National Institute for Health and Care Excellence

Final

Ovarian cancer: identifying and managing familial and genetic risk

[J] Which genes to include in gene panel testing

NICE guideline NG241

Evidence reviews underpinning recommendations 1.5.1 and 1.5.2 in the NICE guideline

March 2024

Final

These evidence reviews were developed by NICE

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Review question

Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

Introduction

Familial ovarian cancer normally arises due to an inherited pathogenic variant in a specific gene. An array of genes have been identified that when mutated lead to familial ovarian cancer. The number of genes continues to grow as technology and methods develop. Assigning the degree of ovarian cancer risk to these genes is complicated and not always certain. In addition, different pathogenic variants in the same gene confer different degrees of risk. Therefore, clinicians need to decide which genes to test and, in some cases, which part of the gene to test. Genes are tested together, on a panel, which can be bespoke or generic. The genes included in a familial ovarian cancer panel needs to include all the clinically important genes and yet it cannot include so many genes that the interpretation of the results becomes very difficult. This is not a static process; the genes included on these panels will change as new genes are discovered. Therefore, familial ovarian cancer panels need to be under constant review and updated regularly. The review will look at evidence around which genes should be included on a familial ovarian cancer panel.

Summary of the protocol

See Table 1 for a summary of the using population, presence or absence of a prognostic factor and outcome (PPO).

Table 1: Summary of the protocol (PPO table)

Population	Women (with or without ovarian cancer)

Prognostic factor	Presence of germline pathogenic variant, such as:
	• *ATM*
	• *BRCA1*
	• *BRCA2*
	• *BRIP1*
	• *CHEK2*
	• *EPCAM*
	• *PALB2*
	• *MLH1*
	• *MSH2*
	• *MSH6*
	• *RAD51C*
	• *RAD51D*
	• *PMS2*
	• Peutz-Jeghers, *DICER1* & small cell ovarian cancer genes (as a separate subgroup analysis:
	  ○ *STK11*
	  ○ *SMARCA4*
	  ○ *DICER1*

Outcomes	**Critical**

	• Frequency of pathogenic variants in people with ovarian cancer versus controls (case control or cross-sectional studies) • Incidence of ovarian cancer in pathogenic variant carriers versus noncarriers (longitudinal studies) **Important** None

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Where the evidence is described in terms of the level of risk associated with different genes, the risk categories used are taken from the systematic review included studies (Suszynska 2019), with odds ratios ≥ 4 denoting high risk, odds ratios < 4 and ≥ 2 denoting moderate risk and odds ratios < 2 denoting low risk. Further 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.

Prognostic evidence

Included studies

Five studies were included for this review, 4 case-control studies (Dicks 2017, Kurian 2017, LaDuca 2020 and Song 2021) and 1 systematic review of case control studies (Suszynska 2019).

Dicks 2017 and Song 2019 reported the prevalence of pathological variants *FANCM* and *PALB2*, respectively, whereas the other 3 studies reported on the prevalence of pathological variants of multiple genes, namely *BRCA2, BRCA1, CHEK2, ATM, PALB2, PMS2, BRIP1, MSH6, NBN, BARD1, MSH2, RAD51C, MLH1, APC, CDKN2A, RAD51D, CDH1, TP53, MUTYH, PTEN, BMPR1A, P14ARF, STK11, SMAD4* and *CDK4* (Kurian 2017); *APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, MLH1, MRE11A, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D* and *TP53* (LaDuca 2020); *APC, ATM, ATR, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FAM175A, FANCC, FANCM, MLH1, MRE11A, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, AD50,RAD51C,RAD51D, SLX4, SMAD4, STK11, TP53, VHL and XRCC2* (Suszynska 2019), all in women with ovarian cancer. The included studies are summarised in Table 2.

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Pathological variants	Outcomes
Dicks 2017 Case-control study USA, UK, Australia and Europe	N=4508 cases Age (mean, range) years: 59 (18-91) N=3368 controls Age (mean, range) years: 55 (18-93) Cases were women with ovarian cancer of high grade serous or other tumour histology. Controls were not described.	*FANCM*	• Frequency of pathogenic variant in people with ovarian cancer versus controls • Frequency of pathogenic variant in people with high grade serous ovarian cancer versus controls
Kurian 2017 Case-control study USA	N=5020 cases Age, median (range) years: 62 (20-97) N= 64649 controls Age, median (range) years: 44 (11-95) Cases were female breast or ovarian cancer patients multigene panel tested for hereditary cancer risk (Myriad Genetic Lab). Controls were women with no cancer history at the time of genetic test.	*BRCA2, BRCA1, CHEK2, ATM, PALB2, PMS2, BRIP1, MSH6, NBN, BARD1, MSH2, RAD51C, MLH1, APC, CDKN2A, RAD51D, CDH1, TP53, MUTYH, PTEN, BMPR1A, P14ARF, STK11, SMAD4* and *CDK4*	• Frequency of pathogenic variant in people with ovarian cancer versus controls
LaDuca 2020 Case-control study USA	N=13474 cases Age, mean (SD) years: Not reported separately for ovarian cancer cases N=111480 controls Age, mean (SD) years: Not reported separately for ovarian cancer controls Cases were women with ovarian, cancer referred to Ambry Genetics for multigene panel genetic testing Controls were non-Finnish European	*APC, ATM, BARD1, BRCA1* *BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, MLH1, MRE11A, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D* and *TP53*	• Frequency of pathogenic variant in people with ovarian cancer versus controls

Study	Population	Pathological variants	Outcomes
	reference controls from gnomAD		
Song 2021 Case-control study UK	For validation analysis: N=14135 cases Age, mean (SD) years: Not reported separately for ovarian cancer cases N=28655 controls Age, mean (SD) years: Not reported separately for ovarian cancer controls Cases with epithelial ovarian cancer and controls were drawn from OCAC and UK Biobank	*PALB2*	• Frequency of pathogenic variant in people with ovarian cancer versus controls • Frequency of pathogenic variant in people with high grade serous ovarian cancer versus controls
Suszynska 2019 Systematic review Primary studies were conducted in various international countries	N= up to 7099 cases (depending on pathological variant) from 48 studies Age, mean (SD) years: not reported N controls not reported Cases were women with breast or ovarian cancer referred for multigene panel testing. Controls were reference controls from gnomAD Included studies were not restricted to only high-risk individuals (familial, bilateral, or early-onset BC).	*APC, ATM, ATR, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FAM175A, FANCC, FANCM, MLH1, MRE11A, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD50,RAD51C,RAD51D, SLX4, SMAD4, STK11, TP53, VHL* and *XRCC2*	• Frequency of pathogenic variant in people with ovarian cancer verses controls

BC: breast cancer; OCAC: ; Ovarian Cancer Association Consortium; gnomAD: Genome Aggregation Database;

See the full evidence tables in appendix D, the forest plots in appendix E and data for pathological variants in appendix L.

Summary of the evidence

Although prevalence of pathological variants was not an outcome in the review protocol, the evidence about the strength of the association of the pathological variants with ovarian

cancer is summarized by prevalence of pathological variant in ovarian cancer cases. This is because some pathological variants may be too rare to justify inclusion in a standard test panel. Pathological variants with fewer than 3 occurrences in all ovarian cancer cases combined were excluded from the analysis of the association with ovarian cancer. For high grade serous ovarian cancer, very limited evidence was found for only 2 genes (FANCM and PALB2). These results are therefore only presented in appendix L.

Pathological variants with prevalence of 0.5% or greater in ovarian cancer cases

Pathological variants of *ATM, BRCA1, BRCA2, BRIP1, FANCM* and *RAD51C* had a prevalence of 0.5% or greater in ovarian cancer cases.

Of these *BRCA1, BRCA2* and *RAD51C* had odds ratios ≥ 4 (high risk) for gene specific ovarian cancer association. The evidence quality was very low to moderate.

Low quality evidence indicated *BRIP1 and FANCM* had an odds ratio ≥ 2 (moderate risk) for gene specific ovarian cancer association.

Pathological variants with prevalence of >0.2% to <0.5% in ovarian cancer cases

Pathological variants of *CHEK2, FANCC, MSH6, NBN* and *PALB2* had a prevalence >0.2% and <0.5% in ovarian cancer cases.

Of these *FANCC, MSH6* and *NBN had* odds ratios ≥ 2 (moderate risk) for gene specific ovarian cancer association. The evidence quality was very low to moderate.

Pathological variants with prevalence of 0.1% to 0.2% in ovarian cancer cases

Pathological variants of *FAM175A, MSH2, PMS2, RAD50 and RAD51D* had a prevalence 0.1% to 0.2% in ovarian cancer cases.

Of these *RAD51D* had an odds ratio ≥ 4 (high risk) for gene specific ovarian cancer association. This evidence was moderate quality.

Moderate quality evidence indicated *MSH2* had an odds ratio ≥ 2 (moderate risk) for gene specific ovarian cancer association.

Pathological variants with prevalence >0% to 0.1% in ovarian cancer cases

Very low to moderate quality evidence indicated that pathological variants of *APC, BARD1, MLH1, MRE11A, PTEN* and *TP53* had a prevalence greater than zero but less than 0.1% in ovarian cancer cases.

Due to the very low numbers of these pathological variants, there was uncertainty in their estimates of gene specific ovarian cancer association.

Pathological variants with prevalence of 0, 1 or 2 occurrences in total

Pathological variants of *ATR, BAP1, BLM, BMPR1A, CDK4, EPCAM, P14ARF, SLX4, SMAD4, VHL* and *XRCC2* had a prevalence of zero in ovarian cancer cases (low quality evidence).

Pathological variants of *CDH1, CDKN2A, MUTYH, NF1 and STK11* had fewer than 3 occurrences in ovarian cancer cases (very low to moderate quality evidence).

See appendix F for full GRADE tables.

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 K.

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.

Evidence statements

Economic

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Ovarian cancer was the critical outcome for this review. This is because the aim of the review was to identify germline pathogenic variants strongly associated with increased familial risk of ovarian cancer in order to design a genetic test panel to identify individuals at risk. This could be done through two methods: either calculating the frequency of pathogenic variants in cases with ovarian cancer versus controls, or the incidence of ovarian cancer in pathogenic variant carriers versus noncarriers.

The quality of the evidence

The quality of the evidence from the included studies was assessed using modified GRADE and ranged from very low to moderate quality. Some of the main issues that lowered the quality of the evidence were: serious risk of bias, imprecision in effect estimates, and serious or very serious heterogeneity unexplained by subgroup analysis. All of the evidence came from case-control studies and no prospective cohort studies were identified.

Benefits and harms

The committee discussed the evidence in relation to the genes that are on the gene panel for ovarian cancer risk in the UK national genomic test directory (which at the time of this review is panel R207 - *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *RAD51C*, *RAD51D, BRIP1* and *PALB2*). They noted that panel R207 had been updated in March 2023 and all panels in the UK national genomic test directory are curated, reviewed and updated by teams of

specialists when evidence emerges. They also acknowledged that the UK national genomic test directory takes into considerations other types of evidence, such as the biological impact that these variants have on cell function as well as unpublished evidence (a detailed biological explanation of all the gene functions is outside the NICE reviewing process). They therefore felt that this was a robust starting point for discussion.

The evidence identified for this review is consistent with the panel of the UK national genomic test directory in relation to *BRCA1*, *BRCA2*, *RAD51C and BRIP1* showing high prevalence of 0.5% and above. Whilst the evidence was classified as very low to moderate only, highlighting some uncertainty, the committee was confident about these based on their knowledge that it is well established that these pathogenic variants can disrupt normal cellular processes, increasing the susceptibility to cancer development. The evidence was not as clear in relation to other pathogenic variants. *PALB2* was less prevalent (>0.2 to <0.5) and *RAD51D* was in the 0.1% to 0.2% category of prevalence. There are biological reasons why these variants would be included. Based on their expertise they discussed that both *RAD51C* and *RAD51D* pathogenic variants are involved in the homologous recombination pathway which is a fundamental genetic process that plays a crucial role in DNA repair and the maintenance of genome stability. Impairing the repair process increases the risk of ovarian and breast cancers. They were therefore confident about adding RAD51D. For *PALB2* the reasoning is that this gene encodes a protein that interacts with both BRCA1 and BRCA2, playing a role in DNA repair and maintaining genomic stability. Mutations in *PALB2* can disrupt these interactions and lead to an increased risk of breast and ovarian cancers.

The committee agreed that the appropriate gene panel to select from the UK national genomic test directory would depend on the person's family or personal history.

They noted that the evidence showed that *ATM* and *CHECK2* had high to moderate prevalence and that these two variants are associated with a family history of breast and ovarian cancer and are therefore on the panel for this combination (R208).

Base on expertise the committee agreed that it was well established that *MLH1*, *MSH2* and *MSH6* are associated with ovarian cancer because they are Lynch syndrome pathogenic variants which amongst other cancers also increases ovarian cancer and are therefore not only included on the ovarian cancer gene panel but also included on the gene panel for Lynch syndrome (R210).

The evidence also suggested that some genes had relatively high gene specific ovarian cancer associations, but low penetrance among the population. These were *FANCC*, *FANCM* and *PMS2*. Low population-level penetrance means that the likelihood of ovarian cancer appearing in a given population based on the presence of these pathogenic variants is low. The committee noted that this seemed to have been the case for FANCC and FANCM with very few cases for these pathogenic variants which may have led to less robust findings. So they were not confident in recommending these to be added. However, they noted based on experience that *PMS2* (which showed it to be in the lower prevalence category) is associated with endometrial but is currently considered to be a variant that increase risks of endometrial cancer alone (and features on the Lynch syndrome gene panel of the UK national genomic test directory) so whilst associated with Lynch syndrome which is in the scope it is outside the scope of the guideline in relation to ovarian cancer. The committee agreed it may be a candidate for an association with ovarian cancer but that this was not yet clear. They did not make a research recommendation, however, because they agreed that such research is already underway and it is on the amber watchlist (moderate evidence) on the Genomics England panel app.

Whilst *NBN* and *FAM175A* were in the second and third highest prevalence category the committee discussed that the evidence for this was only low to moderate quality. They noted that NBN is on the red part of panel R207. Whilst pathogenic variants in the red category are usually benign and are excluded from further clinical analysis and interpretation in some cases, variants classified as red may still be considered relevant in certain clinical contexts.

For instance, if a patient has a strong family history of a specific condition, even a benign variant might be taken into consideration. However, they did not want to be specific about this gene because they felt the evidence was too uncertain (low to moderate quality) with an unclear biological connection. As *BRIP1, FAM175A* is a gene that also produces the BRIP1 protein which interacts with the BRCA1 protein which is a plausible connection. However, it is not on the green, amber or red list of any relevant gene panel because suggesting that despite the evidence identified for this review the wider body of evidence related to this is limited. They therefore did not make a recommendation related to this.

They did not make recommendations based on the pathogenic variants on the lowest prevalence category or those with prevalence of 0, 1 or 2 occurrences in total.

