 0.50 0.65 0.67 0.69 0.70 0.72 0.55	Beta α=49.5; β=49.5 α=34.35; β=18.5 α=32.33; β=15.92 α=30.31; β=13.62 α=29.3; β=12.56 α=27.28; β=10.61 α=44.45; β=36.37	NICE Familial Breast Cancer Clinical Guideline [CG164] cost-effectiveness model and committee expert opinion. Distributions based assuming SE = mean x 0.10. The utility value for advanced disease was obtained from Havrilesky 2009.
Breast cancer Early Advanced Recurrent Remittent	 0.71 0.65 0.45 0.81	Beta α=28.29; β=11.56 α=34.35; β=18.5 α=54.55; β=66.67 α=18.19; β=4.27	The utility values were obtained from various sources. The utility value for "Early breast cancer" was obtained from the NICE Familial Breast Cancer Clinical Guideline [CG164] economic model (breast cancer in year 1 utility value). The utility value for "Advanced breast cancer" was obtained from the NICE Clinical Guideline on Advanced Breast Cancer (referred to as "Stable disease" in the economic model). The utility value for "Recurrent breast cancer" was obtained from the NICE Clinical Guideline on Advanced Breast Cancer (referred to as "Progressive disease" in the economic model). The

Input parameter	Deterministic value	Probability distribution	Source of data – comments
			utility value for "Remittent breast cancer" was obtained from the NICE Clinical Guideline on Advanced Breast Cancer economic model (referred to as the "Response"). Distributions based assuming SE = mean x 0.10.
Utility decrements RRBM RRBSO Genetic testing	 0.03 0.08 0.05	Beta α=96.97; β=3135.36 α=91.92; β=1057.08 α=94.95; β=1804.05	NICE Familial Breast Cancer Clinical Guideline [CG164] cost-effectiveness model and committee expert opinion. Distribution based assuming SE = mean x 0.10.
Utility for end stage cancer	0.160	Beta, α=83.84; β=440.16	The utility value for "End stage breast cancer" was obtained from Peasgood's (2010) systematic review. Distributions based assuming SE = mean x 0.10.
Baseline utility values			
Males aged: 18–24 25–34 35–44 45–54 55–64 65–74 75+	 0.967 0.965 0.943 0.934 0.896 0.900 0.830	Beta α=1.11; β=0.04 α=2.57; β=0.09 α=0.92; β=0.06 α=1.62; β=0.11 α=1.47; β=0.17 α=2.34; β=0.26 α=1.31; β=0.27	Janssen 2021. The utility values from a general population-based survey conducted in 2014, which utilised the Health Survey for England and EQ-5D-3L questionnaire along with the TTO valuation method.
Females aged: 18–24 25–34 35–44 45–54	 0.96 0.95 0.94 0.92	Beta α=1.75; β=0.07 α=2.1; β=0.1 α=1.03; β=0.07 α=1.8; β=0.15	Janssen 2021. The utility values from a general population-based survey conducted in 2014, which utilised the Health Survey for England and EQ-5D-3L questionnaire along with the TTO valuation method.

Input parameter	Deterministic value	Probability distribution	Source of data – comments
55–64 65–74 75+	0.88 0.84 0.76	α=1.59; β=0.23 α=1.55; β=0.3 α=0.89; β=0.29	
Breast cancer stage at diagnosis			
General population DCIS Stage 1 Stage 2 Stage 3 Stage 4	 0.15 0.38 0.34 0.08 0.04	Normal SE: 0.002 SE: 0.077 SE: 0.069 SE: 0.016 SE: 0.009	The staging data in the general population was derived from various sources, including Cancer Research UK 2021 (DCIS), the National Disease Registration Services and the NHS Digital population-based cancer registry for England data for stages 1 to 4 (CancerData 2023). The distributions were derived from 95% CIs.
Under breast cancer surveillance DCIS Stage 1 Stage 2 Stage ≥3	 0.20 0.54 0.25 0.01	Normal SE: 0.04 SE: 0.109 SE: 0.049 SE: 0.002	Evans 2021. The study reported on the outcomes of targeted enhanced breast cancer screening in women aged 30 to 60 with increased familial risk. The screening involved annual mammography starting at age 35 or 5 years younger than the youngest affected relative, with an upper age limit of 50 for moderate-risk individuals and 60 for high-risk individuals. Distributions based assuming SE = mean x 0.20.
Breast cancer relapse, recurrence and progression			
Relapse DCIS To non-invasive stage To invasive stage	 0.125 0.125	Beta α=21.75; β=152.25 α=21.75; β=152.25	NICE Clinical Guideline on Early and locally advanced breast cancer, diagnosis and management [NG101] 2009, DCIS evidence summary,

Input parameter	Deterministic value	Probability distribution	Source of data – comments
			upstaging. These rates were used then calculating annual average breast cancer utilities and cancer costs. Distributions based assuming SE = mean x 0.20.
Recurrence of early and locally advanced breast cancer	0.125	Beta, α=21.75; β=152.25	Sun 2023. The study estimated the recurrence rates for early and locally advanced breast cancer using data from Anderson (2009), which reported rates of 15.9% for node-positive disease and 11% for node-negative disease. These rates were weighted by 31% for node-positive and 69% for node-negative breast cancers. The rate was annualised and was used when calculating average breast cancer utilities and costs. A distribution was applied assuming a standard error equal to the mean multiplied by 0.20. Distributions based assuming SE = mean x 0.20.
Recurrence of an advanced breast cancer	0.660	Beta, α=7.84; β=4.04	Gennari 2005. This was a multivariate analysis to identify factors predicting survival from disease progression to death in people with metastatic breast cancer. The study utilised individual patient data from six trials conducted between 1983 and 2001 and included relapse-free survival as a covariate in the analysis. The rate was annualised and was used when calculating average breast cancer utilities. A

Input parameter	Deterministic value	Probability distribution	Source of data – comments
			distribution was applied based on the 95% confidence intervals.
Progression of early and locally advanced breast cancer to an advanced breast cancer stage	0.350	Beta, α=15.9; β=29.53	NICE Clinical Guideline on Advanced Breast Cancer [CG81]). This rate was annualised and when calculating utilities, it was modelled that each year, individuals with early and locally advanced breast cancers would progress at this rate to advanced breast cancer. The rate was annualised and was used when calculating average breast cancer utilities and cancer costs. Distributions based assuming SE = mean x 0.20.
Discount rate for costs and QALYs	3.5%	No distribution	NICE Guidelines Manual 2014, updated 2022

Results

The deterministic and probabilistic results of the economic analysis are provided in Table 15. This table displays the mean QALYs and mean total costs for every carrier risk in both the genetic testing arm and the no genetic testing arm. It also shows the mean NMBs and ICERs, where higher NMBs indicate greater cost-effectiveness. The table also includes probabilities of cost-effectiveness using lower and upper NICE cost-effectiveness threshold of £20,000/QALY and £30,000/QALY, respectively.

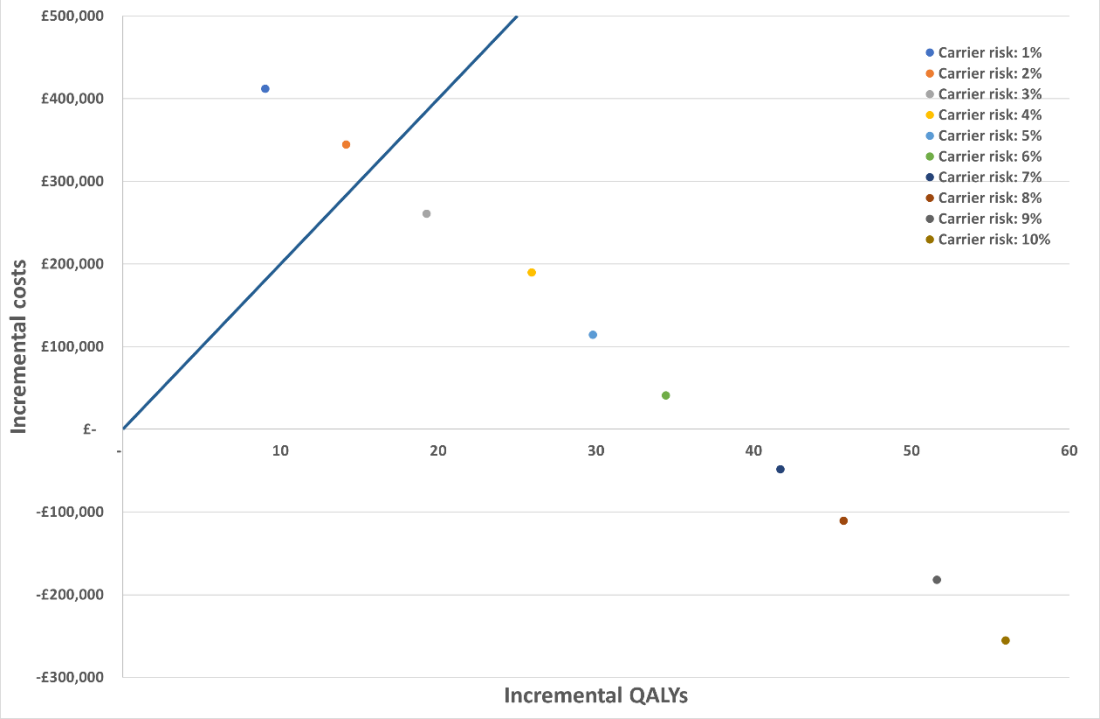
The probabilistic results indicate that when using the lower NICE cost-effectiveness threshold of £20,000 per QALY gained, providing genetic testing to individuals with a carrier risk of 3% is potentially cost-effective. The genetic testing (versus no genetic testing) results in an ICER of £10,782/QALY and has a 72% probability of being cost-effective at this carrier risk.

