National Institute for Health and Care Excellence

Draft for consultation

Ovarian cancer: identifying and managing familial and genetic risk

[G] Carrier probability - family history of a syndrome

NICE guideline number tbc

No recommendations were made based on this evidence review

September 2023

Draft for consultation

These evidence reviews were developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

Contents

Carrier probability - family history of a syndrome

Review question

On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

Introduction

A syndrome is a combination of symptoms, seen consistently, because of a common cause. Certain inheritable changes in an individual's DNA leads not only to an increased risk of ovarian cancer but also a constellation of symptoms that suggest they could have a certain mutation. An example of this is Peutz-Jeghers syndrome, whereby individuals have an inheritable mutation in the *STK11* gene. This increases their lifetime risk of ovarian cancer but also gives them characteristic polyps in their small bowel along with distinctive skin pigmentation in the mouth, lips, fingers, and toes. As this is a familial condition, they also often have family history of cancer along with relatives with the syndromic characteristics. In Lynch syndrome, the syndrome is defined by a pattern of cancers that is seen by those affected by the condition. That is, they do not have physical symptoms other than developing certain cancers.

As syndromes are by their very nature a consistent pattern of symptoms be they physical (such as polyps) or patterns of cancer, clinicians can often recognise them and order tests to diagnose them. However, even syndromes are not always textbook in their presentation. For example, two people with Lynch syndrome may have two very different patterns of cancer in their families. Not everyone with Peutz-Jeghers syndrome has the same number of polyps and not everyone with those polyps has a mutation in *STK11*. Therefore, once more, it is not always clear out of those with features suggestive of a syndrome associated with increased risk of familial ovarian cancer, who should be offered testing for an underlying inheritable cause.

Therefore, when to offer someone who has symptoms suggestive of a syndrome relevant to inheritable ovarian cancer, genetic testing is not clear. The review will explore the various carrier probabilities by which someone should be offered testing for a clinically defined syndrome associated with an increased risk of ovarian cancer.

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 personal or family history of a clinically defined syndrome associated with an increased risk of ovarian cancer following an assessment of their carrier probability for pathogenic variants associated with familial ovarian cancer & assessment of clinical criteria

Intervention	• Germline pathogenic variant analysis only if carrier probability exceeds a threshold value.
	• Germline pathogenic variant analysis if clinical criteria for the clinically defined syndrome are met:
	  ○ Peutz-Jeghers syndrome
	  ○ MUTYH-associated polyposis
	  ○ Ataxia Telangiectasia
	  ○ Fanconi Anemia
	• Germline pathogenic variant analysis if high risk clinical criteria are met:
	  ○ BRCA/Hereditary Breast and Ovarian Syndrome
	  ○ Lynch/Hereditary Non-polyposis Colon Cancer

Comparator	Each other

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

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

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

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

Economic model

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

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

Based on the lack of evidence and that clinical criteria for the syndromes of interest change constantly, the committee agreed not to make recommendations for genetic testing for people with, for example, Peutz-Jeghers syndrome. They discussed that there are other guidelines covering clinical diagnoses of those with suspected syndromes such as Peutz-

Jeghers or Lynch syndrome. For example: Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG) and they thought that in practice such people would be picked up. They also agreed that this review question is partially covered by the review question F in this guideline.

Based on the consensus the committee also decided against a research recommendation because these syndromes are very rare so research would be unlikely or unfeasible to be carried out.

Cost effectiveness and resource use

No existing economic studies were identified that were applicable to this review question. The committee did not make any recommendations in this area and therefore there are no implications in terms of resource use on NHS services.

Recommendations supported by this evidence review

No recommendations were made from this evidence review.

References

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

Appendices

Appendix A Review protocol

Review protocol for review question: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

Table 2: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022351091
1.	Review title	Carrier probability or criteria at which genetic testing should be offered to people with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer
2.	Review question	On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?
3.	Objective	To identify at what carrier probability threshold or criteria people with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer should be offered genetic testing
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE & MEDLINE In-Process • Epistemonikos • International Health Technology Assessment (INAHTA) database Searches will be restricted by: • English language studies

ID	Field	Content
		• 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 personal or family history of a clinically defined syndrome associated with an increased risk of ovarian cancer following an assessment of their carrier probability for pathogenic variants associated with familial ovarian cancer & assessment of clinical criteria. Exclusion: People with ovarian cancer (covered by review question I)
7.	Intervention	Germline pathogenic variant analysis only if carrier probability exceeds a threshold value. Germline pathogenic variant analysis if clinical criteria for the clinically defined syndrome are met: • Peutz-Jeghers syndrome • MUTYH-associated polyposis • Ataxia Telangiectasia • Fanconi Anemia Germline pathogenic variant analysis if high risk clinical criteria are met: • BRCA/Hereditary Breast and Ovarian Syndrome • Lynch/Hereditary Non-polyposis Colon Cancer
8.	Comparator	Each other
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	**Inclusion**:

ID	Field	Content
	criteria	• Full text papers • Observational studies should control for baseline differences in patient groups **Exclusion**: • Conference abstracts • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/ study quality • Non-English language articles
11.	Context	Review question from scope has changed because Lynch syndrome has molecular genetic diagnosis – when a person is diagnosed there will be cascade testing for their relatives. This question is more relevant for syndromes with a clinical diagnosis like Peutz- Jeghers.

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

ID	Field	Content
		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.