Cost effectiveness and resource use

No existing economic evidence was identified for this review. The committee recommended selecting the gene panel testing in accordance with the UK national genomic test directory. Whilst the criteria for gaining access to the tests are changing based on other reviews conducted for this guideline (which will have an impact on implementation), using these specific genes for panel testing in accordance with the test directory is already current practice.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 and 1.5.2 in the NICE guideline.

References – included studies

Prognostic

Dicks 2017

Dicks, E et al.; Germline whole exome sequencing and large-scale replication identifies FANCM as a likely high grade serous ovarian cancer susceptibility gene; Oncotarget; vol. 8 (no. 31); 2017

Kurian 2017

Kurian, A W et al.; Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women.; JCO precision oncology; vol. 1; 1-12, 2017

LaDuca 2020

LaDuca, H et al.; A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000

high-risk patients.; Genetics in medicine : official journal of the American College of Medical Genetics; vol. 22 (no. 2); 407-415, 2020

Song 2021

Song, H et al; Population-based targeted sequencing of 54 candidate genes identifies PALB2 as a susceptibility gene for high-grade serous ovarian cancer.; Journal of medical genetics; vol. 58 (no. 5); 305-313, 2021

Suszynska, 2019

Suszynska, M; Klonowska, K; Jasinska, AJ; Kozlowski, P; Large-scale meta-analysis of mutations identified in panels of breast/ovarian cancer-related genes - Providing evidence of cancer predisposition genes.; Gynecologic oncology;vol. 153 (no. 2); 452-462, 2019

Economic

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

Appendices

Appendix A Review protocols

Review protocol for review question: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022346863
1.	Review title	Genetic testing for familial ovarian cancer
2.	Review question	Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?
3.	Objective	To determine which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language • Human studies The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.

ID	Field	Content
		The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Familial ovarian cancer
6.	Population	Inclusion: Women (with or without ovarian cancer)

7.	Prognostic factor	Presence of germline pathogenic variant, such as:
		• *ATM*
		• *BRCA1*
		• *BRCA2*
		• *BRIP1*
		• *CHEK2*
		• *EPCAM*
		• *PALB2*
		• *MLH1*
		• *MSH2*
		• *MSH6*
		• *RAD51C*
		• *RAD51D*
		• *PMS2*
		• Peutz-Jeghers, *DICER1* & small cell ovarian cancer genes (as a separate subgroup analysis):
		  ○ *STK11*
		  ○ *SMARCA4*
		  ○ *DICER1*

8.	Confounding factors	Potential: Age

ID	Field	Content
		Family ethnicity (for example Ashkenazi Jewish)
9.	Types of study to be included	Study designs: • Longitudinal observational studies • Cross sectional observational studies, in the absence of longitudinal studies
10.	Other exclusion criteria	Inclusion: • Full text papers 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 • Studies using qualitative methods only • Non-English language articles
11.	Context	Potential overlap with National Genomic Test directory panels.
12.	Primary outcomes (critical outcomes)	Frequency of pathogenic variants in people with ovarian cancer versus controls (case control or cross-sectional studies) Incidence of ovarian cancer in pathogenic variant carriers versus noncarriers (longitudinal studies)
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-Reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records); 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.

ID	Field	Content
		The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. 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: QUIPS checklist for prognostic factor studies 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. Data Synthesis Where possible meta-analysis to combine the effect estimates across studies for each prognostic factor will be conducted, if studies have comparable populations. We will extract either OR or HR; however we will conduct separate meta-analysis for those studies reporting OR and those reporting HR, as it is inappropriate to pool OR and HR.

ID	Field	Content
		If no meta-analysis is conducted a narrative summary of the available results for each factor will be provided. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. In the case of serious or very serious unexplained heterogeneity (remaining after pre-specified subgroup and stratified analyses) meta-analysis will be done using a random effects model. Default MIDs will be used for odds and hazard ratios, unless the committee pre-specifies published or other MIDs for specific outcomes For odds and hazard ratios: 0.8 and 1.25. Validity 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/
17.	Analysis of sub-groups	Evidence will be stratified by: • Epithelial ovarian cancer • Peutz Jeghers syndrome • Small cell ovarian cancers • DICER1 tumours • Age • Baseline prevalence of pathogenic variants (for example general population level versus higher prevalence settings such as tertiary care) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:

ID	Field	Content			
		• Next generation sequencing versus older methods • Groups identified in the equality considerations section of the scope • socioeconomic and geographical factors • 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	1 August 2022			
22.	Anticipated completion date	13 March 2024			
23.		Review stage		Started	Completed

ID	Field	Content		
	Stage of review at time of this submission	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 Guideline development team NGA 5b Named contact e-mail foc@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (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		

ID	Field	Content	
		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	Genetic testing for familial ovarian cancer. PROSPERO 2022 CRD42022346863 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022346863	
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	Female; Genetic Testing; Humans; Ovarian Neoplasms	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		Yes	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: Hazard ratio; HTA: Health Technology Assessment; MID: minimally important difference; NGA:

National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; OR: Odds ratio; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

Database: Ovid MEDLINE ALL

Date of last search: 16/01/2023

#	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	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
15	((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.
16	gardner* syndrome*.tw,kf.
17	(MAP or FAP or AFAP).tw,kf.
18	((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.
19	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
20	(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.
21	or/9-20
22	8 and 21
23	exp Fanconi Anemia Complementation Group Proteins/
24	(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 PMS2).tw,kf.
25	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
26	Ataxia Telangiectasia Mutated Proteins/
27	((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.
28	Checkpoint Kinase 2/
29	(((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.
30	Epithelial Cell Adhesion Molecule/
31	Epithelial cell adhesion molecule*.tw,kf.
32	(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.
33	MutL Protein Homolog 1/

#	Searches
34	(MutL adj2 (protein* or "homolog 1")).tw,kf.
35	"DNA mismatch repair protein* Mlh1".tw,kf.
36	(MLH1 or FCC2 or COCA2 or HNPCC or MLH-1 or hMLH1 or HNPCC2 or LYNCH2 or MMRCS1).tw,kf.
37	("mutY DNA glycosylase" or "mutY homolog (E. coli)").tw,kf.
38	(MUTYH or MYH or APC or GS or DP2 or DP3 or BTPS2 or DESMD or DP25 or PPP1R46).tw,kf.
39	(MSH2 or FCC1 or COCA1 or LCFS2 or MSH-2 or hMSH2 or HNPCC1 or LYNCH1 or MMRCS2).tw,kf.
40	"mutS homolog 2".tw,kf.
41	"mutS homolog 6".tw,kf.
42	(MSH6 or GTBP or HSAP or p160 or GTMBP or MSH-6 or HNPCC5 or LYNCH5 or MMRCS3).tw,kf.
43	"RAD51 paralog C".tw,kf.
44	(RAD51C or FANCO or R51H3 or BROVCA3 or RAD51L2).tw,kf.
45	"RAD51 paralog D".tw,kf.
46	(RAD51D or TRAD or R51H3 or BROVCA4 or RAD51L3).tw,kf.
47	"PMS1 homolog 2".tw,kf.
48	(PMS2 or MLH4 or PMS-2 or PMSL2 or HNPCC4 or LYNCH4 or MMRCS4 or PMS2CL).tw,kf.
49	Peutz-Jeghers Syndrome/
50	(peutz* or intestin* polyposis or PJS or (perior* adj1 lentigino*)).tw,kf.
51	"serine threonine kinase 11".tw,kf.
52	(STK11 or LKB1 or PJS or hLKB1).tw,kf.
53	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
54	"dicer 1, ribonuclease III".tw,kf.
55	Carcinoma, Small Cell/ge [Genetics]
56	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
57	(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.
58	exp Genes, Tumor Suppressor/
59	exp Tumor Suppressor Proteins/
60	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
61	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
62	Germ-Line Mutation/
63	((germline* or germ line* or pathogenic) adj2 (carrier* or variant* or mutat*)).tw,kf.
64	or/23-63
65	exp Genetic Testing/
66	((genetic or gene?) adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method* or identif* or frequenc*)).tw,kf.
67	((multigene* or multi* gene* or gene* or sequenc* or screen* or test*) adj3 panel*).tw,kf.
68	or/65-67
69	64 or 68
70	22 and 69
71	exp risk assessment/ or risk factors/
72	((risk* or probabil*) adj3 (high* or increas* or factor* or rais* or low* or reduc* or assess* or predict* or analys?s or profile* or estimat* or factor*)).tw,kf.
73	or/71-72
74	70 and 73
75	letter/ or editorial/ or news/ or exp historical article/ or Anecdotes as Topic/ or comment/ or case report/ or (letter or comment*).ti.
76	randomized controlled trial/ or random*.ti,ab.
77	75 not 76
78	(animals/ not humans/) or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ or (rat or rats or rodent* or mouse or mice).ti.
79	77 or 78
80	74 not 79
81	limit 80 to English language
82	predict.ti.
83	(validat* or rule*).ti,ab.

#	Searches
84	(predict* and (outcome* or risk* or model*)).ti,ab.
85	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
86	decision*.ti,ab. and Logistic models/
87	(decision* and (model* or clinical*)).ti,ab.
88	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
89	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
90	ROC curve/
91	or/82-90
92	81 and 91
93	Observational Studies as Topic/
94	Observational Study/
95	Epidemiologic Studies/
96	exp Case-Control Studies/
97	exp Cohort Studies/
98	Cross-Sectional Studies/
99	Controlled Before-After Studies/
100	Historically Controlled Study/
101	Interrupted Time Series Analysis/
102	Comparative Study.pt.
103	case control$.tw.
104	case series.tw.
105	(cohort adj (study or studies)).tw.
106	cohort analy$.tw.
107	(follow up adj (study or studies)).tw.
108	(observational adj (study or studies)).tw.
109	longitudinal.tw.
110	prospective.tw.
111	retrospective.tw.
112	cross sectional.tw.
113	or/93-112
114	81 and 113
115	92 or 114

Database: Ovid Embase

Date of last search: 16/01/2023

#	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.
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.

#	Searches
12	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
13	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
14	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
15	((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.
16	gardner* syndrome*.tw,kf.
17	(MAP or FAP or AFAP).tw,kf.
18	((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.
19	((hereditary breast and ovarian cancer) or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
20	(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.
21	or/8-20
22	7 and 21
23	*Fanconi anemia protein/ or *brca1 protein/ or *brca2 protein/ or *Rad51 protein/
24	(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 PMS2).tw,kf.
25	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
26	*ATM protein/
27	((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.
28	*checkpoint kinase 2/
29	(((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.
30	*epithelial cell adhesion molecule/
31	Epithelial cell adhesion molecule*.tw,kf.
32	(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.
33	*protein MutL/
34	(MutL adj2 (protein* or "homolog 1")).tw,kf.
35	"DNA mismatch repair protein* Mlh1".tw,kf.
36	(MLH1 or FCC2 or COCA2 or HNPCC or MLH-1 or hMLH1 or HNPCC2 or LYNCH2 or MMRCS1).tw,kf.
37	("mutY DNA glycosylase" or "mutY homolog (E. coli)").tw,kf.
38	(MUTYH or MYH or APC or GS or DP2 or DP3 or BTPS2 or DESMD or DP25 or PPP1R46).tw,kf.
39	(MSH2 or FCC1 or COCA1 or LCFS2 or MSH-2 or hMSH2 or HNPCC1 or LYNCH1 or MMRCS2).tw,kf.
40	"mutS homolog 2".tw,kf.
41	"mutS homolog 6".tw,kf.
42	(MSH6 or GTBP or HSAP or p160 or GTMBP or MSH-6 or HNPCC5 or LYNCH5 or MMRCS3).tw,kf.
43	"RAD51 paralog C".tw,kf.
44	(RAD51C or FANCO or R51H3 or BROVCA3 or RAD51L2).tw,kf.
45	"RAD51 paralog D".tw,kf.
46	(RAD51D or TRAD or R51H3 or BROVCA4 or RAD51L3).tw,kf.
47	"PMS1 homolog 2".tw,kf.
48	(PMS2 or MLH4 or PMS-2 or PMSL2 or HNPCC4 or LYNCH4 or MMRCS4 or PMS2CL).tw,kf.
49	*Peutz Jeghers syndrome/
50	(peutz* or intestin* polyposis or PJS or (perior* adj1 lentigino*)).tw,kf.
51	"serine threonine kinase 11".tw,kf.
52	(STK11 or LKB1 or PJS or hLKB1).tw,kf.
53	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
54	"dicer 1, ribonuclease III".tw,kf.
55	*small cell carcinoma/
56	*genetics/
57	55 and 56

#	Searches
58	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
59	(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.
60	exp *tumor suppressor gene/
61	exp *tumor suppressor protein/
62	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
63	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
64	*germline mutation/
65	((germline* or germ line* or pathogenic) adj2 (carrier* or variant* or mutat*)).tw,kf.
66	or/23-54,57-65
67	exp *genetic screening/
68	((genetic or gene?) adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method* or identif* or frequenc*)).tw,kf.
69	((multigene* or multi* gene* or gene* or sequenc* or screen* or test*) adj3 panel*).tw,kf.
70	or/67-69
71	66 or 70
72	22 and 71
73	exp *risk assessment/ or *risk factor/
74	((risk* or probabil*) adj3 (high* or increas* or factor* or rais* or low* or reduc* or assess* or predict* or analys?s or profile* or estimat* or factor*)).tw,kf.
75	or/73-74
76	72 and 75
77	letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.
78	randomized controlled trial/ or random*.ti,ab.
79	77 not 78
80	(animal/ not human/) or nonhuman/ or exp Animal Experiment/ or exp Experimental Animal/ or animal model/ or exp Rodent/ or (rat or rats or rodent* or mouse or mice).ti.
81	79 or 80
82	76 not 81
83	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
84	82 not 83
85	limit 84 to English language
86	predict.ti.
87	(validat* or rule*).ti,ab.
88	(predict* and (outcome* or risk* or model*)).ti,ab.
89	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
90	decision*.ti,ab. and Statistical model/
91	(decision* and (model* or clinical*)).ti,ab.
92	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
93	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
94	Receiver operating characteristic/
95	or/86-94
96	85 and 95
97	Clinical study/
98	Case control study/
99	Family study/
100	Longitudinal study/
101	Retrospective study/
102	comparative study/
103	Prospective study/
104	Randomized controlled trials/
105	103 not 104
106	Cohort analysis/

#	Searches
107	cohort analy$.tw.
108	(Cohort adj (study or studies)).tw.
109	(Case control$ adj (study or studies)).tw.
110	(follow up adj (study or studies)).tw.
111	(observational adj (study or studies)).tw.
112	(epidemiologic$ adj (study or studies)).tw.
113	(cross sectional adj (study or studies)).tw.
114	case series.tw.
115	prospective.tw.
116	retrospective.tw.
117	or/97-102,105-116
118	85 and 117
119	96 or 118