Table 15: Expected costs, QALYs, NMBs, and ICERs, and probabilities of cost effectiveness across carrier risks ranging from 1% to 10%.

	ICER Deterministic	Genetic testing (Probabilistic results)			No genetic testing (Probabilistic results)			ICER Probabilistic	
Carrier risk for genetic testing	Genetic testing vs no genetic testing	Mean lifetime costs (discounted)	Mean lifetime QALYs (discounted)	Mean NMB (using £20k/QALY threshold)	Mean lifetime costs (discounted)	Mean lifetime QALYs (discounted)	Mean NMB (using £20k/QALY threshold)	Genetic testing vs no genetic testing	Probability cost-effective at £20k and £30k per QALY thresholds
1%	£33,902	£1,038,597	504	£9,043,860	£647,636	495	£9,251,364	£42,622	0.09, 0.29
2%	£15,251	£1,305,246	793	£14,553,314	£1,005,910	778	£14,561,951	£20,594	0.48, 0.68
3%	£6,675	£1,577,113	1,077	£19,966,591	£1,367,459	1,058	£19,787,371	£10,782	0.72, 0.82
4%	£1,746	£1,849,914	1,356	£25,275,801	£1,721,388	1,332	£24,908,861	£5,188	0.84, 0.89
5%	Dominant	£2,128,660	1,647	£30,804,706	£2,098,743	1,617	£30,239,750	£1,006	0.88, 0.91
6%	Dominant	£2,415,709	1,926	£36,105,132	£2,473,560	1,891	£35,347,399	Dominant	0.93, 0.94
7%	Dominant	£2,679,696	2,208	£41,480,731	£2,825,451	2,168	£40,540,108	Dominant	0.95, 0.95
8%	Dominant	£2,943,254	2,517	£47,403,466	£3,164,185	2,471	£46,245,908	Dominant	0.96, 0.97
9%	Dominant	£3,237,057	2,813	£53,017,219	£3,572,402	2,760	£51,628,994	Dominant	0.97, 0.97
10%	Dominant	£3,511,976	3,072	£57,931,160	£3,917,876	3,016	£56,396,818	Dominant	0.97, 0.96

Figure 3 provides the cost effectiveness plane of the analysis. Genetic testing at each carrier risk is placed on the plane according to its incremental costs and QALYs, compared with no genetic testing which is at the origin. The line's slope represents the NICE lower cost effectiveness threshold of £20,000/QALY gained. This implies that providing genetic testing to individuals with carrier risks below 3% may not be cost-effective since incremental costs and QALYs for these carrier risks fall on the left side of the line.

Figure 3: Cost effectiveness plane of genetic testing at various carrier risks. The incremental costs and QALYs for each carrier risk were estimated against no genetic testing alternative, per initial 1,000 index cases.



Abbreviations: QALY: Quality-adjusted life years

At the carrier risk of 3% there are approximately 105 true positive cases identified. This includes 21 index female cases and 17 male index cases. From these index cases an additional 146 FDRs would be tested. The testing of these FDRs would result in 68 true positive cases including 35 first-degree female relatives and 33 male relatives.

The benefit of identifying first-degree male relatives is to identify female second-degree relatives (SDRs) who may be carriers of the pathogenic variants. Since the analysis did not consider the impact on SDRs, these first-degree male relatives were not considered further in the analysis.

The final cohort of true positive FDRs at the carrier risk of 3% included 10 mothers, 8 female siblings and 17 female children. This cohort was used to estimate long term costs and QALYs associated with genetic testing at this carrier risk.

The probabilistic analysis also indicates that at a carrier risk above 5%, genetic testing becomes the dominant strategy when compared with no genetic testing. This means that genetic testing results in lower costs and higher QALYs. At these carrier risks, the additional costs associated with genetic testing are outweighed by the cost

savings associated with averted ovarian and breast cancers in an index population and also in eligible FDRs.

The findings revealed a considerable degree of uncertainty in the results. Notably, in the deterministic analysis (Table 15) all the ICERs were more favourable. According to the deterministic analysis, offering genetic testing to individuals with a carrier risk of 2% would be deemed cost-effective (compared to no testing), based on NICE's lower cost-effectiveness threshold of £20,000/QALY gained. The carrier risk threshold point at which the ICER of genetic testing (compared to no testing) would fall just below £20,000/QALY gained, was 1.6%.

However, the results from the probabilistic analysis are preferred because they account for input parameter uncertainty where according to this analysis, it would be cost-effective to offer genetic testing to people only with a carrier risk of 3% and above. As a result, all subsequent sensitivity analyses were undertaken assuming that genetic testing would be offered at a carrier risk of 3%.

Results: sensitivity analyses

The conclusions remained largely unaffected by the scenarios examined through deterministic sensitivity analyses

Table 16 and Figure 4).

Table 16 outlines the key model inputs that had the most significant influence on the ICERs and the ranges used in the deterministic sensitivity analyses. Figure 4 provides a summary of the results of deterministic sensitivity analyses in terms of their impact on the ICER of genetic testing (versus no genetic testing). Full results of the deterministic sensitivity analyses can be found in the appendix 1 (Deterministic sensitivity analyses – full results).

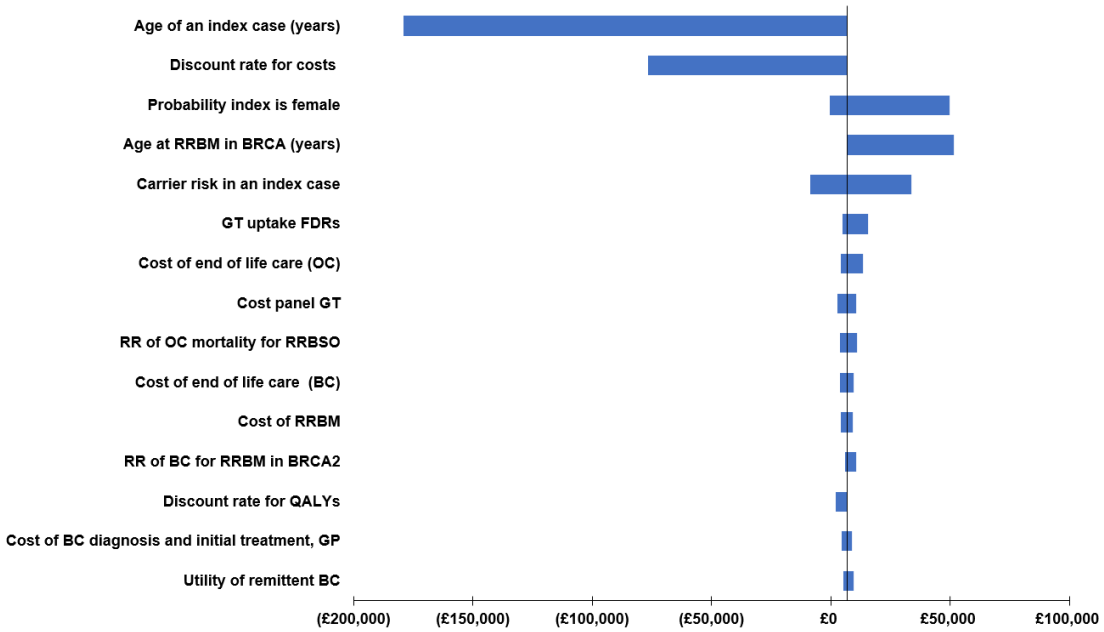
Table 16: Deterministic sensitivity analyses (parameter inputs with the greatest impact. Base-case values and ranges used), assuming a carrier risk of 3% for genetic testing eligibility.