ID	Field	Content
		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

<table>
<tr><th>ID</th><th>Field</th><th>Content</th></tr>
<tr><td></td><td></td><td>assume the interventions will have similar effects in that group compared with others.</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td>☒ Intervention
☐ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☐ Other (please specify)</td></tr>
<tr><td>19.</td><td>Language</td><td>English</td></tr>
<tr><td>20.</td><td>Country</td><td>England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td>October 2022</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td>13 March 2024</td></tr>
<tr><td>23.</td><td>Stage of review at time of this submission</td><td>
<table>
<tr><th>Review stage</th><th>Started</th><th>Completed</th></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
</table>
</td></tr>
</table>

ID	Field	Content		
		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		

ID	Field	Content
		guideline webpage].
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=351091
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Genetic testing, familiar ovarian cancer
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	None
36.	Details of final publication	https://www.nice.org.uk

1 *MID: minimally important difference; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; ROBs: risk of bias*
2

Appendix B Literature search strategies

Literature search strategies for review question: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) 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.

#	Searches
33	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
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

1 Database: Ovid Embase

2 Date of last search: 25/01/2023

#	Searches
1	exp ovary tumor/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.

#	Searches
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/
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/

#	Searches
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.
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/

#	Searches
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

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

3 **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
#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

#	Searches
#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
#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

#	Searches
#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

1 Database: Epistemonikos

2 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

3 Database: INAHTA International HTA Database

4 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]
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]

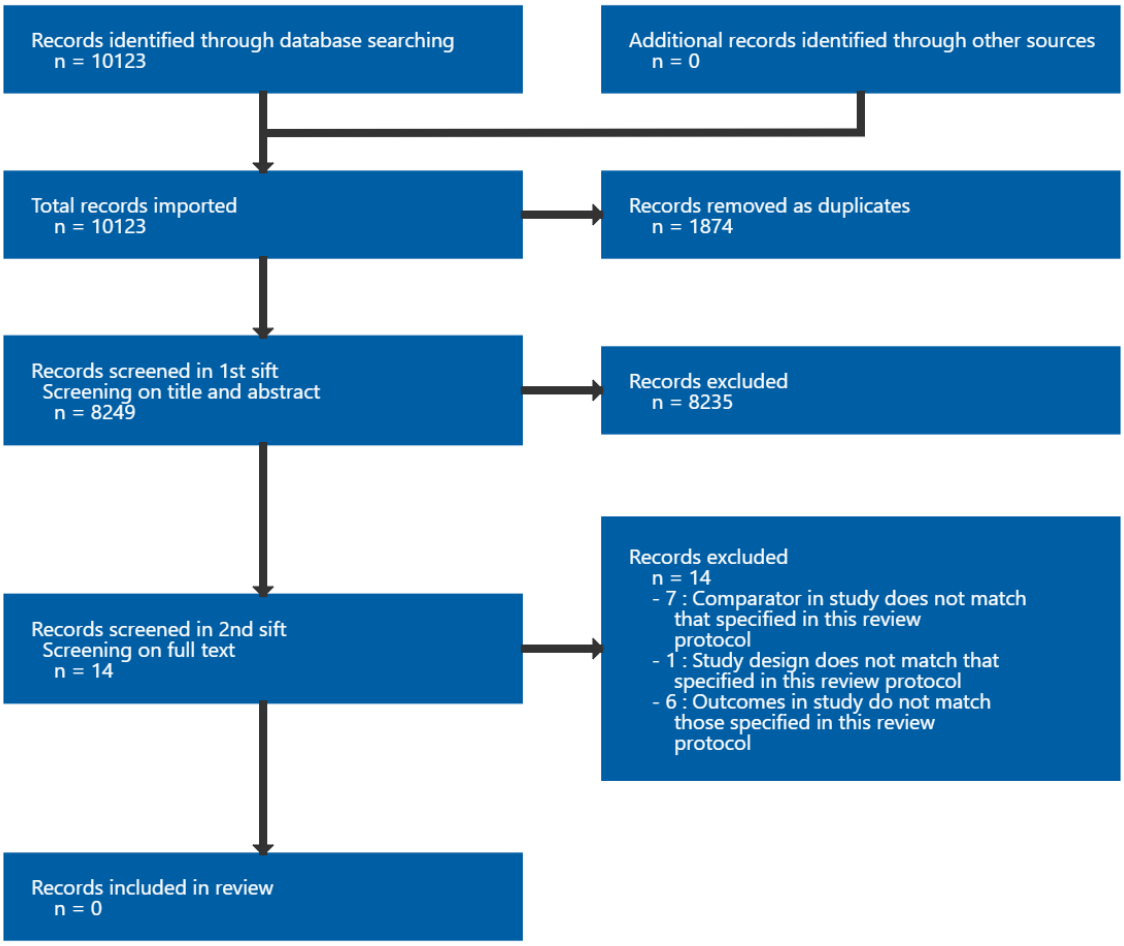
#	Searches
10	((peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1))[Title] OR ((peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1))[abs]
11	(((hereditary or inherit* or familial or adenomato* or attenuated) AND polyp* AND (coli or colon or colorectal or bowel or rectum or intestin* 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]
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: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) 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: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

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

Appendix E Forest plots

Forest plots for review question: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

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

Appendix F GRADE tables

GRADE tables for review question: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

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

Appendix G Economic evidence study selection

Study selection for: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) 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: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

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

Appendix I Economic model

Economic model for review question: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

Excluded effectiveness studies

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

Table 3: 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	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
susceptibility: a regional trial. Genetic testing 2(4): 305-13	
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 specified 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
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

No economic evidence was identified for this review. See supplementary material 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: On the basis of what carrier probability or criteria should a person with a personal or family history suggestive of a clinically defined syndrome associated with an increased risk of ovarian cancer (for example Peutz-Jeghers syndrome) be offered genetic testing?

No research recommendations were made for this review question.