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

Date of last search: 16/01/2023

#	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	#4 OR #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	((hamartoma* or "polyps and spots" or cowden*) NEAR/2 (syndrome* or polyp*)):ti,ab,kw
#15	((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
#16	gardner* NEXT syndrome*:ti,ab,kw
#17	(MAP or FAP or AFAP):ti,ab,kw
#18	((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
#19	("hereditary breast and ovarian cancer" or HBOC or "Li Fraumeni syndrome" or SBLA or LFS):ti,ab,kw
#20	(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
#21	{OR #9-#20}
#22	#8 AND #21
#23	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#24	(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 PMS2):ti,ab,kw
#25	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw
#26	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only

#	Searches
#27	(("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
#28	MeSH descriptor: [Checkpoint Kinase 2] this term only
#29	(((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
#30	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#31	Epithelial NEXT cell NEXT adhesion NEXT molecule*:ti,ab,kw
#32	(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):ti,ab,kw
#33	MeSH descriptor: [MutL Protein Homolog 1] this term only
#34	(MutL NEAR/2 (protein* or "homolog 1")):ti,ab,kw
#35	DNA NEXT mismatch NEXT repair NEXT protein* NEXT Mlh1:ti,ab,kw
#36	(MLH1 or FCC2 or COCA2 or HNPCC or MLH-1 or hMLH1 or HNPCC2 or LYNCH2 or MMRCS1):ti,ab,kw
#37	("mutY DNA glycosylase" or "mutY homolog (E. coli)"):ti,ab,kw
#38	(MUTYH or MYH or APC or GS or DP2 or DP3 or BTPS2 or DESMD or DP25 or PPP1R46):ti,ab,kw
#39	(MSH2 or FCC1 or COCA1 or LCFS2 or MSH-2 or hMSH2 or HNPCC1 or LYNCH1 or MMRCS2):ti,ab,kw
#40	mutS homolog 2:ti,ab,kw
#41	mutS homolog 6:ti,ab,kw
#42	(MSH6 or GTBP or HSAP or p160 or GTMBP or MSH-6 or HNPCC5 or LYNCH5 or MMRCS3):ti,ab,kw
#43	RAD51 paralog C:ti,ab,kw
#44	(RAD51C or FANCO or R51H3 or BROVCA3 or RAD51L2):ti,ab,kw
#45	RAD51 paralog D:ti,ab,kw
#46	(RAD51D or TRAD or R51H3 or BROVCA4 or RAD51L3):ti,ab,kw
#47	PMS1 homolog 2:ti,ab,kw
#48	(PMS2 or MLH4 or PMS-2 or PMSL2 or HNPCC4 or LYNCH4 or MMRCS4 or PMS2CL):ti,ab,kw
#49	MeSH descriptor: [Peutz-Jeghers Syndrome] this term only
#50	(peutz* or intestin* NEXT polyposis or PJS or (perior* NEAR/1 lentigino*)):ti,ab,kw
#51	serine threonine kinase 11:ti,ab,kw
#52	(STK11 or LKB1 or PJS or hLKB1):ti,ab,kw
#53	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4 NEXT 8 NEXT LIKE):ti,ab,kw
#54	dicer 1, ribonuclease III:ti,ab,kw
#55	MeSH descriptor: [Carcinoma, Small Cell] this term only and with qualifier(s): [genetics - GE]
#56	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#57	(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 NEXT beta):ti,ab,kw
#58	MeSH descriptor: [Genes, Tumor Suppressor] explode all trees
#59	MeSH descriptor: [Tumor Suppressor Proteins] explode all trees
#60	((tumo?r* or cancer* or metastasis or metastases or growth*) NEAR/2 (suppress* NEAR/1 (gene* or protein*))):ti,ab,kw
#61	(anti NEXT oncogene* or antioncogene* or onco NEXT suppressor* or oncosuppressor*):ti,ab,kw
#62	MeSH descriptor: [Germ-Line Mutation] this term only
#63	((germline* or germ NEXT line* or pathogenic) NEAR/2 (carrier* or variant* or mutat*)):ti,ab,kw
#64	{OR #23-#63}
#65	MeSH descriptor: [Genetic Testing] explode all trees
#66	((genetic or gene?) NEAR/2 (test* or screen* or analysis or analyses or assess* or evaluat* or detect* or incidence* or method* or identif* or frequenc*)):ti,ab,kw
#67	((multigene* or multi* NEXT gene* or gene* or sequenc* or screen* or test*) NEAR/3 panel*):ti,ab,kw
#68	{OR #65-#67}
#69	#64 OR #68
#70	#22 AND #69
#71	MeSH descriptor: [Risk Assessment] explode all trees
#72	MeSH descriptor: [Risk Factors] this term only
#73	((risk* or probabil*) NEAR/3 (high* or increas* or factor* or rais* or low* or reduc* or assess* or predict* or analysis or analyses or profile* or estimat* or factor*)):ti,ab,kw
#74	{OR #71-#73}

#	Searches
#75	#70 AND #74
#76	conference:pt or (clinicaltrials or trialsearch):so
#77	#75 NOT #76

Database: Epistemonikos

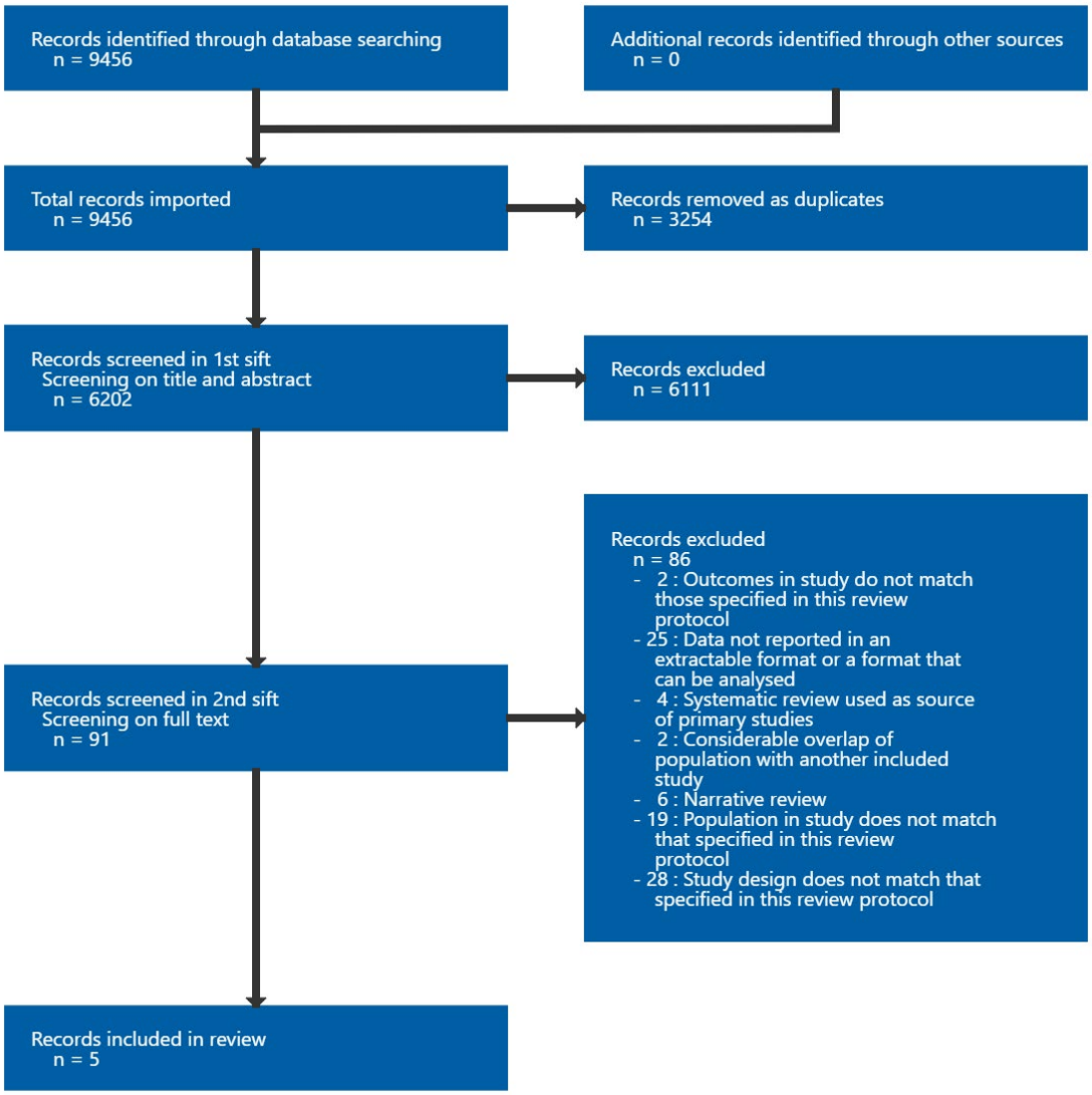
Date of last search: 16/01/2023

#	Searches
1	(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:((ATM OR BRCA* OR BRIP1 OR CHEK2 OR EPCAM OR PALB2 OR MLH1 OR MSH2 OR MSH6 OR RAD51C OR RAD51D OR PMS2 OR DICER* OR STK11 OR SMARCA4 OR Peutz-Jegher* OR Peutz jegher* OR PJS OR "small cell ovarian cancer gene" OR "small cell ovarian cancer genes")) OR advanced_abstract_en:((ATM OR BRCA* OR BRIP1 OR CHEK2 OR EPCAM OR PALB2 OR MLH1 OR MSH2 OR MSH6 OR RAD51C OR RAD51D OR PMS2 OR DICER* OR STK11 OR SMARCA4 OR Peutz-Jegher* OR Peutz jegher* OR PJS OR "small cell ovarian cancer gene" OR "small cell ovarian cancer genes"))
3	(advanced_title_en:(((genetic OR gene*) AND (test* OR screen* OR analysis OR analyses OR assess* OR evaluat* OR detect* OR incidence* OR method* OR identif* OR frequenc*))) OR advanced_abstract_en:(((genetic OR gene*) AND (test* OR screen* OR analysis OR analyses OR assess* OR evaluat* OR detect* OR incidence* OR method* OR identif* OR frequenc*))
4	(advanced_title_en:(((multigene* OR multi* gene* OR gene* OR sequenc* OR screen* OR test*) AND panel*)) OR advanced_abstract_en:(((multigene* OR multi* gene* OR gene* OR sequenc* OR screen* OR test*) AND panel*)
5	2 OR 3 OR 4
6	1 AND 5

Appendix C Prognostic evidence study selection

Study selection for: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

Dicks, 2017

Bibliographic Reference	Dicks, E.; Song, H.; Ramus, S.J.; Van Oudenhove, E.; Tyrer, J.P.; Intermaggio, M.P.; Kar, S.; Harrington, P.; Bowtell, D.D.; Cicek, M.S.; Cunningham, J.M.; Fridley, B.L.; Alsop, J.; Jimenez-Linan, M.; Piskorz, A.; Goranova, T.; Kent, E.; Siddiqui, N.; Paul, J.; Crawford, R.; Poblete, S.; Lele, S.; Sucheston-Campbell, L.; Moysich, K.B.; Sieh, W.; McGuire, V.; Lester, J.; Odunsi, K.; Whittemore, A.S.; Bogdanova, N.; Durst, M.; Hillemanns, P.; Karlan, B.Y.; Gentry-Maharaj, A.; Menon, U.; Tischkowitz, M.; Levine, D.; Brenton, J.D.; Dork, T.; Goode, E.L.; Gayther, S.A.; Pharoah, P.D.P.; Wozniak, E.; Ryan, A.; Ford, J.; Balogun, N.; Pye, C.; Mack, M.; Luccarini, C.; Baynes, C.; Maranian, M.; Germline whole exome sequencing and large-scale replication identifies FANCM as a likely high grade serous ovarian cancer susceptibility gene; Oncotarget; 2017; vol. 8 (no. 31); 50930-50940

Study details

Country/ies where study was carried out	USA, UK, Australia and Europe
Study type	Case-control study
Study dates	Not reported
Inclusion criteria	High grade serous ovarian cancer cases from The Cancer Genome Atlas Project. These included 8 ovarian cancer case-control studies, 1 familial ovarian cancer registry from the USA and 1 case series. 988 cases with other tumour histologies were also selected as some common alleles that predispose to high grade serous ovarian cancer are also associated with an increased risk of other subtypes. Controls were not described.
Exclusion criteria	If <80 percent of the target bases from patients had read depth ≥15.
Patient characteristics	Cases: N=4508

	Age (mean, range) years: 59 (18-91) **Epithelial ovarian cancer:** 100%: High-grade serous: 3017 (67%) Stage 3/4: 2924 (81%) **Peutz Jeghers syndrome**: 0% **Small cell ovarian cancers:** 0%: ***DICER1* tumours:** 0%: **Baseline prevalence of pathogenic variants**: High grade serous ovarian cancer cases **Ethnicity**: not reported Control: N=3368 **Age** (mean, range) years: 55 (18-93) **Epithelial ovarian cancer:** 0%: **Peutz Jeghers syndrome**: 0%: **Small cell ovarian cancers:** 0%: ***DICER1* tumours:** 0%: **Baseline prevalence of pathogenic variants**: general population

	Ethnicity: not reported
Risk factor(s) of interest	Presence of pathogenic variants
Confounding factor(s) of interest	Not reported
Duration of follow-up	None
Setting	Genome project
Sources of funding	American Cancer Society Early Detection Professorship, the Cancer Councils of New South Wales, Victoria, Queensland, South Australia and Tasmania, the Cancer Foundation of Western Australia, Cancer Research UK, the Eve Appeal (The Oak Foundation), the Fred C. and Katherine B. Andersen Foundation, the National Institutes for Health, the National Center for Advancing Translational Sciences, the National Health & Medical Research Council of Australia , Cancer Australia, the Peter MacCallum Cancer Foundation and Ovarian Cancer Australia, Roswell Park Cancer Institute Alliance Foundation, Target Ovarian Cancer, the UK Department of Health, the UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge and University College London Hospitals Biomedical Research Centre; the U.S. Army Medical Research and Materiel Command
Other information	For results, please see Appendix L

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Unclear description of method used to identify population (refer to other studies for sampling frame). Recruitment period is not described)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias (*Ethnicity not reported*)
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Moderate risk of bias in study participation and study confounding domains)*
Overall risk of bias and directness	Directness	Directly applicable

Kurian, 2017

Bibliographic Reference	Kurian, Allison W; Hughes, Elisha; Handorf, Elizabeth A; Gutin, Alexander; Allen, Brian; Hartman, Anne-Renee; Hall, Michael J; Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women.; JCO precision oncology; 2017; vol. 1; 1-12