Parameter input	Base-case value	Range tested	ICER of genetic testing (vs no genetic testing) using upper and lower value tested	Source for the range tested
Age of an index case (years)	30	30 to 70	£6,675; -£179,184	Assumption
Discount rate for costs	0.035	0 to 0.035	-£76,504; £6,675	Assumption for the lower estimate and NICE 2014 for the upper estimate
Probability index is female	0.56	0 to 1.0	£49,752; -£387	Assumption
Age at RRBM in *BRCA* (years)	31	31 to 50	£6,675; £51,406	Assumption based on the GC expert opinion and related recommendations
Carrier risk in an index case	0.03	0.01 to 0.1	£33,902; -£8,485	Assumption
GT uptake FDRs	0.83	0.3 to 1.0	£15,747; £4,769	Assumption for the upper limit, the lower from the uptake rates reported in the international studies
Cost of end of life care (OC)	£19,224	£8,203 to £23,069	£13,324; £4,355	Sun 2023 (in publication), lower estimate set to be the same as cost of end-of-life care for BC and upper assumption (mean + 20%)
Cost panel GT	£493	£394 to £591	£2,781; £10,569	Assumption (mean ± 20%)
RR of OC mortality for RRBSO	0.36	0.21 to 0.60	£3,710; £11,072	95% confidence intervals from the guideline systematic review
Cost of end of life care (BC)	£8,203	£6,562 to £9,844	£9,525; £3,824	Assumption (mean ± 20%)
Cost of RRBM	£11,768	£9,414 to £14,122	£4,031; £9,318	Assumption (mean ± 20%)
RR of BC for RRBM in *BRCA2*	0.09	0.02 to 0.38	£5,804; £10,736	Rebbeck 2004
Discount rate for QALYs	0.035	0 to 0.035	£1,913; £6,675	Assumption for the lower estimate and NICE 2014 for the upper estimate
Cost of BC diagnosis and initial treatment, GP	£20,024	£16,019 to £24,029	£8,857; £4,492	Assumption (mean ± 20%)

Parameter input	Base-case value	Range tested	ICER of genetic testing (vs no genetic testing) using upper and lower value tested	Source for the range tested
Utility of remittent BC	0.81	0.65 to 0.97	£5,181; £9,380	Assumption (mean ± 20%)
Age of sibling relative to index	0.00	-5 to 5	£7,466; £11,495	Eccleston 2017

Abbreviations: BC: Breast cancer; FDRs: First degree relatives; GC: Guideline committee; GT: Genetic testing; NICE: National Institute for Health and Care Excellence; OC: Ovarian cancer; QALY: Quality-adjusted life year; RR: Relative risk; RRBM: Risk reducing bilateral salpingo-oophorectomy

Figure 4: Tornado diagram summarising the results of multiple one-way deterministic sensitivity analyses, at carrier risk of 3%.



Abbreviations: BC: Breast cancer; FDR: First-degree relative; GP: General population; GT: Genetic testing; OC: Ovarian cancer; QALY: Quality-adjusted life year; RR: Relative risk; RRBM: Risk reducing bilateral mastectomy; RRBSO: Risk reducing bilateral salpingo-oophorectomy.

As expected, the results were sensitive to the discount rate used for costs (Figure 4). For example, at a carrier risk of 3% in the sensitivity analysis where no discounting of costs was undertaken, the alternative of genetic testing was dominant. That is, it resulted in lower costs and higher QALYs. This is because the analysis adopted the lifetime horizon of each individual considered and discounting means that the present value of any cost savings and benefits is less.

Considering the impact on, for example, children of an index case, the cost savings associated with genetic testing will not start to accrue until 60 years in the future (assuming that their age relative to an index is -30 years). The impact of this is a substantial reduction in the value of any cost savings due to cancers prevented and QALYs gained.

The sensitivity analysis also revealed that the results were influenced by the probability of an index case being female (Figure 4). For example, assuming that all index cases were female, genetic testing became dominant when compared with no genetic testing at a carrier risk of 3%. In contrast, when the entire index population comprised of males, the ICER of genetic testing increased to as much as £ £49,752/QALY gained at a carrier risk of 3%. The benefits associated with genetic testing are driven by identifying index cases who would directly benefit from preventive measures.

A further two-way sensitivity analysis was conducted where both the probability of an index case being female and carrier risk in an index case were simultaneously varied (Table 17). The analysis revealed that if the index population comprised of females only, genetic testing would be cost-effective at a carrier risk of 1%, resulting in an ICER of £17,155 when compared with no genetic testing. However, it should be noted that the deterministic ICERs are more favourable than the probabilistic results and there may be less confidence in recommending genetic testing at this lower carrier risk.

Table 17: Two-way sensitivity analysis of genetic testing cost-effectiveness (ICER): varying carrier risk and the probability of an index case being female simultaneously.

		The probabilty of an index being female										
		0.00	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1.00
Carrier risk	1%	£ 141,102	£ 96,667	£ 72,062	£ 56,434	£ 45,629	£ 37,712	£ 31,661	£ 26,887	£ 23,024	£ 19,834	£ 17,155
	2%	£ 77,715	£ 52,256	£ 37,898	£ 28,679	£ 22,260	£ 17,533	£ 13,907	£ 11,037	£ 8,710	£ 6,784	£ 5,164
	3%	£ 49,752	£ 32,329	£ 22,421	£ 16,029	£ 11,564	£ 8,268	£ 5,735	£ 3,728	£ 2,099	£ 749	Dominant
	4%	£ 34,003	£ 21,013	£ 13,592	£ 8,791	£ 5,431	£ 2,947	£ 1,037	Dominant	Dominant	Dominant	Dominant
	5%	£ 23,900	£ 13,719	£ 7,885	£ 4,104	£ 1,454	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	6%	£ 16,869	£ 8,625	£ 3,892	£ 821	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	7%	£ 11,693	£ 4,868	£ 943	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	8%	£ 7,723	£ 1,981	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	9%	£ 4,583	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	10%	£ 2,036	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant

Deterministic sensitivity analyses also indicated that the ICER was sensitive to the genetic testing uptake in eligible FDRs (Figure 4). For example, using a lower genetic testing uptake of 30% in FDRs as reported in international literature (Landsbergen 2005, Jeong 2021), the ICER of genetic testing (versus no genetic testing) became less favourable. That is, it was £15,747/QALY gained at a carrier risk of 3%.

A further two-way sensitivity analysis, where both carrier risk and the uptake rate of genetic testing in FDRs were varied simultaneously (Table 17), showed that even though there was a variation in the ICERs, overall the conclusions were unchanged. However, as the uptake increases there may be greater confidence to offer genetic testing at a lower carrier risk of 2% since the ICER of genetic testing is substantially lower than NICE's lower cost-effectiveness threshold of £20,000/QALY gained.

Using the base-case uptake rate in FDRs (83%), genetic testing also results in an ICER of £15,747/QALY at a carrier risk of 2%. However, the probabilistic analysis indicated that the deterministic ICER is likely to be an underestimate of the true ICER due to parameter uncertainty and therefore there is less confidence in this result.

Table 18: Two-way sensitivity analysis of genetic testing cost-effectiveness (ICER): varying carrier risk and the uptake rate of genetic testing in eligible first-degree relatives simultaneously.

		The uptake of genetic testing in first-degree relatives							
		30%	40%	50%	60%	70%	80%	90%	100%
Carrier risk	1%	£ 53,445	£ 48,741	£ 44,617	£ 40,973	£ 37,729	£ 34,822	£ 32,203	£ 29,832
	2%	£ 27,564	£ 24,611	£ 22,017	£ 19,720	£ 17,671	£ 15,834	£ 14,175	£ 12,672
	3%	£ 15,747	£ 13,575	£ 11,665	£ 9,972	£ 8,461	£ 7,105	£ 5,880	£ 4,769
	4%	£ 8,979	£ 7,249	£ 5,727	£ 4,377	£ 3,172	£ 2,089	£ 1,112	£ 224
	5%	£ 4,594	£ 3,148	£ 1,876	£ 747	Dominant	Dominant	Dominant	Dominant
	6%	£ 1,522	£ 274	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	7%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	8%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	9%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	10%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant

Similarly, the results indicated that the findings were sensitive to the age at which RRS is initiated (Figure 4). The base-case analysis assumed that RRS is initiated in the early 30s. However, as the age of RRBSO and RRBM increases, the ICERs of genetic testing (versus no genetic testing) become less favourable.

A further two-way sensitivity analysis, where carrier risk and age of RRS initiation in individuals with *BRCA* pathogenic variants was varied simultaneously, showed

variation in the cost-effectiveness of genetic testing (Table 19). For example, if RRBM is initiated at age 40 and RRBSO at 45, the ICER for genetic testing (versus no testing) increases to £11,093/QALY gained at a 3% carrier risk. However, if RRS is initiated in the early 50s, offering genetic testing would not be cost-effective for those with a carrier risk below 5%.

Table 19: Two-way sensitivity analysis of genetic testing cost-effectiveness (ICER): varying carrier risk and the age (in years) at which RRS initiation occurs in individuals with *BRCA* simultaneously.