Study details

Country/ies where study was carried out	USA
Study type	Case-control study
Study dates	September 2013 to September 2015
Inclusion criteria	Female cancer patients who underwent testing for hereditary cancer risk with a 25-gene hereditary cancer panel. Cases were defined as female patients with a single diagnosis of breast cancer or ovarian cancer. Controls were women with no

	cancer history at the time of genetic testing. Cases and controls were matched 1:1 according to age (±3 years), ancestry (exact match), and family cancer history (breast, ovarian, colon, uterine).
Exclusion criteria	Incomplete test requisition forms, if they had testing using the 25-gene panel after receiving negative test results from a single/limited gene panel, or if results suggested mosaicism.
Patient characteristics	Ovarian cancer patients N= 5020 **Age at hereditary cancer testing, median (range) years:** 62 (20-97) **Epithelial ovarian cancer, %:** 100 **Peutz Jeghers syndrome, %:** 0 **Small cell ovarian cancers, %: 0** ***DICER1* tumours, %: 0** **Baseline prevalence of pathogenic variants:** women with ovarian cancer **Ethnicity, N (%):** Western/Northern European: N=3359 (67%) Central/Eastern European: N=543 (11%) Latin American/Caribbean: N=405 (8%) African: N=254 (5%) Native American: N=174 (3%) Asian: N=169 (3%) Ashkenazi: N=80 (2%)

	Near/Middle Eastern: N=35 (1%) Controls N=64649 **Age at hereditary cancer testing, median (range) years:** 44 (11-95) **Epithelial ovarian cancer, %:** 0 **Peutz Jeghers syndrome, %:** 0 **Small cell ovarian cancers, %:** 0 ***DICER1* tumours, %:** 0 **Baseline prevalence of pathogenic variants:** general population **Ethnicity, N (%):** Western/Northern European: N=34906 (54%) Central/Eastern European: N=10225 (16%) Latin American/Caribbean: N=6287 (10%) African 5843: N= (9%) Native American: N=2931 (5%) Asian 2043: N= (3%) Ashkenazi: N=1735 (3%)

	Near/Middle Eastern: N=680 (1%)
Risk factor(s) of interest	Presence of a pathogenic variant
Confounding factor(s) of interest	Not reported
Duration of follow-up	None
Setting	Genetic testing
Sources of funding	Myriad Genetics, Invitae, Ambry Genetics, Genomic Health, GeneDx/ BioReference; Genentech, Pfizer
Other information	For results, please see Appendix L

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

LaDuca, 2020

Bibliographic Reference	LaDuca, Holly; Polley, Eric C; Yussuf, Amal; Hoang, Lily; Gutierrez, Stephanie; Hart, Steven N; Yadav, Siddhartha; Hu, Chunling; Na, Jie; Goldgar, David E; Fulk, Kelly; Smith, Laura Panos; Horton, Carolyn; Profato, Jessica; Pesaran, Tina; Gau, Chia-Ling; Pronold, Melissa; Davis, Brigette Tippin; Chao, Elizabeth C; Couch, Fergus J; Dolinsky, Jill S; A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients.; Genetics in medicine : official journal of the American College of Medical Genetics; 2020; vol. 22 (no. 2); 407-415

Study details

Country/ies where study was carried out	USA
Study type	Case-control study
Study dates	March 2012 to December 2016
Inclusion criteria	Women with ovarian, breast, pancreatic, colorectal or endometrial cancer referred to Ambry Genetics for genetic testing. Case selection was limited to one individual per family. In the instance where multiple individuals from the same family underwent MGPT, the first family member to undergo panel testing was selected for inclusion in this study. Controls were non-Finnish European reference controls from gnomAD. Only information pertaining to ovarian cancer have been extracted.
Exclusion criteria	The frequency in gnomAD controls was restricted to PASS-only PVs, and if a variant was non-PASS in gnomAD and seen in the cancer case it was excluded from the frequency calculation. Copy-number variants and large structural

	rearrangements identified in the cases were excluded from the frequency calculation to be consistent with gnomAD frequencies.
Patient characteristics	Cases N=13,474 **Age at testing, mean (SD) years:** Not reported separately for ovarian cancer cases **Epithelial ovarian cancer, %:** 100 **Peutz Jeghers syndrome, %:** 0 **Small cell ovarian cancers, %:** 0 ***DICER1* tumours, %:** 0 **Baseline prevalence of pathogenic variants:** women with cancer **Ethnicity (N, %)** Not reported separately for ovarian cancer cases **Gender** female (N, %): 13,474 (100%) Controls N=111,480 **Age at testing, mean (SD) years:** Not reported separately for ovarian cancer controls **Epithelial ovarian cancer, %:** 0 **Peutz Jeghers syndrome, %:** 0 **Small cell ovarian cancers, %:** 0 ***DICER1* tumours, %:** 0

	Baseline prevalence of pathogenic variants: general population **Ethnicity (N, %):** Not reported separately for ovarian cancer controls **Gender:** not reported
Risk factor(s) of interest	Presence of a pathogenic variant
Confounding factor(s) of interest	Age, family history of cancer, racial background
Duration of follow-up	None
Setting	Gene panel testing
Sources of funding	Not reported
Other information	For results, please see Appendix L

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Song, 2021

Bibliographic Reference	Song, Honglin; Dicks, Ed M; Tyrer, Jonathan; Intermaggio, Maria; Chenevix-Trench, Georgia; Bowtell, David D; Traficante, Nadia; Group, Aocs; Brenton, James; Goranova, Teodora; Hosking, Karen; Piskorz, Anna; van Oudenhove, Elke; Doherty, Jen; Harris, Holly R; Rossing, Mary Anne; Duerst, Matthias; Dork, Thilo; Bogdanova, Natalia V; Modugno, Francesmary; Moysich, Kirsten; Odunsi, Kunle; Ness, Roberta; Karlan, Beth Y; Lester, Jenny; Jensen, Allan; Kruger Kjaer, Susanne; Hogdall, Estrid; Campbell, Ian G; Lazaro, Conxi; Pujara, Miguel Angel; Cunningham, Julie; Vierkant, Robert; Winham, Stacey J; Hildebrandt, Michelle; Huff, Chad; Li, Donghui; Wu, Xifeng; Yu, Yao; Permuth, Jennifer B; Levine, Douglas A; Schildkraut, Joellen M; Riggan, Marjorie J; Berchuck, Andrew; Webb, Penelope M; Group, Opal Study; Cybulski, Cezary; Gronwald, Jacek; Jakubowska, Anna; Lubinski, Jan; Alsop, Jennifer; Harrington, Patricia; Chan, Isaac; Menon, Usha; Pearce, Celeste L; Wu, Anna H; de Fazio, Anna; Kennedy, Catherine J; Goode, Ellen; Ramus, Susan; Gayther, Simon; Pharoah, Paul; Population-based targeted sequencing of 54 candidate genes identifies PALB2 as a susceptibility gene for high-grade serous ovarian cancer.; Journal of medical genetics; 2021; vol. 58 (no. 5); 305-313

Study details

Country/ies where study was carried out	UK
Study type	Case-control study
Study dates	Not reported. Before 2019

Inclusion criteria	Sequencing of the coding region of 54 candidate genes: 5914 epithelial ovarian cancer cases and 5479 controls of European ancestries from 19 studies were included. High grade serous ovarian cancer cases were preferentially plated out for sequencing where possible. Validation of genes identified at an increased frequency of putative deleterious variants was then performed in an independent dataset consisting of 14,135 epithelial ovarian cancer cases and 28,655 and controls from the Ovarian Cancer Association Consortium and the UK Biobank. *These are the data reported here.*
Exclusion criteria	<80% of the target sequence bases had a read depth of at least 15
Patient characteristics	Cases OCAC: N=13,277 UK Biobank: N=858 **Age, mean (range) years:** Not reported for validation cohort **Epithelial ovarian cancer, %:** 100 **Peutz Jeghers syndrome, %:** 0 **Small cell ovarian cancers, %:** 0 ***DICER1* tumours, %:** 0 **Baseline prevalence of pathogenic variants:** Women with epithelial ovarian cancer **Ethnicity:** Not reported Controls

	OCAC: N=18,930 UK Biobank: N=9,725 **Age, mean (range) years:** Not reported for validation cohort **Epithelial ovarian cancer, %:** 0 **Peutz Jeghers syndrome, %:** 0 **Small cell ovarian cancers, %:** 0 ***DICER1* tumours, %:** 0 **Baseline prevalence of pathogenic variants:** General population **Ethnicity:** Not reported
Risk factor(s) of interest	Presence of pathogenic variant
Confounding factor(s) of interest	Age, race, family history
Duration of follow-up	None
Setting	Genetic testing
Sources of funding	American Cancer Society, Cancer Councils of New South Wales, Victoria, Queensland, South Australia and Tasmania, Cancer Foundation of Western Australia, Cancer Institute NSW, Cancer Research UK, Cambridge Cancer Centre, Kræftens Bekæmpelse, Medical Research Council, U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, U.S. Department of Health and Human Services, National Institutes of Health, National Center for Advancing Translational Sciences, National Health and Medical Research Council of Australia, National Institutes of Health Research,Cambridge Biomedical Research Centre, University College London Hospitals Biomedical Research Centre, The Eve Appeal, UKOPS Study, U.S. Army Medical Research and Materiel Command, U.S Department of Defense, Ovarian Cancer Research Program. The University of Cambridge has received salary support in respect of

	PDPP from the NHS in the East of England through the Clinical Academic Reserve. One author is a recipient of the Barth Family Chair in Cancer Genetics.
Other information	For results, please see Appendix L

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias (*Method used to identify population is not directly reported, only through reference to other studies. Recruitment period and ethnicity not reported)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Ethnicity not reported)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate (*Method used to identify population is not directly reported, only through reference to other studies. Recruitment period and ethnicity not reported*)
Overall risk of bias and directness	Directness	Directly applicable

Suszynska, 2019

Bibliographic Reference	Suszynska, M; Klonowska, K; Jasinska, AJ; Kozlowski, P; Large-scale meta-analysis of mutations identified in panels of breast/ovarian cancer-related genes - Providing evidence of cancer predisposition genes.; Gynecologic oncology; 2019; vol. 153 (no. 2); 452-462

Study details

Country/ies where study was carried out	International
Study type	Systematic review
Study dates	Until July 2017
Inclusion criteria	Ovarian and breast cancer patients and multi-gene panels as a mutation detection method. The systematic review included unselected breast cancer and ovarian cancer studies that were not restricted to only high-risk individuals (familial, bilateral, or early-onset breast cancer). Control data from the public database were not perfectly matched in terms of sex, age, ethnicity, geographical area or sequencing platforms to the case groups.
Exclusion criteria	Studies concerning only the BRCA1/2 genes.
Patient characteristics	N= Up to 7099 cases depending on pathological variant from 48 studies **Age, mean (SD) years:** Not reported **Epithelial ovarian cancer, %:** Not reported **Peutz Jeghers syndrome, %:** Not reported **Small cell ovarian cancers, %:** Not reported ***DICER1* tumours, %:** Not reported

	Baseline prevalence of pathogenic variants: Women with breast or ovarian cancer **Ethnicity:** Not reported N= Not reported **Age, mean (SD) years:** Not reported **Epithelial ovarian cancer, %:** not reported **Peutz Jeghers syndrome, %:** Not reported **Small cell ovarian cancers, %:** Not reported ***DICER1* tumours, %:** Not reported **Baseline prevalence of pathogenic variants:** Women with breast or ovarian cancer **Ethnicity:** Not reported
Risk factor(s) of interest	Presence of pathogenic variants
Confounding factor(s) of interest	Not reported
Duration of follow-up	N/A
Setting	Multiple, genetic testing
Sources of funding	Polish National Science Centre
Other information	For results, please see Appendix L

Critical appraisal - NGA Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Unclear *(The eligibility criteria were not described in great detail.)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(Only PubMed searched)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	High *(Unclear how data extraction was undertaken, no risk of bias assessment of included studies)*
Synthesis and findings	Concerns regarding the synthesis and findings	High *(Risk of bias in included studies not addressed in analysis)*
Overall study ratings	Overall risk of bias	High *(High risk of bias in 3 domains)*
Overall study ratings	Applicability as a source of data	Fully applicable

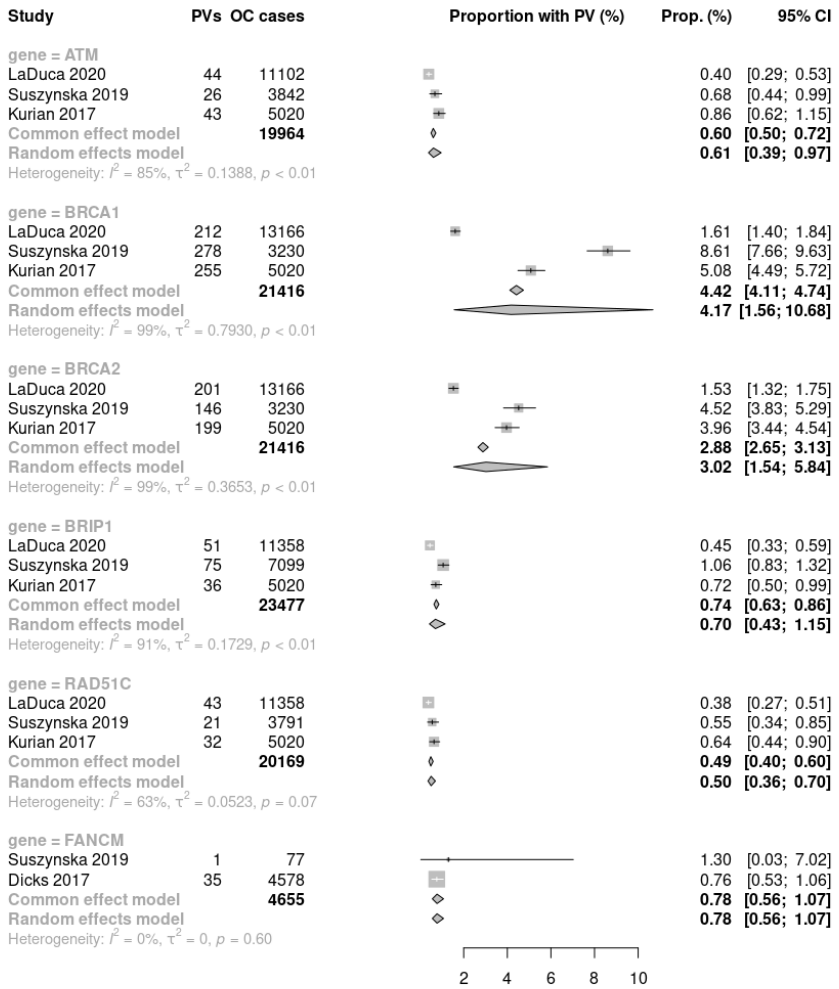
Appendix E Forest plots

Forest plots for review question: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

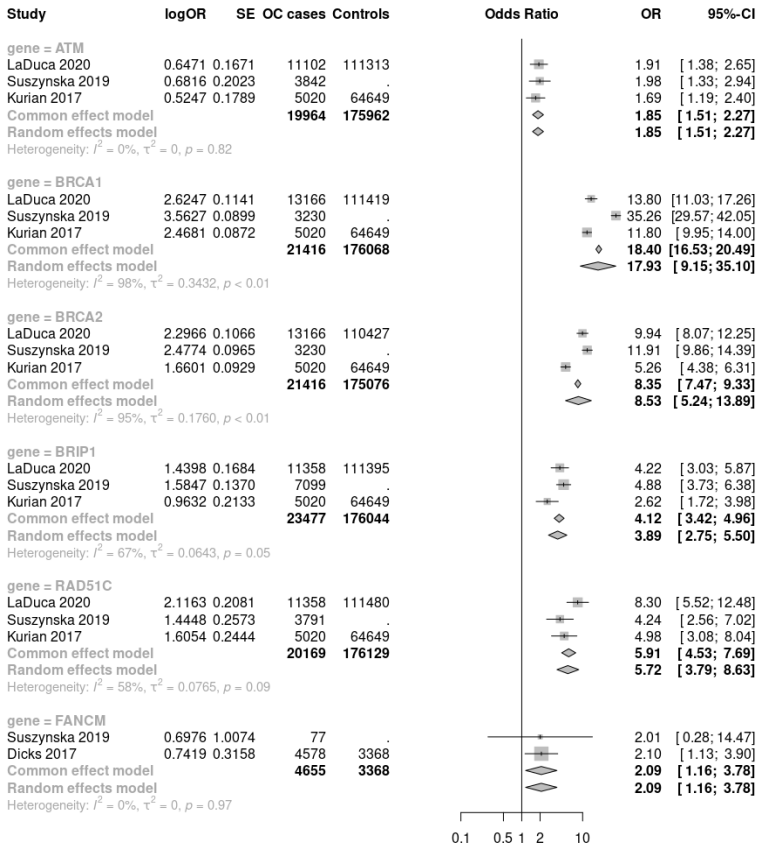
Please note that although some individual studies observed pathological variant prevalences slightly outside the prevalence categories below, the evidence is summarised according to the mean pooled prevalence of the pathological variant in ovarian cancer cases.