		Age (years) at which RRS initiation occurs in individuals with BRCA		
		RRBM: 30, RRBSO: 35	RRBM: 40, RRBSO: 45	RRBM: 50, RRBSO: 55
Carrier risk	1%	£ 33,902	£ 60,706	£ 188,929
	2%	£ 15,251	£ 26,558	£ 92,658
	3%	£ 6,675	£ 11,093	£ 51,406
	4%	£ 1,746	£ 2,271	£ 28,490
	5%	Dominant	Dominant	£ 13,908
	6%	Dominant	Dominant	£ 3,813
	7%	Dominant	Dominant	Dominant
	8%	Dominant	Dominant	Dominant
	9%	Dominant	Dominant	Dominant
	10%	Dominant	Dominant	Dominant

Abbreviations: RRBM: Risk reducing bilateral mastectomy; RRBSO: Risk reducing bilateral salpingo-oophorectomy; RRS: Risk reducing surgery

Deterministic sensitivity analyses also indicated that the findings were sensitive to the relative risk of ovarian cancer mortality for RRBSO (Figure 4). The use of an upper confidence interval of 0.60 (base-case: 0.36) resulted in a slightly higher ICER of genetic testing but it remained well below the lower NICE cost-effectiveness threshold of £20,000/QALY gained. This finding is expected since genetic testing benefits are driven by the uptake of RRS and associated reduction in cancer risk and associated mortality.

The model was also sensitive to the unit cost of panel genetic test (Figure 4). For example, the use of an upper limit of £591 (base-case: £493) increased the ICER of genetic testing (versus no genetic testing). However, the ICER remained well below the lower NICE cost-effectiveness threshold of £20,000/QALY gained.

A more detailed two-way sensitivity analysis was conducted, where both the carrier risk and the unit cost of panel genetic test were varied simultaneously (Table 20). The results indicated that if the unit cost of panel genetic test was reduced to £300, it would be potentially cost-effective to offer genetic testing to people with lower carrier risks. For example, at a carrier risk of 1% and a unit cost of genetic test of £300, the ICER of genetic testing (versus no genetic testing) was below the lower NICE cost-effectiveness threshold of £20,000/QALY gained (£17,348). However, the probabilistic analysis indicated that the deterministic ICER is likely to be an underestimate of the true ICER due to parameter uncertainty. Therefore, there is less confidence in this result.

Generally, as the unit cost of panel genetic test increased, the cost-effectiveness of genetic testing (versus no genetic testing) declined. However, even at the unit cost of £1,000, it would be potentially cost-effective to offer genetic testing to people with a carrier risk of 4-5%, that is the ICER of genetic testing (versus no genetic testing) was below the lower NICE cost-effectiveness threshold of £20,000/QALY gained.

At a carrier risk of 3%, the unit cost of genetic testing would need to exceed £800 for genetic testing to be deemed unlikely to be cost-effective.

Table 20: Two-way sensitivity analysis of genetic testing cost-effectiveness (ICER): varying carrier risk and unit cost of panel testing simultaneously.

		The unit cost of panel genetic testing									
		£ 100	£ 200	£ 300	£ 400	£ 500	£ 600	£ 700	£ 800	£ 900	£ 1,000
Carrier risk	1%	£ 155	£ 8,752	£ 17,348	£ 25,944	£ 34,540	£ 43,136	£ 51,732	£ 60,328	£ 68,924	£ 77,520
	2%	Dominant	Dominant	£ 4,822	£ 10,237	£ 15,653	£ 21,068	£ 26,483	£ 31,899	£ 37,314	£ 42,730
	3%	Dominant	Dominant	Dominant	£ 3,015	£ 6,968	£ 10,921	£ 14,873	£ 18,826	£ 22,779	£ 26,732
	4%	Dominant	Dominant	Dominant	Dominant	£ 1,977	£ 5,089	£ 8,201	£ 11,313	£ 14,426	£ 17,538
	5%	Dominant	Dominant	Dominant	Dominant	Dominant	£ 1,303	£ 3,869	£ 6,435	£ 9,002	£ 11,568
	6%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	£ 830	£ 3,013	£ 5,197	£ 7,380
	7%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	£ 479	£ 2,379	£ 4,279
	8%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	£ 210	£ 1,891
	9%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	10%	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant

The model was also sensitive to the cost of end-of-life care, cost of RRBM, age of siblings and relative risk of breast cancer for RRBM in *BRCA2* (Figure 4). However, at a carrier risk of 3%, the ICERs in all these sensitivity analyses remained well below the lower NICE cost-effectiveness threshold of £20,000/QALY gained. The sensitivity analysis conducted using pre-COVID pandemic general population mortality data had a minimal impact on the ICER of genetic testing.

Results: scenario analyses

Index case's age

The results of the scenario analysis where the age of an index case was varied are summarised in Table 21.

Table 21: Two-way sensitivity analysis of genetic testing cost-effectiveness (ICER): varying carrier risk and the age of an index case simultaneously. Index population comprises females and males.

		The age of the index case (years)				
		30	40	50	60	70
Carrier risk	1%	£ 33,902	£ 45,174	£180,579	£1,788,299	Dominated
	2%	£ 15,251	£ 17,965	£ 79,684	£ 657,566	Dominated
	3%	£ 6,675	£ 5,559	£ 36,661	£ 363,266	Dominated
	4%	£ 1,746	Dominant	£ 12,816	£ 227,888	Dominated
	5%	Dominant	Dominant	Dominant	£ 150,072	Dominated
	6%	Dominant	Dominant	Dominant	£ 99,542	Dominated
	7%	Dominant	Dominant	Dominant	£ 64,087	Dominated
	8%	Dominant	Dominant	Dominant	£ 37,837	Dominated
	9%	Dominant	Dominant	Dominant	£ 17,619	Dominated
	10%	Dominant	Dominant	Dominant	£ 1,568	Dominated

The results demonstrated that the cost effectiveness of genetic testing was similar for an index case aged 40 compared to an index case aged 30 as per base-case analysis. However, for an index case aged 50, genetic testing is unlikely to be cost-effective for carrier risks below 4%. Similarly, for an index case aged 60, genetic testing does not appear to be cost-effective for carrier risks below 9%. For an index case aged 70 it would not be cost-effective to offer genetic testing at any carrier risk

ranging from 1% to 10%. The QALY gains and cost savings due to cancer reduction are not sufficient to outweigh the additional costs associated with genetic testing and risk-reducing surgery.

Index case's gender and age

A further sensitivity analysis was conducted to evaluate the cost-effectiveness of genetic testing, assuming that all index cases are females or males and varying age of index cases.

The sensitivity analysis showed that in the all-female index population, the carrier risk threshold at which genetic testing became cost-effective increased with the age of the index female case (Table 22).

In general, when the index case was a female aged 30, it was deemed cost-effective to offer genetic testing at a carrier risk of 1%. The ICER for genetic testing (versus no genetic testing) at this carrier risk was £17,155/QALY gained. However, there was less confidence in this result because deterministic ICERs tend to underestimate the true cost-effectiveness of genetic testing. Therefore, in females aged 30 it would be cost-effective to offer genetic testing at a carrier risk of approximately 2% (the ICER of £5,164/QALY).

Similar findings were observed for female index cases aged 40. For those aged 50 it would be cost-effective to offer genetic testing at a carrier risk of 3%. For female cases aged 60, the recommended carrier risk threshold for cost-effective genetic testing was 6% and above. Also, according to the sensitivity analysis, offering genetic testing to female index cases aged 70 would not be cost-effective at any carrier risk ranging from 1% to 10%.

As previously explained, the findings are influenced by the benefits to the index cases themselves. As the age of the index cases increase, both the benefits to the index cases and their first-degree relatives are reduced. For example, in the case of index cases aged 70, their parents would be around 100 years old in the base-case analysis, surpassing the age limit of 80 years for an individual to be considered in the model.

Consequently, their parents would not be eligible for genetic testing. Similarly, the benefits to siblings, who would be of similar age, would also be diminished. Thus, the primary advantages in these cases would be in identifying only eligible female children for testing. However, in these females aged 70 and over and their relatives, the benefits due to reduced cancer risk would not be sufficient to outweigh the additional costs associated with genetic testing and risk reducing surgery.

Table 22: Two-way sensitivity analysis of genetic testing cost-effectiveness: varying carrier risk and the age of an index case simultaneously. Index population comprises females only.

		The age of the index case (years)				
		30	40	50	60	70
Carrier risk	1%	£ 17,155	£ 18,866	£ 72,577	£ 369,798	Dominated
	2%	£ 5,164	£ 2,242	£ 22,767	£ 175,398	Dominated
	3%	Dominant	Dominant	£ 554	£ 98,148	Dominated
	4%	Dominant	Dominant	Dominant	£ 56,672	Dominated
	5%	Dominant	Dominant	Dominant	£ 30,791	Dominated
	6%	Dominant	Dominant	Dominant	£ 13,102	Dominated
	7%	Dominant	Dominant	Dominant	£ 247	Dominated
	8%	Dominant	Dominant	Dominant	Dominant	Dominated
	9%	Dominant	Dominant	Dominant	Dominant	Dominated
	10%	Dominant	Dominant	Dominant	Dominant	Dominated

The cost-effectiveness of genetic testing is driven by the benefits for index cases themselves. When considering the male index population, higher carrier risks were required to justify genetic testing (**Error! Not a valid bookmark self-reference.**). For example, in male index cases aged 30, genetic testing would be cost-effective at a carrier risk of approximately 6% and above.

For male index cases aged 40, a higher carrier risk of 9% would be necessary to justify genetic testing. Even though the deterministic ICER of genetic testing (versus no genetic testing) was £17,633/QALY gained at a carrier risk of 8%, the probabilistic analysis suggested that the deterministic ICER is likely to be an underestimate of the true ICER due to parameter uncertainty.

For male index cases aged 50 and older, it would not be cost-effective to offer genetic testing at any carrier risk ranging from 1% to 10%. This can be attributed to the lack of benefits to index case themselves and limited benefits to their first-degree relatives. For example, in the base-case analysis, if an index case was aged 50, mothers would be in their 80s surpassing the age limit of 80 years for an individual to be considered in the analysis. Therefore, the primary benefits would only apply to any female siblings in their 50s and children aged 20, with reduced benefits due to discounting.

Table 23: Two-way sensitivity analysis of genetic testing cost-effectiveness: varying carrier risk and the age of an index case simultaneously. Index population comprises males only.

		The age of the index case (years)				
		30	40	50	60	70
Carrier risk	1%	£ 141,102	£ 300,290	Dominated	Dominated	Dominated
	2%	£ 77,715	£ 159,581	Dominated	Dominated	Dominated
	3%	£ 49,752	£ 101,283	Dominated	Dominated	Dominated
	4%	£ 34,003	£ 69,395	Dominated	Dominated	Dominated
	5%	£ 23,900	£ 49,285	Dominated	Dominated	Dominated
	6%	£ 16,869	£ 35,445	Dominated	Dominated	Dominated
	7%	£ 11,693	£ 25,338	Dominated	Dominated	Dominated
	8%	£ 7,723	£ 17,633	Dominated	Dominated	Dominated
	9%	£ 4,583	£ 11,565	Dominated	Dominated	Dominated
	10%	£ 2,036	£ 6,662	Dominated	Dominated	Dominated

Alternative breast cancer utilities values

As explained in the methods section, average breast cancer annual utility values were estimated and considered relapse, recurrence and progression rates. This approach accounted for different breast cancer stages in individuals who undergo genetic testing and have intensified breast cancer surveillance in comparison to those who did not and have only age-related breast cancer screening.

Based on the stage specific published relapse, recurrence and progression rates, it was estimated that the annual average breast cancer utilities ranged from 0.70 in year 1 to 0.66 in year 10. However, the economic modelling for the NICE Familial Breast Cancer Guideline (CG164) used higher utility values that increased over time. For example, the utility of breast cancer in year 1 was 0.71 and increased to 0.77 in year 10. These are summarised in Table 24.

A sensitivity analysis was conducted using these alternative utility weights from the NICE Familial Breast Cancer Guideline (CG164) economic model. The ICERs for genetic testing (versus no genetic testing) were slightly less favourable but the conclusions remained unchanged. The ICERs using alternative utility estimates are summarised in Table 25.

Table 24: Average annual breast cancer utility values used in the model and explored in the sensitivity analyses.

	Average annual breast cancer utility values used in the base-case model		**Average annual breast cancer utility values that were used in NICE Familial Breast Cancer Guideline (CG164) economic model**
	Genetic testing	No genetic testing	Same utilities across all arms
Year 1	0.698	0.693	0.710
Year 2	0.696	0.691	0.720
Year 3	0.693	0.688	0.730
Year 4	0.689	0.684	0.740
Year 5	0.685	0.680	0.760
Year 6	0.680	0.676	0.770
Year 7	0.675	0.671	0.770
Year 8	0.670	0.666	0.770
Year 9	0.665	0.660	0.770
Year 10	0.659	0.655	0.770

Note: Annual breast cancer utility values in base-case model consider stage-specific relapse, recurrence and progression rates and account for differences in breast cancer staging at diagnosis due to intensified surveillance in genetic testing arm.

Table 25: The results of the sensitivity analysis which used alternative breast cancer utility values.

	ICERs of genetic testing (versus no genetic testing, cost per QALY gained) using:	
Carrier risk	Base-case breast cancer utility values	Utility values from the NICE Familial Breast Cancer Guideline (CG164) economic model
1%	£33,902	£40,022

	ICERs of genetic testing (versus no genetic testing, cost per QALY gained) using:	
2%	£15,251	£17,963
3%	£6,675	£7,853
4%	£1,746	£2,053
5%	Dominant	Dominant
6%	Dominant	Dominant
7%	Dominant	Dominant
8%	Dominant	Dominant
9%	Dominant	Dominant
10%	Dominant	Dominant

Abbreviations: ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year; NICE: National Institute for Health and Care Excellence

Optimistic scenarios

Optimistic scenarios were undertaken where key model inputs were set to favour the cost-effectiveness of genetic testing (Table 26).

In the optimistic scenario where the uptake of both genetic testing in FDRs and the uptake of RRS was set to 100% (scenario 1), the ICER of genetic testing (versus no genetic testing) at a carrier risk of 3% was reduced to £528/QALY gained and it may potentially be cost-effective to offer genetic testing to people at a lower carrier risk.

The ICER was even further improved where the index population comprised females only and the uptake of both genetic testing in FDRs and the uptake of RRS was set to 100% (scenario 2). The resulting ICERs under both scenarios are summarised in Table 26.

However, it must be noted that deterministic ICERs are likely to be underestimated, as shown by the probabilistic analyses. Also, this is not likely to be achievable in the real world. Nevertheless, these results indicate that under these 'ideal' scenarios, the carrier risk at which genetic testing could be offered could be reduced even further.

Table 26: Cost effectiveness of genetic testing in the optimistic scenarios (varying assumptions around an index population, genetic testing and risk reducing surgery uptake).

	ICERs of genetic testing (versus no genetic testing, cost per QALY gained) for:	
	Scenario 1	**Scenario 2**
Carrier risk for genetic testing eligibility	Index population includes males and females, genetic testing uptake in FDRs and RRS is 100%	Index population includes only females, genetic testing uptake in FDRs and RRS uptake is 100%
1%	£15,348	£7,392
2%	£5,224	Dominant
3%	£528	Dominant
4%	Dominant	Dominant
5%	Dominant	Dominant
6%	Dominant	Dominant

	ICERs of genetic testing (versus no genetic testing, cost per QALY gained) for:	
7%	Dominant	Dominant
8%	Dominant	Dominant
9%	Dominant	Dominant
10%	Dominant	Dominant

Abbreviations: FDR: First-degree relative; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year; RRS: Risk reducing surgery; NICE: National Institute for Health and Care Excellence

Discussion – conclusions, strengths and limitations

The economic analysis of the guideline evaluated the cost-effectiveness of providing genetic testing to adult individuals with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes at carrier risks ranging from 1% to 10%. When considering the impact on both the index cases and eligible first-degree relatives, offering genetic testing was found to be cost-effective when compared to no genetic testing, at carrier risks over 3%. The probability of genetic testing at this carrier risk being cost-effective was 0.72 at the NICE lower cost-effectiveness threshold of £20,000/QALY gained.

The carrier risk at which genetic testing was cost-effective was even lower (2%) when considering females only, as part of an index population. This is due to the substantial benefits in terms of cancer risk reduction and associated cost savings and QALY gains to female index cases.

Generally, the cost-effectiveness of panel genetic testing decreased as the index cases age increased. As the ages of index cases increased, the benefits to index cases themselves, their older mothers and female siblings of a similar age decreased. Therefore, in older index cases, the benefits were mainly derived from identifying younger children who might carry pathogenic variants in ovarian cancer predisposition genes. Consequently, for the benefits of panel genetic testing to outweigh the additional costs, the carrier risk in the older age groups needs to be higher.

A carrier risk of 2-3% would suggest that it is potentially cost-effective to provide genetic testing to second-degree relatives (SDRs). For example, if a mother has a carrier risk of 10% for *BRCA1*, her daughter's carrier risk would be 5%. This is because there is a 50% chance that the mother will pass on the mutation to each of her children. Similarly, the children of the daughter would have a 50% chance of inheriting the mutation, resulting in a carrier risk of 2.5% for SDRs. The economic analysis suggests that it would be potentially cost-effective to offer genetic testing at this carrier risk.

The results of the economic analysis results were overall robust in relation to different scenarios explored through deterministic sensitivity analyses. There was variation in the ICER of genetic testing when using, for example, different assumptions about the uptake rate of genetic testing in FDRs, the age at which RRS surgery was initiated and the relative risk of ovarian cancer mortality for RRBOS. However, in all these sensitivity analyses the conclusions were unchanged. Similarly, an analysis which used alternative annual utility values for people with breast cancer did not change the conclusions.

The economic analysis prioritised the modelling of *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, and *BRIP1* genes due to the large scope of the analysis. However, the panel genetic test includes many other genes that are associated with an increased risk of ovarian cancer, such as *PALB2* and Lynch syndrome genes such as MLH1 and MSH2. Consequently, in clinical practice, panel genetic testing may potentially identify more people with pathogenic variants associated with an increased risk of ovarian cancer for the same cost.