Figure 2: Pathological variants with prevalence of 0.5% or greater in ovarian cancer cases



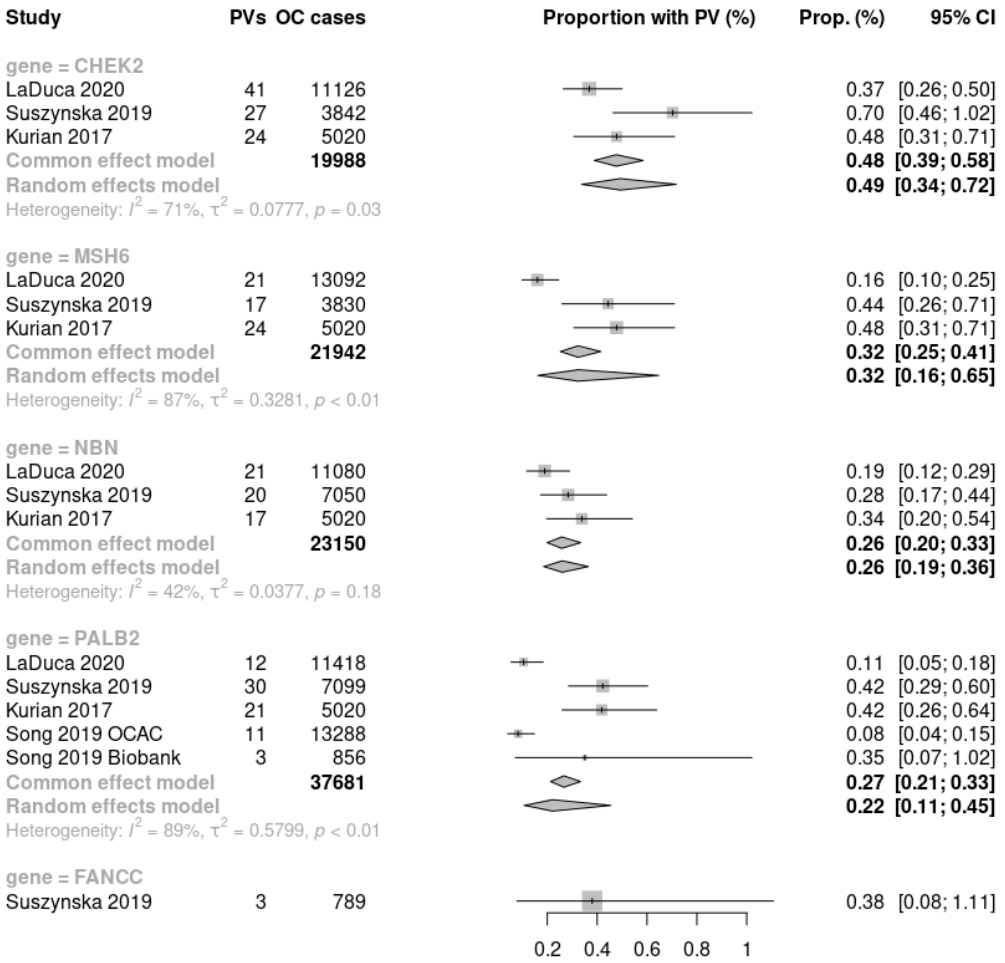
CI: confidence interval; OC: ovarian cancer; PV: pathological variant

Figure 3: Gene specific cancer associations for pathological variants with prevalence of 0.5% or greater in ovarian cancer cases



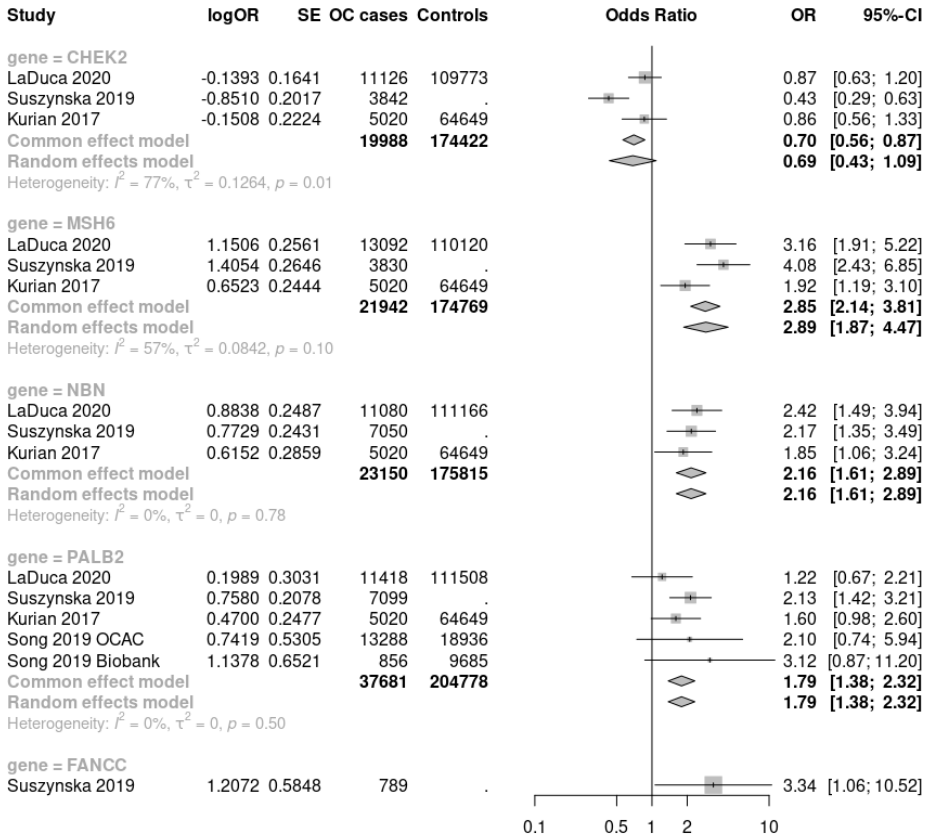
CI: confidence interval; OC: ovarian cancer; OR: odds ratio; SE: standard error

Figure 4: Pathological variants with prevalence of 0.2% to 0.5% in ovarian cancer cases



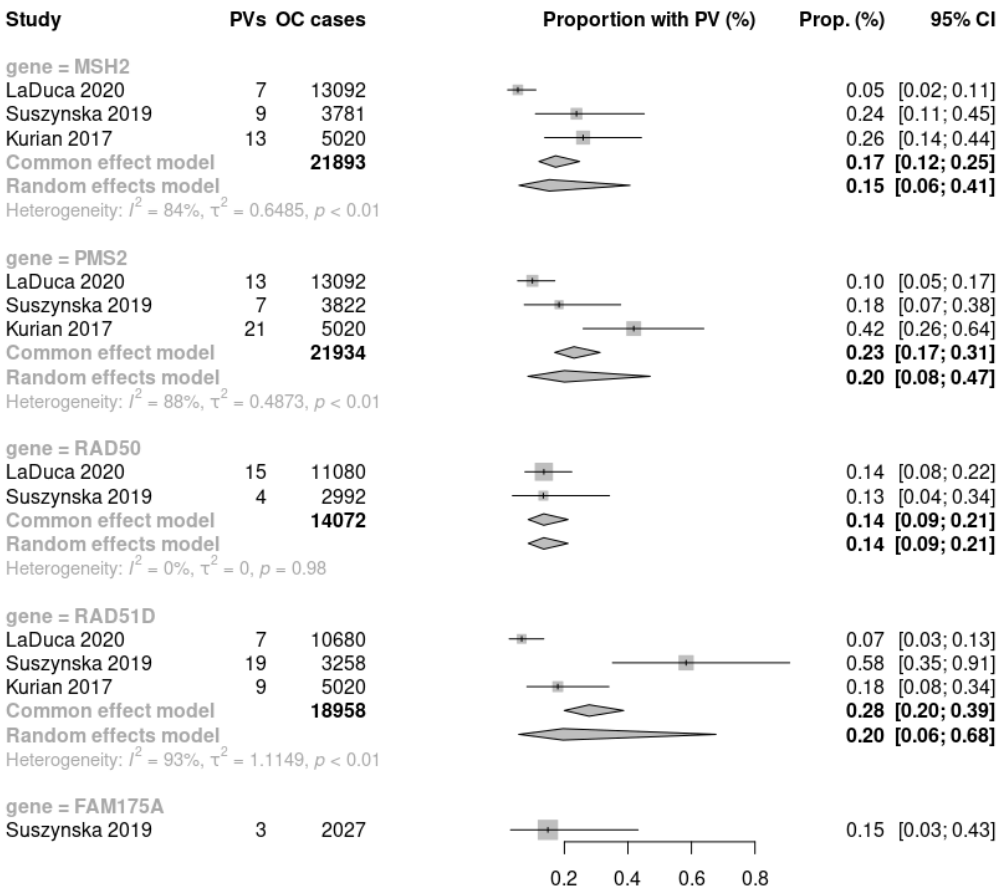
CI: confidence interval; OC: ovarian cancer; PV: pathological variant

Figure 5: Gene specific cancer associations for pathological variants with prevalence of >0.2% to <0.5% in ovarian cancer cases



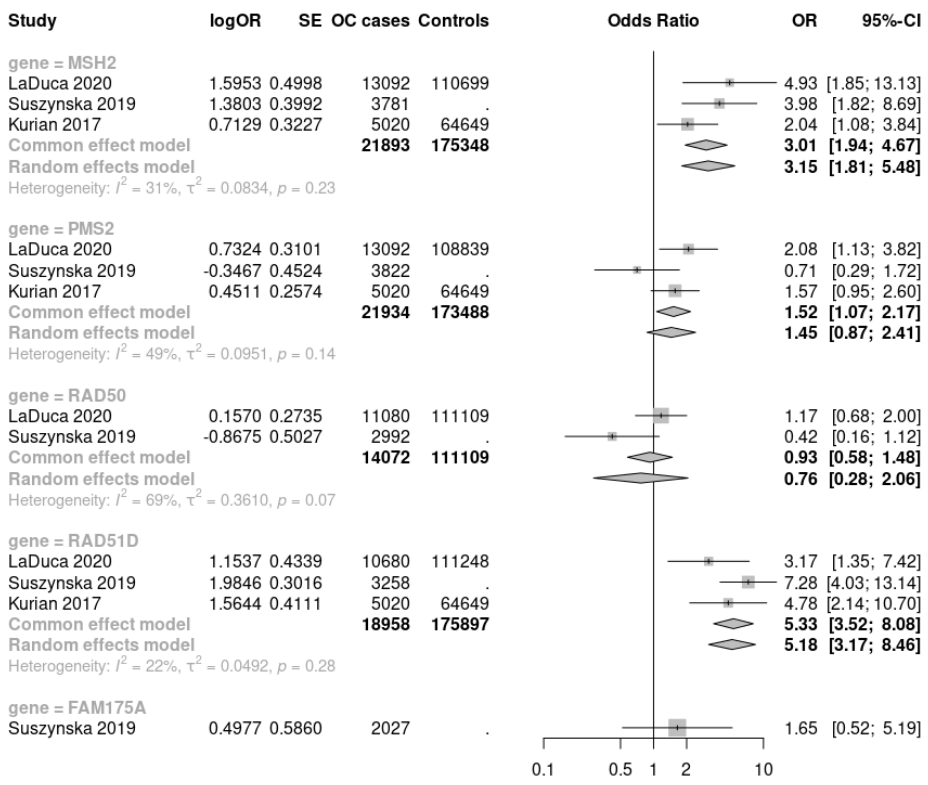
CI: confidence interval; OC: ovarian cancer; OR: odds ratio; SE: standard error

Figure 6: Pathological variants with prevalence of 0.1% to 0.2% in ovarian cancer cases



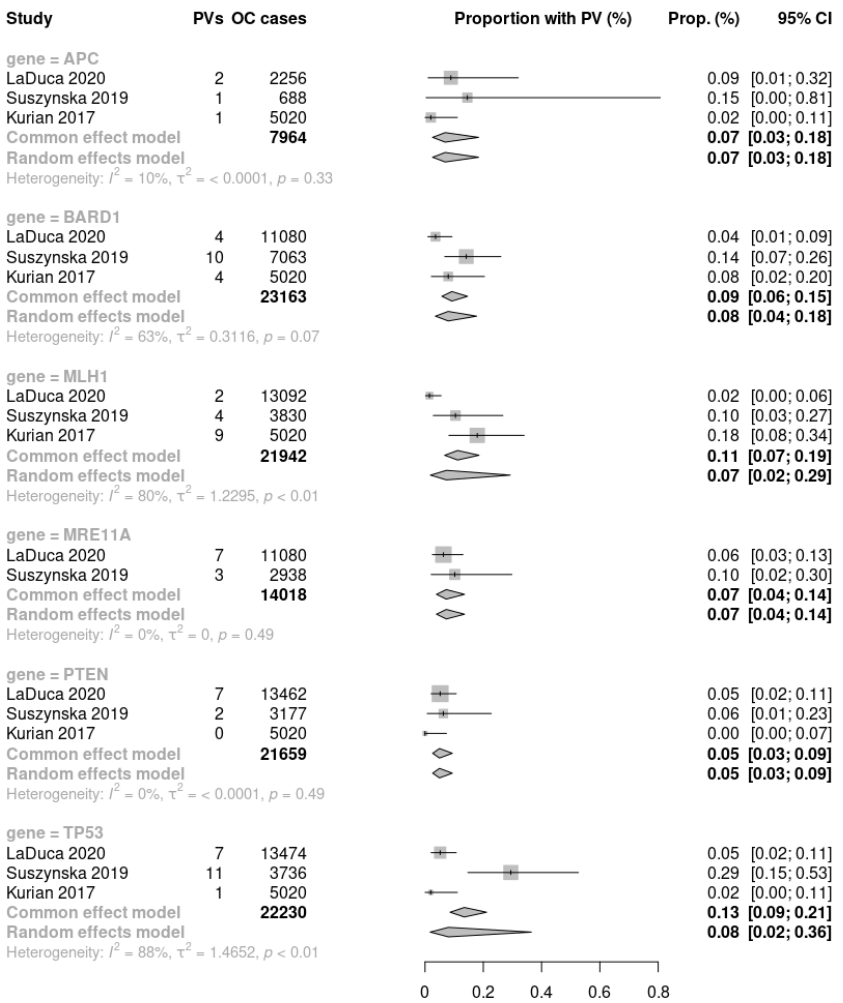
CI: confidence interval; OC: ovarian cancer; PV: pathological variant

Figure 7: Gene specific cancer associations for pathological variants with prevalence of 0.1% to 0.2% in ovarian cancer cases



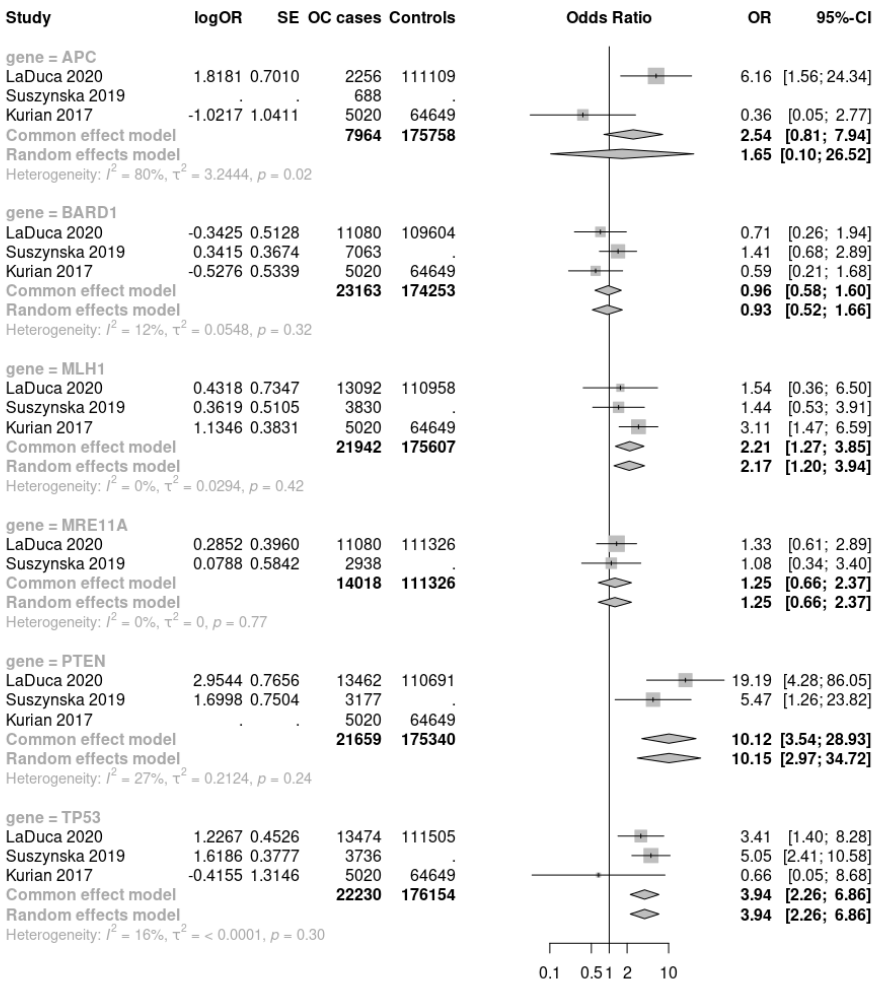
CI: confidence interval; OC: ovarian cancer; OR: odds ratio; SE: standard error

Figure 8: Pathological variants with prevalence of >0% to 0.1% in ovarian cancer cases



CI: confidence interval; OC: ovarian cancer; PV: pathological variant

Figure 9: Gene specific cancer associations for pathological variants with prevalence of >0% to 0.1% or greater in ovarian cancer cases



CI: confidence interval; OC: ovarian cancer; OR: odds ratio; SE: standard error

Appendix F GRADE tables

GRADE tables for review question: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

Please note that although some individual studies observed pathological variant prevalences slightly outside the prevalence categories below, the evidence is summarised according to the mean pooled prevalence of the pathological variant in ovarian cancer cases.

Table 4: Gene specific cancer associations for pathological variants with prevalence of 0.5% or greater in ovarian cancer cases

No. of studies	Study design	No. Cases (PV prevalence)	No. Controls	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
***ATM* association with ovarian cancer**										
3[1]	Case-control	113/19964 (0.40% to 0.86%)	175962[2]	OR 1.85 (1.51 to 2.27)	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL
***BRCA1* association with ovarian cancer**										
3[1]	Case-control	745/21416 (1.61% to 8.61%)	176068[2]	ORs ranged from 11.80 to 35.26	Serious[3]	Very serious inconsistency[4]	No serious indirectness	No serious imprecision	VERY LOW	CRITICAL
***BRCA2* association with ovarian cancer**										
3[1]	Case-control	546/21416 (1.53% to 4.52%)	175076[2]	ORs ranged from 5.26 to 11.91	Serious[3]	Very serious inconsistency[4]	No serious indirectness	No serious imprecision	VERY LOW	CRITICAL
***BRIP1* association with ovarian cancer**										
3[1]	Case-control	162/23477 (0.45% to 1.46%)	176044[2]	OR 3.89 (2.75 to 5.50)	Serious[3]	Serious inconsistency[5]	No serious indirectness	No serious imprecision	LOW	CRITICAL
***RAD51C* association with ovarian cancer**										
3[1]	Case-control	96/20169 (0.38% to 0.64%)	176129[2]	OR 5.72 (3.79 to 8.63)	Serious[3]	Serious inconsistency[5]	No serious indirectness	No serious imprecision	LOW	CRITICAL
***FANCM* association with ovarian cancer**										
2[6]	Case-control	36/4655 (0.76% to 1.30%)	3368[2]	OR 2.09 (1.16 to 3.78)	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	LOW	CRITICAL

CI: confidence interval; OR: odds ratio; PV: pathological variant
1 LaDuca 2020, Suszynska 2019, Kurian 2017
2 Number of controls not reported in Suszynska 2019
3 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS/ROBIS
4 Very serious heterogeneity unexplained by subgroup analysis
5 Serious heterogeneity unexplained by subgroup analysis
6 Susynska 2019, Dicks 2017
7 95% CI crosses 1 MID

Table 5: Gene specific cancer associations for pathological variants with prevalence of >0.2% to <0.5% in ovarian cancer cases

No. of studies	Study design	No. Cases (PV prevalence)	No. Controls	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
***CHEK2* association with ovarian cancer**										
3[1]	Case-control	92/19988 (0.37% to 0.70%)	174422[2]	OR 0.69 (0.43 to 1.09)	Serious[3]	Serious inconsistency[4]	No serious indirectness	Serious imprecision[5]	VERY LOW	CRITICAL
***MSH6* association with ovarian cancer**										
3[1]	Case-control	62/21942 (0.16% to 0.48%)	174769[2]	OR 2.89 (1.87 to 4.47)	Serious[3]	Serious inconsistency[5]	No serious indirectness	No serious imprecision	LOW	CRITICAL
***NBN* association with ovarian cancer**										
3[1]	Case-control	58/23150 (0.19% to 0.34%)	175815[2]	OR 2.16 (1.61 to 2.89)	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL
***PALB2* association with ovarian cancer**										
4[6]	Case-control	77/37681 (0.08% to 0.42%)	204778[2]	OR 1.79 (1.38 to 2.32)	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL
***FANCC* association with ovarian cancer**										
Suszynska 2019	Case-control	3/789 (0.38%)	789[2]	OR 3.34 (1.06 to 10.52)	Serious[3]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	LOW	CRITICAL

CI: confidence interval; OR: odds ratio; PV: pathological variant
1 LaDuca 2020, Suszynska 2019, Kurian 2017
2 Number of controls not reported in Suszynska 2019
3 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS /ROBIS
4 Serious heterogeneity unexplained by subgroup analysis
5 95% CI crosses 1 MID
6 LaDuca 2020, Suszynska 2019, Kurian 2017, Song 2019 (OCAC and Biobank datasets)

Table 6: Gene specific cancer associations for pathological variants with prevalence of 0.1% to 0.2% in ovarian cancer cases

No. of studies	Study design	No. Cases (PV prevalence)	No. Controls	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
***MSH2* association with ovarian cancer**										
3[1]	Case-control	29/21893 (0.05% to 0.26%)	175348[2]	OR 3.01 (1.94 to 4.67)	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL
***PMS2* association with ovarian cancer**										
3[1]	Case-control	41/21934 (0.10% to 0.42%)	173488[2]	OR 1.52 (1.07 to 2.17)	Serious[3]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	LOW	CRITICAL

No. of studies	Study design	No. Cases (PV prevalence)	No. Controls	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
***RAD50* association with ovarian cancer**										
2[5]	Case-control	19/14072 (0.13% to 0.14%)	111109[2]	OR 0.76 (0.28 to 2.06)	Serious[3]	Serious inconsistency[6]	No serious indirectness	Very serious imprecision[7]	VERY LOW	CRITICAL
***RAD51D* association with ovarian cancer**										
3[1]	Case-control	35/18958 (0.07% to 0.58%)	175897[2]	OR 5.33 (3.52 to 8.08)	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL
***FAM175A* association with ovarian cancer**										
Suszynska 2019	Case-control	3/2027 (0.15%)	Not reported[2]	OR 1.65 (0.52 to 5.19)	Serious[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[7]	VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; PV: pathological variant
1 LaDuca 2020, Suszynska 2019, Kurian 2017
2 Number of controls not reported in Suszynska 2019
3 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS/ROBIS
4 95% CI crosses 1 MID
5 LaDuca 2020, Suszynska 2019
6 Serious heterogeneity unexplained by subgroup analysis
7 95% CI crosses 2 MIDs

Table 7: Gene specific cancer associations for pathological variants with prevalence of >0% to 0.1% or greater in ovarian cancer cases

No. of studies	Study design	No. Cases (PV prevalence)	No. Controls	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
***APC* association with ovarian cancer**										
3[1]	Case-control	4/7964 (0.02% to 0.15%)	175758[2]	ORs ranged from 0.36 to 6.16	Serious[3]	Very serious inconsistency[4]	No serious indirectness	Very serious imprecision[5]	VERY LOW	CRITICAL
***BARD1* association with ovarian cancer**										
3[1]	Case-control	18/23163 (0.04% to 0.14%)	174253[2]	OR 0.96 (0.58 to 1.60)	Serious[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[5]	VERY LOW	CRITICAL
***MLH1* association with ovarian cancer**										
3[1]	Case-control	15/21942 (0.02% to 0.18%)	175607[2]	OR 2.21 (1.27 to 3.85)	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL
***MRE11A* association with ovarian cancer**										
2[6]	Case-control	10/14018 (0.06% to 0.10%)	111326[2]	OR 1.25 (0.66 to 2.37)	Serious[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[5]	VERY LOW	CRITICAL
***PTEN* association with ovarian cancer**										
3[1]	Case-control	9/21659 (0.00% to 0.06%)	175340[2]	OR 10.12 (3.54 to 28.93)	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL

No. of studies	Study design	No. Cases (PV prevalence)	No. Controls	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
***TP53* association with ovarian cancer**										
3[1]	Case-control	19/22230 (0.02% to 0.29%)	176154[2]	OR 3.94 (2.26 to 6.86)	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL

CI: confidence interval; OR: odds ratio
1 LaDuca 2020, Suszynska 2019, Kurian 2017
2 Number of controls not reported in Suszynska 2019
3 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS/ROBIS
4 Very serious heterogeneity unexplained by subgroup analysis
5 95% CI crosses 2 MIDs
6 LaDuca 2020, Suszynska 2019

Table 8: Gene specific cancer associations for other pathological variants in ovarian cancer cases

No. of studies	Study design	No. Cases (PV prevalence)	No. Controls	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
***ATR* association with ovarian cancer**										
Suszynska 2019	Case-control	0/160	N/A[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***BAP1* association with ovarian cancer**										
Suszynska 2019	Case-control	0/508	N/A[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***BLM* association with ovarian cancer**										
Suszynska 2019	Case-control	0/85	N/A[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***BMPR1A* association with ovarian cancer**										
2[3]	Case-control	0/5659	64649[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***CDK4* association with ovarian cancer**										
2[3]	Case-control	0/5659	64649[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***EPCAM* association with ovarian cancer**										
Suszynska 2019	Case-control	0/836	N/A[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***P14ARF* association with ovarian cancer**										
2[3]	Case-control	0/5020	64649	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***SLX4* association with ovarian cancer**										

No. of studies	Study design	No. Cases (PV prevalence)	No. Controls	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Suszynska 2019	Case-control	0/1992	N/A[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***STK11* association with ovarian cancer**										
2[3]	Case-control	2/6233	64649[1]	OR 41.9 (5.55 to 315)	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	MODERATE	CRITICAL
***VHL* association with ovarian cancer**										
Suszynska 2019	Case-control	0/514	N/A[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***XRCC2* association with ovarian cancer**										
Suszynska 2019	Case-control	0/175	N/A[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***CDH1* association with ovarian cancer**										
3[4]	Case-control	1/17625	173842[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
CDKN2A association with ovarian cancer										
3[4]	Case-control	2/7846	168938[1]	Not calculable	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL
***MUTYH* association with ovarian cancer**										
2[3]	Case-control	1/5020	64649	OR 0.4 (0.05 to 3.26)	Serious[2]	No serious inconsistency	No serious indirectness	Very serious imprecision[7]	VERY LOW	CRITICAL
***NF1* association with ovarian cancer**										
2[5]	Case-control	2/10439	11100[1]	OR 1.7 (0.18 to 4.38)	Serious[2]	No serious inconsistency	No serious indirectness	Very serious imprecision[7]	VERY LOW	CRITICAL
***SMAD4* association with ovarian cancer**										
2[3]	Case-control	0/5658	64649[1]	N/A	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	LOW	CRITICAL