The economic analysis also considered the impact of pathogenic variants on ovarian and breast cancer risks only. However, genes included in the panel genetic test are also associated with an increased risk of several other types of cancer including pancreatic and peritoneal cancer.

The above suggests that the economic analysis may have underestimated the cost-effectiveness of genetic testing. However, considering the exhaustive list of genes and associated cancers was beyond the scope of this analysis.

To simplify the analysis, false positives and false negatives associated with the genetic test were not considered. The committee noted that genetic testing generally has high sensitivity and specificity and produces accurate results. This is supported by recent literature reporting favourable diagnostic accuracy associated with panel genetic tests (Chan 2020). Furthermore, according to the committee, false positive or false negative results are very rare in their clinical practice. Based on the above the exclusion of false positive or false negative genetic test outcomes was unlikely to have overestimated the cost effectiveness of genetic testing.

The analysis assumed that individuals with a true negative result would not incur any additional healthcare costs beyond the genetic test itself. However, the committee acknowledged that in certain cases, an individual with a negative gene test but a strong family history of ovarian cancer may still be offered RRBSO. Nevertheless, the uptake of RRS in such cases is expected to be low and it will depend on the individual's specific circumstances and risk factors. Therefore, the assumption that those with a true negative result would not incur any additional healthcare costs beyond the genetic test itself was unlikely to have overestimated the cost-effectiveness of genetic testing. This is supported by evidence that even in people with a confirmed true positive result, RRS uptake is highly variable and can be as low as 30%. Overall, while RRS may be considered in certain cases with a true negative genetic test result, it is not expected to happen often in clinical practice.

Evidence regarding the impact of pathogenic variants on ovarian cancer mortality is uncertain. A recent study (Candido-dos-Reis 2015) examined the effect of germline mutations in *BRCA* on mortality in ovarian cancer patients for up to 10 years after diagnosis. It concluded that *BRCA* mutations were associated with better short-term survival but this advantage decreased over time and was eventually reversed in *BRCA1* carriers.

The study also reported a 10-year overall survival rate of 25% for *BRCA1* carriers, 35% for *BRCA2* carriers, which is similar to the rate in the general population of 35% (Cancer Research 2020). No pathogenic variant-specific data were available for *RAD51C*, *RAD51D* and *BRIP1* genes. Therefore, general population mortality data were used for the analysis. Despite this limitation, the sensitivity analysis showed that varying the rate by 20% in either direction had little effect on the ICERs and did not change the conclusions.

The committee also noted that the relative risk estimate of ovarian cancer for *BRIP1* from a case-control study (Ramus 2015) of 3.41 (95% CI = 2.12 to 5.54) may be an underestimate. The committee explained that this study used estimates from The UK Familial Ovarian Cancer Screening Study (UKFOCCS) for controls with a segregation analysis.

The committee explained that segregation analysis has many limitations; for example it requires accurate data on the number of affected and unaffected individuals in a family, their relationships and their genotypes. However, such data is often limited and can lead to biased estimates.

It was also explained that people entering the UKFOCCS study had to be unaffected with ovarian cancer at the time of recruitment (Jacobs 2015). This may have created bias against ovarian cancer because ovarian cancer is often diagnosed at later stages. Therefore, many individuals with a family history of ovarian cancer may have already been diagnosed and therefore would not be ineligible to participate in the study. This could lead to an underestimation of the true risk associated with a family history of ovarian cancer.

The committee explained that there is evidence that this study produced a significant underestimation of cancer risk associated with *PALB2* and a similar underestimation may also apply for *BRIP1.* For example, they noted that there is emerging unpublished evidence suggesting that *BRIP1* could increase ovarian cancer risk by up to eight times. The sensitivity analysis using this higher estimate of relative risk showed that at a carrier risk of 3%, the ICER of genetic testing (versus no genetic testing) decreased from £6,675/QALY to £6,111/QALY.

Additionally, when estimating costs and utilities for individuals with pathogenic variants who do not undergo genetic testing (and are not under breast cancer surveillance), breast cancer staging data from the general population was used. It is possible that the staging of breast cancer at diagnosis may differ between the general population and individuals with pathogenic variants, such as *BRCA*.

Evidence suggests that triple-negative cancers disproportionately affect people with pathogenic variants, such as, *BRCA* and *PALB2* (Howard 2021). This indicates that breast cancer in mutation carriers may have a more aggressive biological phenotype, leading to a higher grade at diagnosis. However, the deterministic sensitivity analysis indicated that the results were robust to changes in this model input. For example, assuming that individuals who are carriers and have no genetic testing have more advanced stage breast cancers only marginally improved the cost-effectiveness of genetic testing.

To simplify the modelling, it was assumed that all individuals who undergo pre-menopausal RRBSO would receive HRT following surgery. However, there is a possibility that some people will need more expensive bisphosphonates. For example, those who have had breast cancer and thus cannot have HRT after RRBSO. However, the sensitivity analysis indicated that the findings were robust to this model input. For example, using an extreme cost of HRT of £1,000 per annum did not change the conclusions and it remained cost-effective to offer genetic testing at a carrier risk of 3%.

Overall offering genetic testing to people at a carrier risk of 3% appeared to be cost-effective and had a relatively high probability of being cost effective option at the NICE lower cost effectiveness threshold of £20,000/QALY gained. The threshold for

offering genetic testing could be lowered when considering only females or younger age groups as part of the index population.

The results of the analysis were characterised by considerable uncertainty, as reflected by probabilistic results. However, deterministic sensitivity analysis suggested that the results were overall robust under the different scenarios explored.

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I.1 Deterministic sensitivity analyses (full results)

Table 27: Deterministic sensitivity analyses including base-case values, ranges and associated incremental cost-effectiveness ratios for people with a 3% carrier risk of an ovarian cancer-associated pathogenic variant.

Parameter input	Base-case value	Range tested	ICER of genetic testing (vs no genetic testing) using upper and lower value tested
Age of an index case (years)	30	30 to 70	£6,675; -£179,184
Discount rate for costs	0.035	0 to 0.035	-£76,504; £6,675
Probability index is female	0.560	0 to 1	£49,752; -£387
Age at RRBM in BRCA (years)	31	31 to 50	£6,675; £51,406
Carrier risk in an index case	0.030	0.01 to 0.1	£33,902; -£8,485
GT uptake FDRs	0.834	0.3 to 1	£15,747; £4,769
Cost of end of life care (OC)	£19,224	£8,203 to £23,069	£13,324; £4,355
Cost panel GT	£493	£394 to £591	£2,781; £10,569
RR of OC mortality for RRBSO	0.360	0.21 to 0.6	£3,710; £11,072
Cost of end of life care (BC)	£8,203	£6,562 to £9,844	£9,525; £3,824
Cost of RRBM	£11,768	£9,414 to £14,122	£4,031; £9,318
RR of BC for RRBM in BRCA2	0.09	0.02 to 0.38	£5,804; £10,736
Discount rate for QALYs	0.035	0 to 0.04	£1,913; £6,675
Cost of BC diagnosis and initial treatment, GP	£20,025	£16,020 to £24,030	£8,857; £4,492
Utility of remittent BC	0.810	0.65 to 0.97g	£5,181; £9,380
Age of sibling relative to index	0	-5 to 5	£7,466; £11,495
Cost HRT (annual)	£88	£70 to £1,000	£6,604; £10,344
Probability female	0.56	0.45 to 0.67	£8,683; £4,994
Utility of advanced BC	0.65	0.52 to 0.78	£5,314; £8,973
Age of mother relative to index	30	25 to 35	£5,222; £8,603
BRCA2 - BC incidence: aged 31-40	0.01	0.01 to 0.02	£8,032; £4,960
RR of BC for RRBM in BRCA1	0.09	0.02 to 0.38	£6,101; £9,124
Utility of early BC	0.71	0.57 to 0.85	£5,592; £8,278
BRCA2 - OC incidence: aged 61-70	0.0103	0.0055 to 0.0191	£7,619; £5,070
Number of pre-counselling sessions	1	1 to 3	£6,675; £9,128
BRCA2 - BC incidence: aged 41-50	0.0275	0.0216 to 0.0351	£7,811; £5,424
BRCA2 - OC incidence: aged 51-60	0.0065	0.0037 to 0.0115	£7,409; £5,422
Uptake of RRBM in BRCA1 and BRCA2: aged <36	0.863	0.6907 to 1	£7,877; £5,947
Number of FDR siblings	0.910	0.73 to 1.09	£7,673; £5,761
VUS re-classified as positive	0.087	0.07 to 0.1	£7,652; £5,769