CI; confidence interval; OR: odds ratio
1 Number of controls not reported in Suszynska 2019
2 Serious risk of bias in the evidence contributing to the outcomes as per QUIPS/ROBIS
3 Suszynska 2019, Kurian 2017
4 LaDuca 2020, Suszynska 2019, Kurian 2017
5 LaDuca 2020, Suszynska 2019
6 95% CI of effect not estimable
7 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

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

Appendix H Economic evidence tables

Economic evidence tables for review question: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

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

Appendix I Economic model

Economic model for review question: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

Excluded prognostic studies

Table 9: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Akbari, Mohammad R, Lepage, Pierre, Rosen, Barry et al. (2014) PPM1D mutations in circulating white blood cells and the risk for ovarian cancer. Journal of the National Cancer Institute 106(1): djt323	- Study design does not match that specified in this review protocol
Arcand, Suzanna L, Provencher, Diane, Mes-Masson, Anne-Marie et al. (2005) OGG1 Cys326 variant, allelic imbalance of chromosome band 3p25.3 and TP53 mutations in ovarian cancer. International journal of oncology 27(5): 1315-20	- Study design does not match that specified in this review protocol
Azribi, Fathi, Abdou, Ehab, Dawoud, Emad et al. (2021) Prevalence of BRCA1 and BRCA2 pathogenic sequence variants in ovarian cancer patients in the Gulf region: the PREDICT study. BMC cancer 21(1): 1350	- Data not reported in an extractable format or a format that can be analysed
Bjorge, T, Lie, A K, Hovig, E et al. (2004) BRCA1 mutations in ovarian cancer and borderline tumours in Norway: a nested case-control study. British journal of cancer 91(10): 1829-34	- Study design does not match that specified in this review protocol
Bonache, Sandra, Esteban, Irene, Moles-Fernandez, Alejandro et al. (2018) Multigene panel testing beyond BRCA1/2 in breast/ovarian cancer Spanish families and clinical actionability of findings. Journal of cancer research and clinical oncology 144(12): 2495-2513	- Population in study does not match that specified in this review protocol
Bono, M., Fanale, D., Incorvaia, L. et al. (2021) Impact of deleterious variants in other genes beyond BRCA1/2 detected in breast/ovarian and pancreatic cancer patients by NGS-based multi-gene panel testing: looking over the hedge. ESMO Open 6(4): 100235	- Data not reported in an extractable format or a format that can be analysed
Chen, Sining and Parmigiani, Giovanni (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 25(11): 1329-33	- Narrative review
Chu, DT, Vu Ngoc Suong, M, Vu Thi, H et al. (2023) The expression and mutation of BRCA1/2 genes in ovarian cancer: a global systematic study. Expert review of molecular diagnostics	- Study design does not match that specified in this review protocol
Corso, G, Feroce, I, Intra, M et al. (2018) BRCA1/2 germline missense mutations: a systematic review. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 27(3): 279-286	- Study design does not match that specified in this review protocol
Cummings, Shelly, Alfonso, Andrew, Hughes, Elisha et al. (2023) Cancer Risk Associated With PTEN Pathogenic Variants Identified Using Multigene Hereditary Cancer Panel Testing. JCO precision oncology 7: e2200415	- Population in study does not match that specified in this review protocol
Cummings, Shelly, Roman, Susana San, Saam, Jennifer et al. (2021) Age of ovarian cancer diagnosis among BRIP1, RAD51C, and RAD51D mutation carriers identified through multi-gene panel testing. Journal of ovarian research 14(1): 61	- Population in study does not match that specified in this review protocol

Study	Code [Reason]
Cury, Nathalia M; Ferraz, Victor Ef; Silva, Wilson A Jr (2014) TP53 p.R337H prevalence in a series of Brazilian hereditary breast cancer families. Hereditary cancer in clinical practice 12(1): 8	- Population in study does not match that specified in this review protocol
da Costa E Silva Carvalho, Simone, Cury, Nathalia Moreno, Brotto, Danielle Barbosa et al. (2020) Germline variants in DNA repair genes associated with hereditary breast and ovarian cancer syndrome: analysis of a 21 gene panel in the Brazilian population. BMC medical genomics 13(1): 21	- Population in study does not match that specified in this review protocol
Desmond, Andrea, Kurian, Allison W, Gabree, Michele et al. (2015) Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment. JAMA oncology 1(7): 943-51	- Population in study does not match that specified in this review protocol
Dominguez-Valentin, Mev, Sampson, Julian R, Seppala, Toni T et al. (2020) Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genetics in medicine : official journal of the American College of Medical Genetics 22(1): 15-25	- Population in study does not match that specified in this review protocol
Edwinsdotter Ardnor, Christina, Rosen, Anna, Ljuslinder, Ingrid et al. (2019) The BRCA1 exon 13 duplication: clinical characteristics of 22 families in Northern Sweden. Familial cancer 18(1): 37-42	- Study design does not match that specified in this review protocol
Engel, Christoph, Loeffler, Markus, Steinke, Verena et al. (2012) Risks of less common cancers in proven mutation carriers with lynch syndrome. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30(35): 4409-15	- Data not reported in an extractable format or a format that can be analysed
Farra, Chantal, Dagher, Christelle, Hamadeh, Lama et al. (2019) BRCA mutations in a cohort of Iraqi patients presenting to a tertiary referral center. BMC medical genetics 20(1): 154	- Data not reported in an extractable format or a format that can be analysed
Felicio, Paula S, Grasel, Rebeca S, Campacci, Natalia et al. (2021) Whole-exome sequencing of non-BRCA1/BRCA2 mutation carrier cases at high-risk for hereditary breast/ovarian cancer. Human mutation 42(3): 290-299	- Data not reported in an extractable format or a format that can be analysed
Foglietta, Jennifer, Ludovini, Vienna, Bianconi, Fortunato et al. (2020) Prevalence and Spectrum of BRCA Germline Variants in Central Italian High Risk or Familial Breast/Ovarian Cancer Patients: A Monocentric Study. Genes 11(8)	- Population in study does not match that specified in this review protocol
Frank, T S, Manley, S A, Olopade, O I et al. (1998) Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 16(7): 2417-25	- Data not reported in an extractable format or a format that can be analysed
Gansmo, Liv B, Bjornslett, Merete, Halle, Mari Kylleso et al. (2016) The MDM4 SNP34091 (rs4245739) C-allele is associated with increased risk of ovarian-but not endometrial cancer. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine 37(8): 10697-702	- Study design does not match that specified in this review protocol
Han, Fei-fei; Guo, Chang-long; Liu, Li-hong (2013) The effect of CHEK2 variant I157T on cancer susceptibility: evidence from a meta-analysis. DNA and cell biology 32(6): 329-35	- Narrative review
Ingham, Sarah Louise, Warwick, Jane, Buchan, Iain et al. (2013) Ovarian cancer among 8,005 women from a breast cancer family history clinic: no increased risk of invasive	- Population in study does not match that specified in this review protocol

Study	Code [Reason]
ovarian cancer in families testing negative for BRCA1 and BRCA2. Journal of medical genetics 50(6): 368-72	
Jafrin, Sarah; Aziz, Md Abdul; Islam, Mohammad Safiqul (2022) Association between TP73 G4C14-A4T14 polymorphism and different cancer types: an updated meta-analysis of 55 case-control studies. The Journal of international medical research 50(10): 3000605221133173	- Narrative review
Janatova, Marketa, Soukupova, Jana, Stribrna, Jana et al. (2015) Mutation Analysis of the RAD51C and RAD51D Genes in High-Risk Ovarian Cancer Patients and Families from the Czech Republic. PloS one 10(6): e0127711	- Data not reported in an extractable format or a format that can be analysed
Janssen, Boris, Bellis, Sarah, Koller, Thomas et al. (2020) A systematic review of predicted pathogenic PALB2 variants: an analysis of mutational overlap between epithelial cancers. Journal of human genetics 65(2): 199-205	- Study design does not match that specified in this review protocol
Kluska, Anna, Balabas, Aneta, Piatkowska, Magdalena et al. (2017) PALB2 mutations in BRCA1/2-mutation negative breast and ovarian cancer patients from Poland. BMC medical genomics 10(1): 14	- Data not reported in an extractable format or a format that can be analysed
Kowalik, Artur, Siolek, Monika, Kopczynski, Janusz et al. (2018) BRCA1 founder mutations and beyond in the Polish population: A single-institution BRCA1/2 next-generation sequencing study. PloS one 13(7): e0201086	- Study design does not match that specified in this review protocol
Kuchenbaecker, Karoline B, Hopper, John L, Barnes, Daniel R et al. (2017) Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA 317(23): 2402-2416	- Population in study does not match that specified in this review protocol
Kuusisto, Kirsi M, Bebel, Aleksandra, Vihinen, Mauno et al. (2011) Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals. Breast cancer research : BCR 13(1): r20	- Population in study does not match that specified in this review protocol
Kwong, Ava, Shin, Vivian Y, Au, Chun H et al. (2016) Detection of Germline Mutation in Hereditary Breast and/or Ovarian Cancers by Next-Generation Sequencing on a Four-Gene Panel. The Journal of molecular diagnostics : JMD 18(4): 580-94	- Systematic review used as source of primary studies
Lee, K, Seifert, BA, Shimelis, H et al. (2019) Clinical validity assessment of genes frequently tested on hereditary breast and ovarian cancer susceptibility sequencing panels. Genetics in medicine : official journal of the American College of Medical Genetics 21(7): 1497-1506	- Population in study does not match that specified in this review protocol
Li W, Shao D, Li L et al. (2019) Germline and somatic mutations of multi-gene panel in Chinese patients with epithelial ovarian cancer: a prospective cohort study. Journal of ovarian research 12(1): 80	- Population in study does not match that specified in this review protocol
Li, A, Xie, R, Zhi, Q et al. (2018) BRCA germline mutations in an unselected nationwide cohort of Chinese patients with ovarian cancer and healthy controls. Gynecologic oncology 151(1): 145-152	- Study design does not match that specified in this review protocol
Li, Qiuyan, Guan, Rongwei, Qiao, Yuandong et al. (2017) Association between the BRCA2 rs144848 polymorphism and cancer susceptibility: a meta-analysis. Oncotarget 8(24): 39818-39832	- Narrative review
Lilyquist, Jenna, LaDuca, Holly, Polley, Eric et al. (2017) Frequency of mutations in a large series of clinically	- Considerable overlap of population with another included study

Study	Code [Reason]
ascertained ovarian cancer cases tested on multi-gene panels compared to reference controls. Gynecologic oncology 147(2): 375-380	*Overlap with LaDuca 2020: cases from Ambry Genetics Lab*
Lu, Hsiao-Mei, Li, Shuwei, Black, Mary Helen et al. (2019) Association of Breast and Ovarian Cancers With Predisposition Genes Identified by Large-Scale Sequencing. JAMA oncology 5(1): 51-57	- Considerable overlap of population with another included study *Cases come from Ambry Genetics Lab - overlap with LaDuca 2020*
Maksimenko, J, Irmejs, A, Trofimovics, G et al. (2018) High frequency of pathogenic non-founder germline mutations in BRCA1 and BRCA2 in families with breast and ovarian cancer in a founder population. Hereditary cancer in clinical practice 16: 12	- Data not reported in an extractable format or a format that can be analysed
Malander, Susanne, Rambech, Eva, Kristoffersson, Ulf et al. (2006) The contribution of the hereditary nonpolyposis colorectal cancer syndrome to the development of ovarian cancer. Gynecologic oncology 101(2): 238-43	- Data not reported in an extractable format or a format that can be analysed
Maleva Kostovska, Ivana, Wang, Jing, Bogdanova, Natalia et al. (2016) Rare ATAD5 missense variants in breast and ovarian cancer patients. Cancer letters 376(1): 173-7	- Study design does not match that specified in this review protocol
Manchana, Tarinee; Phowthongkum, Prasit; Teerapakpinyo, Chinachote (2019) Germline mutations in Thai patients with nonmucinous epithelial ovarian cancer. World journal of clinical oncology 10(11): 358-368	- Population in study does not match that specified in this review protocol
Marouf, Chaymaa, Hajji, Omar, Diakite, Brehima et al. (2015) The CHEK2 1100delC allelic variant is not present in familial and sporadic breast cancer cases from Moroccan population. SpringerPlus 4: 38	- Population in study does not match that specified in this review protocol
Miresmaeili, SM, Kordi Tamandani, DM, Kalantar, SM et al. (2016) Haplotype analysis of BRCA1 intragenic markers in Iranian patients with familial breast and ovarian cancer. International journal of reproductive biomedicine 14(4): 271-4	- Population in study does not match that specified in this review protocol
Modan, B, Gak, E, Sade-Bruchim, RB et al. (1996) High frequency of BRCA1 185delAG mutation in ovarian cancer in Israel. National Israel Study of Ovarian Cancer. JAMA 276(22): 1823-5	- Study design does not match that specified in this review protocol
Momozawa, Yukihide, Sasai, Rumi, Usui, Yoshiaki et al. (2022) Expansion of Cancer Risk Profile for BRCA1 and BRCA2 Pathogenic Variants. JAMA oncology 8(6): 871-878	- Study design does not match that specified in this review protocol
Morari, Elaine Cristina, Lima, Andre Bacellar Costa, Bufalo, Natassia Elena et al. (2006) Role of glutathione-S-transferase and codon 72 of P53 genotypes in epithelial ovarian cancer patients. Journal of cancer research and clinical oncology 132(8): 521-8	- Study design does not match that specified in this review protocol
Moslehi, R, Chu, W, Karlan, B et al. (2000) BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. American journal of human genetics 66(4): 1259-72	- Outcomes in study do not match those specified in this review protocol
Muto, M G, Cramer, D W, Tangir, J et al. (1996) Frequency of the BRCA1 185delAG mutation among Jewish women with ovarian cancer and matched population controls. Cancer research 56(6): 1250-2	- Study design does not match that specified in this review protocol
Norquist, Barbara M, Harrell, Maria I, Brady, Mark F et al. (2016) Inherited Mutations in Women With Ovarian Carcinoma. JAMA oncology 2(4): 482-90	- Systematic review used as source of primary studies