Parameter input	Base-case value	Range tested	ICER of genetic testing (vs no genetic testing) using upper and lower value tested
Cost of BC diagnosis and initial treatment	£18,378	£14,702 to £22,053	£5,838; £7,512
BRCA2 - OC incidence: aged 31-40	0.0003	0.0001 to 0.0024	£6,818; £5,212
BRCA1 - OC incidence: aged 61-70	0.0294	0.0197 to 0.0438	£7,357; £5,766
BRCA1 - BC incidence: aged 31-40	0.0235	0.0191 to 0.0289	£7,369; £5,912
BRCA2 - BC incidence: aged 61-70	0.0229	0.0136 to 0.0387	£7,263; £5,808
Panel GT VUS rate	0.08	0.07 to 0.11	£7,422; £5,982
Utility decrement for GT	0.05	0 to 0.06	£5,528; £6,964
Number of FDR children	1.91	1.53 to 2.29	£7,377; £6,018
BRCA1 - OC incidence: aged 41-50	0.007	0.0047 to 0.0104	£7,231; £5,880
BRCA2 - BC incidence: aged 51-60	0.031	0.023 to 0.041	£7,292; £5,944
Age of children relative to index	-30.000	-35 to -25	£7,301; £5,984
Annual BC mortality in general population	0.028	0.026 to 0.029	£7,338; £6,086
Cost of BC follow-up, GP (annual)	£774	£619 to £929	£7,279; £6,070
BRCA1 - OC incidence: aged 51-60	0.0138	0.0092 to 0.0205	£7,175; £5,984
Cost panel GT plus VUS	£750	£600 to £900	£6,103; £7,246
Annual OC mortality in general population	0.104	0.1 to 0.107	£7,180; £6,206
BRCA1 - BC incidence: aged 41-50	0.028	0.023 to 0.035	£7,051; £6,251
RR of OC for RRBSO in BRCA1	0.100	0.34 to 0.03	£7,269; £6,495
BRCA1 - OC incidence: aged 31-40	0.002	0.001 to 0.0034	£6,926; £6,182
RR of OC for BRIP1	3.41	2.12 to 8	£6,838; £6,111
Utility of advanced OC	0.55	0.44 to 0.66	£6,358; £7,024
Cost of RRBSO procedure	£4,254	£3,404 to £5,105	£6,350; £7,000
Uptake of RRBSO in BRCA1 and BRCA2: aged <36	0.23	0.19 to 0.28	£6,979; £6,375
RR of BC mortality for RRBM in BRCA1	0.06	0.01 to 0.46	£6,612; £7,177
Annual OC mortality in BRCA1, BRCA2, RAD51C, RAD51D, BRIP1	0.104	0.1 to 0.11	£6,391; £6,947
Cost counselling session	£23.67	£18.93 to £28.4	£6,401; £6,948
Utility of OC in year 6 onwards	0.72	0.58 to 0.86	£6,950; £6,420
Cost of BC follow-up	£757	£606 to £909	£6,410; £6,939

Parameter input	Base-case value	Range tested	ICER of genetic testing (vs no genetic testing) using upper and lower value tested
BRCA2 - BC incidence: aged 71-80	0.0219	0.0098 to 0.0486	£6,851; £6,344
BRCA2 - OC incidence: aged 71-80	0.0023	0.0003 to 0.0163	£6,735; £6,273
RR of OC for RRBSO in BRCA2	0.10	0.34 to 0.03	£7,027; £6,571
BRCA1 - BC incidence: aged 61-70	0.025	0.016 to 0.039	£6,833; £6,458
BRCA1 - BC incidence: aged 51-60	0.026	0.019 to 0.034	£6,842; £6,473
Annual BC mortality in BRCA2	0.005	0.001 to 0.034	£6,633; £6,971
Cost GT single pathogenic variant	£124.1	£99.3 to £149.0	£6,521; £6,829
Number of post-counselling sessions	1	1 to 3	£6,675; £6,954
RAD51C - OC incidence: aged 61-70	0.007	0.004 to 0.011	£6,784; £6,533
Utility of end-stage cancer	0.160	0.128 to 0.192	£6,552; £6,802
Age at RRBSO in RAD51C, RAD51D, BRIP1 (years)	45	45 to 60	£6,675; £6,890
Cost of OC diagnosis and initial treatment	£25,554	£20,443 to £30,665	£6,764; £6,586
BRCA1 - OC incidence: aged 71-80	0.006	0.001 to 0.023	£6,711; £6,538
Annual BC mortality in BRCA1	0.009	0.003 to 0.024	£6,632; £6,792
Utility of recurrent BC	0.45	0.36 to 0.54	£6,597; £6,754
Uptake of RRBSO in BRCA1 and BRCA2: aged >45	0.50	0.40 to 0.60	£6,751; £6,599
Cost of OC follow-up in years 1 to 2 (annual)	£18,568	£14,855 to £22,282	£6,750; £6,599
Progression of early and locally advanced BC to advanced stage	0.35	0.28 to 0.42	£6,723; £6,624
BRCA1 - BC incidence: aged 71-80	0.017	0.006 to 0.044	£6,704; £6,608
Utility decrement for RRBM	0.030	0.02 to 0.04	£6,630; £6,720
Cost of OC follow-up in years 3 to 10 (annual)	£1,560	£1,248 to £1,872	£6,630; £6,719
Utility decrement for RRBSO	0.080	0.06 to 0.1	£6,634; £6,716
Osteo-protection costs (RRBSO)	£511	£409 to £613	£6,636; £6,714
RAD51C - OC incidence: aged 51-60	0.002	0.001 to 0.003	£6,714; £6,636
RAD51C - OC incidence: aged 71-80	0.003	0.001 to 0.008	£6,697; £6,620
Recurrence rate of advanced BC	0.66	0.53 to 0.79	£6,706; £6,635
RR of OC for RRBSO in BRIP1	0.10	0.34 to 0.03	£6,722; £6,661

Parameter input	Base-case value	Range tested	ICER of genetic testing (vs no genetic testing) using upper and lower value tested
RR of OC for RRBSO in RAD51C	0.10	0.34 to 0.03	£6,719; £6,662
RR of OC for RRBSO in RAD51D	0.10	0.34 to 0.03	£6,717; £6,662
Age of father relative to index	32	27 to 37	£6,689; £6,653
Probability of stage 3 BC, GP	0.08	0.06 to 0.09	£6,691; £6,659
Utility of OC in year 5	0.70	0.56 to 0.84	£6,691; £6,659
RAD51C - OC incidence: aged 41-50	0.0003	0.0002 to 0.0008	£6,680; £6,650
Uptake of RRBSO in BRIP1: aged >45	0.50	0.40 to 0.60	£6,661; £6,689
Probability of stage 1 BC, GP	0.38	0.31 to 0.46	£6,660; £6,687
Probability of stage 2 BC, GP	0.34	0.27 to 0.41	£6,662; £6,686
Utility of OC in year 1	0.50	0.40 to 0.60	£6,663; £6,686
Utility of OC in year 4	0.69	0.55 to 0.83	£6,686; £6,663
Uptake of RRBSO in RAD51C: aged 36-45	0.76	0.61 to 0.91	£6,686; £6,663
Uptake of RRBSO in RAD51D: aged 36-45	0.76	0.61 to 0.91	£6,686; £6,664
Annual BC mortality in RAD51C	0.017	0.013 to 0.021	£6,664; £6,685
Uptake of RRBM in BRCA1 and BRCA2: aged >45	0.199	0.160 to 0.239	£6,685; £6,665
Annual BC mortality in RAD51D	0.017	0.014 to 0.021	£6,665; £6,684
Probability of stage 4 BC, GP	0.043	0.035 to 0.052	£6,684; £6,666
Recurrence rate of early and locally advanced BC	0.125	0.1 to 0.15	£6,683; £6,666
Relapse rate for DCIS BC to invasive stage	0.125	0.1 to 0.15	£6,682; £6,668
Individual pathogen GT VUS rate	0.018	0.01 to 0.02	£6,680; £6,669
Utility of OC in year 3	0.670	0.54 to 0.8	£6,680; £6,669
Cost GT single pathogenic variant plus VUS	£189	£151 to £227	£6,670; £6,679
RAD51C - BC incidence: aged 41-50	0.002	0.00001 to 0.0002	£6,678; £6,671
RAD51C - OC incidence: aged 31-40	0.0001	0.00001 to 0.0002	£6,676; £6,670
Utility of OC in year 2	0.65	0.52 to 0.78	£6,672; £6,677
RAD51C - BC incidence: aged 61-70	0.006	0.004 to 0.009	£6,676; £6,672
RAD51D - BC incidence: aged 61-70	0.006	0.004 to 0.009	£6,676; £6,672
Probability of stage 1 BC, under surveillance	0.54	0.43 to 0.65	£6,677; £6,673

Parameter input	Base-case value	Range tested	ICER of genetic testing (vs no genetic testing) using upper and lower value tested
Probability of DCIS BC, under surveillance	0.20	0.16 to 0.24	£6,673; £6,677
RAD51D - BC incidence: aged 41-50	0.0020	0.001 to 0.002	£6,678; £6,675
RAD51D - BC incidence: aged 51-60	0.0040	0.003 to 0.006	£6,676; £6,673
RAD51C - BC incidence: aged 51-60	0.0050	0.003 to 0.006	£6,676; £6,674
RAD51D - BC incidence: aged 31-40	0.0003	0.0002 to 0.0005	£6,675; £6,673
RAD51C - BC incidence: aged 31-40	0.0004	0.0002 to 0.0005	£6,676; £6,674
Probability of stage 3 plus BC, under surveillance	0.010	0.008 to 0.012	£6,674; £6,676
Probability of stage 2 BC, under surveillance	0.246	0.197 to 0.295	£6,676; £6,674
Annual BC mortality in BRIP1	0.028	0.026 to 0.029	£6,674; £6,675
Uptake of RRBSO in BRIP1: aged 36-45	0.76	0.61 to 0.91	£6,675; £6,674
Relapse rate for DCIS BC to non-invasive stage	0.13	0.10 to 0.15	£6,674; £6,675
RAD51C - BC incidence: aged 71-80	0.007	0.005 to 0.01	£6,675; £6,674
RAD51D - BC incidence: aged 71-80	0.007	0.004 to 0.01	£6,675; £6,674
Uptake of RRBSO in RAD51C: aged >45	0.5	0.4 to 0.6	£6,675; £6,674
Uptake of RRBSO in RAD51D: aged >45	0.5	0.4 to 0.6	£6,675; £6,675
Probability of DCIS BC, GP	0.15	0.12 to 0.18	£6,675; £6,675
BRCA2 - OC incidence: aged 41-50	0.000	0.000 to 0.000	£6,675; £6,675
RAD51C - BC incidence: aged 80+	0.008	0.005 to 0.011	£6,675; £6,675
RAD51C - OC incidence: aged 80+	0.001	0.0002 to 0.008	£6,675; £6,675
RAD51D - BC incidence: aged 80+	0.007	0.005 to 0.011	£6,675; £6,675
RAD51D - OC incidence: aged 31-40	<0.001	<0.001 to 0.0001	£6,675; £6,675
RAD51D - OC incidence: aged 41-50	<0.001	0.0001 to 0.0007	£6,675; £6,675
RAD51D - OC incidence: aged 51-60	0.002	0.001 to 0.003	£6,675; £6,675
RAD51D - OC incidence: aged 61-70	0.006	0.004 to 0.008	£6,675; £6,675

Parameter input	Base-case value	Range tested	ICER of genetic testing (vs no genetic testing) using upper and lower value tested
RAD51D - OC incidence: aged 71-80	0.005	0.002 to 0.009	£6,675; £6,675
RAD51D - OC incidence: aged 80+	0.003	0.0009 to 0.012	£6,675; £6,675
Uptake of RRBSO in BRIP1: aged <36	0.232	0.185 to 0.278	£6,675; £6,675
Uptake of RRBSO in RAD51D: aged <36	0.232	0.185 to 0.278	£6,675; £6,675
Uptake of RRBSO in RAD51C: aged <36	0.232	0.185 to 0.278	£6,675; £6,675
Uptake of RRBSO in BRCA1 and BRCA2: aged 36-45	0.760	0.608 to 0.913	£6,675; £6,675

Abbreviations: BC: Breast cancer; DCIS: Ductal carcinoma in situ; FDR: First-degree relative; GP: General population; GT: Genetic testing; HRT: Hormone replacement therapy; ICER: Incremental cost-effectiveness ratio; OC: Ovarian cancer; QALYs: Quality-adjusted life years; RR: Relative risk; RRBM: Risk-reducing bilateral mastectomy; RRBSO: Risk-reducing bilateral salpingo-oophorectomy; VUS: Variant of unknown significance

I.2 Pathogenic variant carrier risks in first-degree relatives

Table 28: Pathogenic variant carrier risks in first-degree relatives conditional on an index case having a pathogenic variant (estimates derived from CanRisk Tool, a web interface to BOADICEA).

		Carrier risk in a first-degree relative of a pathogenic variant identified in a 30-year-old female index case					Carrier risk in a first-degree relative of a pathogenic variant identified in a 30-year-old male index case				
FDR	**FDR age at model entry**	**BRCA1**	**BRCA2**	**RAD51C**	**RAD51D**	**BRIP1**	**BRCA1**	**BRCA2**	**RAD51C**	**RAD51D**	**BRIP1**
Mother	**60**	0.264	0.359	0.476	0.479	0.495	0.261	0.358	0.476	0.479	0.495
Father	**62**	0.494	0.458	0.499	0.499	0.499	0.494	0.458	0.499	0.499	0.499
Sibling (female)	**30**	0.493	0.497	0.498	0.499	0.498	0.493	0.497	0.498	0.499	0.498
Sibling (male)	**30**	0.501	0.501	0.498	0.499	0.499	0.501	0.501	0.498	0.499	0.499
Children (female)	**0**	0.501	0.500	0.498	0.499	0.498	0.501	0.500	0.498	0.499	0.498
Children (male)	**0**	0.501	0.500	0.498	0.499	0.499	0.501	0.501	0.498	0.499	0.499

Abbreviations: FDR: First-degree relative

** For example, the cell highlighted in yellow indicates the carrier risk of the BRCA1 variant in a 60-year-old mother, given that her 30-year-old daughter (the index case) carries a BRCA1 pathogenic variant*

Appendix J Excluded studies

Excluded studies for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

Excluded effectiveness studies

One literature search was performed for the review questions F and G.

Table 29: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Barbalho, D., Sandoval, R., Santos, E. et al. (2022) Novel Insights From the Germline Landscape of Breast Cancer in Brazil. Frontiers in Oncology 11: 743231	- Outcomes in study do not match those specified in this review protocol
Bellcross, C.A., Lemke, A.A., Pape, L.S. et al. (2009) Evaluation of a breast/ovarian cancer genetics referral screening tool in a mammography population. Genetics in Medicine 11(11): 783-789	- Comparator in study does not match that specified in this review protocol
Berry, Donald A, Iversen, Edwin S Jr, Gudbjartsson, Daniel F et al. (2002) BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 20(11): 2701-12	- Outcomes in study do not match those specified in this review protocol
Best, A.F., Tucker, M.A., Frone, M.N. et al. (2019) A pragmatic testing-eligibility framework for population mutation screening: The example of BRCA1/2. Cancer Epidemiology Biomarkers and Prevention 28(2): 293-302	- Outcomes in study do not match those specified in this review protocol
Crawford, B., Adams, S.B., Sittler, T. et al. (2017) Multi-gene panel testing for hereditary cancer predisposition in unsolved high-risk breast and ovarian cancer patients. Breast Cancer Research and Treatment 163(2): 383-390	- Outcomes in study do not match those specified in this review protocol
Hoskins, Paul, Eccleston, Anthony, Hurry, Manjusha et al. (2019) Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. A Canadian model. Gynecologic oncology 153(1): 87-91	- Outcomes in study do not match those specified in this review protocol
Katki, Hormuzd A (2019) Quantifying risk stratification provided by diagnostic tests and risk predictions: Comparison to AUC and decision curve analysis. Statistics in medicine 38(16): 2943-2955	- Outcomes in study do not match those specified in this review protocol
Loader, S; Levenkron, J C; Rowley, P T (1998) Genetic testing for breast-ovarian cancer susceptibility: a regional trial. Genetic testing 2(4): 305-13	- Comparator in study does not match that specified in this review protocol
Manchanda, Ranjit, Patel, Shreeya, Antoniou, Antonis C et al. (2017) Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. American journal of obstetrics and gynecology 217(5): 578e1-578e12	- Study design does not match that in this review protocol
Mariani, C., Carnevali, I., Lapi, F. et al. (2020) STELO: A new tool for family physicians for the correct identification of inherited cancer syndromes. Family Practice 37(1): 43-48	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
Ozanne, Elissa M, Howe, Rebecca, Mallinson, David et al. (2019) Evaluation of National Comprehensive Cancer Network guideline-based Tool for Risk Assessment for breast and ovarian Cancer (N-TRAC): A patient-reported survey for genetic high-risk assessment for breast and ovarian cancers in women. Journal of genetic counseling 28(3): 507-515	- Comparator in study does not match that specified in this review protocol
Rao, Smita K, Thomas, Kimberly A, Singh, Rajbir et al. (2021) Increased ease of access to genetic counseling for low-income women with breast cancer using a point of care screening tool. Journal of community genetics 12(1): 129-136	- Comparator in study does not match that specified in this review protocol
Sandoval, R.L., Leite, A.C.R., Barbalho, D.M. et al. (2021) Germline molecular data in hereditary breast cancer in Brazil: Lessons from a large single-center analysis. PLoS ONE 16(2february2021): e0247363	- Comparator in study does not match that specified in this review protocol
Smallwood, K.G., Crockett, S., Huang, V. et al. (2022) Changing patterns of referral into a family history clinic and detection of ovarian cancer: a retrospective 10-year review. Journal of Obstetrics and Gynaecology	- Comparator in study does not match that specified in this review protocol

Excluded economic studies

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

Appendix K Research recommendations – full details

Research recommendations for review question: At what carrier probability should people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes be offered genetic testing?

No research recommendations were made for this review question.