Study	Code [Reason]
Osorio, Ana, Bogliolo, Massimo, Fernandez, Victoria et al. (2013) Evaluation of rare variants in the new fanconi anemia gene ERCC4 (FANCQ) as familial breast/ovarian cancer susceptibility alleles. Human mutation 34(12): 1615-8	- Study design does not match that specified in this review protocol
Ossa, Carlos Andres and Torres, Diana (2016) Founder and Recurrent Mutations in BRCA1 and BRCA2 Genes in Latin American Countries: State of the Art and Literature Review. The oncologist 21(7): 832-9	- Narrative review
Pelttari, Liisa M, Heikkinen, Tuomas, Thompson, Deborah et al. (2011) RAD51C is a susceptibility gene for ovarian cancer. Human molecular genetics 20(16): 3278-88	- Study design does not match that specified in this review protocol
Pelttari, Liisa M, Kiiski, Johanna, Nurminen, Riikka et al. (2012) A Finnish founder mutation in RAD51D: analysis in breast, ovarian, prostate, and colorectal cancer. Journal of medical genetics 49(7): 429-32	- Study design does not match that specified in this review protocol
Pelttari, Liisa M, Kinnunen, Laura, Kiiski, Johanna I et al. (2016) Screening of HELQ in breast and ovarian cancer families. Familial cancer 15(1): 19-23	- Study design does not match that specified in this review protocol
Pelttari, LM, Kiiski, JI, Ranta, S et al. (2015) RAD51, XRCC3, and XRCC2 mutation screening in Finnish breast cancer families. SpringerPlus 4: 92	- Data not reported in an extractable format or a format that can be analysed
Peng, M, Bakker, JL, Dicioccio, RA et al. (2013) Inactivating Mutations in GT198 in Familial and Early-Onset Breast and Ovarian Cancers. Genes & cancer 4(12): 15-25	- Study design does not match that specified in this review protocol
Pharoah, Paul D P, Palmieri, Rachel T, Ramus, Susan J et al. (2011) The role of KRAS rs61764370 in invasive epithelial ovarian cancer: implications for clinical testing. Clinical cancer research : an official journal of the American Association for Cancer Research 17(11): 3742-50	- Study design does not match that specified in this review protocol
Ramus, Susan J, Song, Honglin, Dicks, Ed et al. (2015) Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. Journal of the National Cancer Institute 107(11)	- Systematic review used as source of primary studies
Rashid, MU, Khan, FA, Muhammad, N et al. (2019) Prevalence of PALB2 Germline Mutations in Early-onset and Familial Breast/Ovarian Cancer Patients from Pakistan. Cancer research and treatment 51(3): 992-1000	- Data not reported in an extractable format or a format that can be analysed
Rivera-Herrera, A.-L., Cifuentes-C, L., Gil-Vera, J.A. et al. (2018) Absence of the CHEK2 c.1100delc mutation in familial breast and ovarian cancer in colombia: A case-control study. F1000Research 7: 1032	- Data not reported in an extractable format or a format that can be analysed
Rosenthal, Eric T, Bernhisel, Ryan, Brown, Krystal et al. (2017) Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories. Cancer genetics 218219: 58-68	- Data not reported in an extractable format or a format that can be analysed
Sanchez-Chaparro, M.M., Garza-Veloz, I., Zayas-Villanueva, O.A. et al. (2020) Genetic variants in the 3'UTR of BRCA1 and BRCA2 genes and their putative effects on the microrna mechanism in hereditary breast and ovarian cancer. Diagnostics 10(5): diagnostics10050298	- Data not reported in an extractable format or a format that can be analysed
Satagopan, Jaya M, Boyd, Jeff, Kauff, Noah D et al. (2002) Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clinical cancer research : an official journal of the American Association for Cancer Research 8(12): 3776-81	- Study design does not match that specified in this review protocol

Study	Code [Reason]
Schayek, Hagit, De Marco, Luiz, Starinsky-Elbaz, Sigal et al. (2016) The rate of recurrent BRCA1, BRCA2, and TP53 mutations in the general population, and unselected ovarian cancer cases, in Belo Horizonte, Brazil. Cancer genetics 209(12): 50-2	- Data not reported in an extractable format or a format that can be analysed
Schlebusch, C M, Dreyer, G, Sluiter, M D et al. (2010) Cancer prevalence in 129 breast-ovarian cancer families tested for BRCA1 and BRCA2 mutations. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 100(2): 113-7	- Data not reported in an extractable format or a format that can be analysed
Shen, Chunyan, Sheng, Qifang, Zhang, Xiaojie et al. (2016) Hypermethylated APC in serous carcinoma based on a meta-analysis of ovarian cancer. Journal of ovarian research 9(1): 60	- Narrative review
Shen, Jie; Medico, Leo; Zhao, Hua (2011) Allelic imbalance in BRCA1 and BRCA2 gene expression and familial ovarian cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 20(1): 50-6	- Data not reported in an extractable format or a format that can be analysed
Shi, Tingyan, Wang, Pan, Xie, Caixia et al. (2017) BRCA1 and BRCA2 mutations in ovarian cancer patients from China: ethnic-related mutations in BRCA1 associated with an increased risk of ovarian cancer. International journal of cancer 140(9): 2051-2059	- Population in study does not match that specified in this review protocol
Singh, Jaya, Thota, Nishita, Singh, Suhasini et al. (2018) Screening of over 1000 Indian patients with breast and/or ovarian cancer with a multi-gene panel: prevalence of BRCA1/2 and non-BRCA mutations. Breast cancer research and treatment 170(1): 189-196	- Population in study does not match that specified in this review protocol
Siraj, Abdul K, Masoodi, Tariq, Bu, Rong et al. (2017) Expanding the spectrum of germline variants in cancer. Human genetics 136(1112): 1431-1444	- Data not reported in an extractable format or a format that can be analysed
Skasko, E, Paszko, Z, Niwinska, A et al. (2004) The presence of hereditary BRCA1 gene mutations in women with familial breast or ovarian cancer and the frequency of occurrence of these tumours in their relatives. European journal of gynaecological oncology 25(4): 470-4	- Data not reported in an extractable format or a format that can be analysed
Song, Honglin, Dicks, Ed, Ramus, Susan J et al. (2015) Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(26): 2901-7	- Data not reported in an extractable format or a format that can be analysed
Song, Honglin, Ramus, Susan J, Quaye, Lydia et al. (2006) Common variants in mismatch repair genes and risk of invasive ovarian cancer. Carcinogenesis 27(11): 2235-42	- Data not reported in an extractable format or a format that can be analysed
Southey, Melissa C, Goldgar, David E, Winqvist, Robert et al. (2016) PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. Journal of medical genetics 53(12): 800-811	- Outcomes in study do not match those specified in this review protocol
Stradella, A., del Valle, J., Rofes, P. et al. (2020) ERCC3, a new ovarian cancer susceptibility gene?. European Journal of Cancer 141: 1-8	- Data not reported in an extractable format or a format that can be analysed
Svajdler, P., Vasovcak, P., Svajdler, M. et al. (2022) CHEK2p.I157T Mutation Is Associated with Increased Risk of Adult-Type Ovarian Granulosa Cell Tumors. Cancers 14(5): 1208	- Study design does not match that specified in this review protocol
Tedaldi, Gianluca, Tebaldi, Michela, Zampiga, Valentina et al. (2017) Multiple-gene panel analysis in a case series of 255	- Systematic review used as source of primary studies

Study	Code [Reason]
women with hereditary breast and ovarian cancer. Oncotarget 8(29): 47064-47075	
ten Broeke, Sanne W, Brohet, Richard M, Tops, Carli M et al. (2015) Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(4): 319-25	- Population in study does not match that specified in this review protocol
Thompson, Ella R, Rowley, Simone M, Sawyer, Sarah et al. (2013) Analysis of RAD51D in ovarian cancer patients and families with a history of ovarian or breast cancer. PloS one 8(1): e54772	- Study design does not match that specified in this review protocol
Tran, VT, Nguyen, ST, Pham, XD et al. (2021) Pathogenic Variant Profile of Hereditary Cancer Syndromes in a Vietnamese Cohort. Frontiers in oncology 11: 789659	- Data not reported in an extractable format or a format that can be analysed
Vaca-Paniagua, F, Alvarez-Gomez, RM, Fragoso-Ontiveros, V et al. (2012) Full-exon pyrosequencing screening of BRCA germline mutations in Mexican women with inherited breast and ovarian cancer. PloS one 7(5): e37432	- Data not reported in an extractable format or a format that can be analysed
Van Der Looij, M, Szabo, C, Besznyak, I et al. (2000) Prevalence of founder BRCA1 and BRCA2 mutations among breast and ovarian cancer patients in Hungary. International journal of cancer 86(5): 737-40	- Study design does not match that specified in this review protocol
Verma, Sonali, Bakshi, Divya, Sharma, Varun et al. (2020) Genetic variants of DNAH11 and LRFN2 genes and their association with ovarian and breast cancer. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 148(1): 118-122	- Study design does not match that specified in this review protocol
Wang, W W, Spurdle, A B, Kolachana, P et al. (2001) A single nucleotide polymorphism in the 5' untranslated region of RAD51 and risk of cancer among BRCA1/2 mutation carriers. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 10(9): 955-60	- Study design does not match that specified in this review protocol
Yang, Xiao-Yun, Yu, Hai, Xi, Ming-Rong et al. (2009) Association of the ARLTS1 variants with familial ovarian cancer risk in China. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 19(4): 585-90	- Study design 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: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

No research recommendations were made for this review question.

Appendix L Data for pathological variants

Data for pathological variants: Which genes should be included in a gene panel when testing for pathogenic variants that increase the risk of familial ovarian cancer?

Key to variables

- **study**: study identifier
- **gene**: pathological variant (PV)
- **prev_grp**: PV prevalence group (high [≥0.5%], medium [>0.2% to <0.5%], low [0.1% to 0.2%], very low [>0% to <0.1%])
- **include**: include in analysis (if n_cases > 2)
- **oc_type**: histological type of ovarian cancer
- **n_cases**: number of ovarian cancer cases who carried the PV
- **total_cases:** total number of ovarian cancer cases
- **n_controls:** number of controls who carried the PV
- **total_controls:** total number of controls
- **or:** odds ratio reported in study
- **or_ci_low , or_ci_high**: 95% CI limits of reported CI
- **log_or**: log odds ratio
- **se_log_or**: standard error of the log odds ratio

Table 10: Data for analysis of gene specific ovarian cancer association

study	gene	prev_grp	include	oc_type	n_cases	total_cases	n_controls	total_controls	or	or_ci_low	or_ci_high	log_or	se_log_or
LaDuca 2020	APC	very low	y	any	2	2256	16	111109	6.16	1.01	24.34	1.82	0.70
LaDuca 2020	ATM	high	y	any	44	11102	231	111313	1.91	1.37	2.65	0.65	0.17
LaDuca 2020	BARD1	very low	y	any	4	11080	56	109604	0.71	0.23	1.94	-0.34	0.51
LaDuca 2020	BRCA1	high	y	any	212	13166	132	111419	13.8	11.1	17.26	2.62	0.11
LaDuca 2020	BRCA2	high	y	any	201	13166	172	110427	9.94	8.09	12.25	2.30	0.11
LaDuca 2020	BRIP1	high	y	any	51	11358	119	111395	4.22	3.02	5.87	1.44	0.17
LaDuca 2020	CDH1	very low	n	any	0	11390	8	109193	0	0	5.5	NA	NA
LaDuca 2020	CDKN2A	very low	n	any	0	2138	13	104289	0	0	14.15	NA	NA
LaDuca 2020	CHEK2	medium	y	any	41	11126	467	109773	0.87	0.63	1.2	-0.14	0.16
LaDuca 2020	MLH1	very low	y	any	2	13092	11	110958	1.54	0.24	6.5	0.43	0.73
LaDuca 2020	MRE11A	very low	y	any	7	11080	53	111326	1.33	0.6	2.89	0.29	0.40
LaDuca 2020	MSH2	low	y	any	7	13092	12	110699	4.93	1.8	13.13	1.60	0.50
LaDuca 2020	MSH6	medium	y	any	21	13092	56	110120	3.16	1.85	5.22	1.15	0.26
LaDuca 2020	NBN	medium	y	any	21	11080	87	111166	2.42	1.48	3.94	0.88	0.25
LaDuca 2020	NF1	low	n	any	2	10402	20	111100	1.07	0.18	4.38	0.07	0.72
LaDuca 2020	PALB2	medium	y	any	12	11418	96	111508	1.22	0.66	2.21	0.20	0.30
LaDuca 2020	PMS2	low	y	any	13	13092	52	108839	2.08	1.1	3.82	0.73	0.31
LaDuca 2020	PTEN	very low	y	any	7	13462	3	110691	19.19	5.05	86.05	2.95	0.77
LaDuca 2020	RAD50	low	y	any	15	11080	129	111109	1.17	0.65	2	0.16	0.27
LaDuca 2020	RAD51C	high	y	any	43	11358	51	111480	8.3	5.43	12.48	2.12	0.21
LaDuca 2020	RAD51D	low	y	any	7	10680	23	111248	3.17	1.31	7.42	1.15	0.43
LaDuca 2020	TP53	very low	y	any	7	13474	17	111505	3.41	1.34	8.28	1.23	0.45
Suszynska 2019	APC	very low	y	any	1	688	NA	NA	NA	NA	NA	NA	NA

study	gene	prev_grp	include	oc_type	n_cases	total_cases	n_controls	total_controls	or	or_ci_low	or_ci_high	log_or	se_log_or
Suszynska 2019	ATM	high	y	any	26	3842	NA	NA	1.977	1.33	2.939	0.68	0.20
Suszynska 2019	ATR	very low	n	any	0	160	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	BAP1	very low	n	any	0	508	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	BARD1	very low	y	any	10	7063	NA	NA	1.407	0.685	2.891	0.34	0.37
Suszynska 2019	BLM	very low	n	any	0	85	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	BMPR1A	very low	n	any	0	639	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	BRCA1	high	y	any	278	3230	NA	NA	35.26	29.56	42.05	3.56	0.09
Suszynska 2019	BRCA2	high	y	any	146	3230	NA	NA	11.91	9.865	14.39	2.48	0.10
Suszynska 2019	BRIP1	high	y	any	75	7099	NA	NA	4.878	3.729	6.38	1.58	0.14
Suszynska 2019	CDH1	very low	n	any	0	1215	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	CDK4	very low	n	any	0	631	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	CDKN2A	very low	n	any	0	688	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	CHEK2	medium	y	any	27	3842	NA	NA	0.427	0.287	0.634	-0.85	0.20
Suszynska 2019	EPCAM	very low	n	any	0	836	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	FAM175A	low	y	any	3	2027	NA	NA	1.645	0.522	5.188	0.50	0.59
Suszynska 2019	FANCC	medium	y	any	3	789	NA	NA	3.344	1.063	10.52	1.21	0.58
Suszynska 2019	FANCM	high	y	any	1	77	NA	NA	2.009	0.279	14.47	0.70	1.01
Suszynska 2019	MLH1	very low	y	any	4	3830	NA	NA	1.436	0.528	3.906	0.36	0.51
Suszynska 2019	MRE11A	very low	y	any	3	2938	NA	NA	1.082	0.344	3.4	0.08	0.58
Suszynska 2019	MSH2	low	y	any	9	3781	NA	NA	3.976	1.818	8.695	1.38	0.40
Suszynska 2019	MSH6	medium	y	any	17	3830	NA	NA	4.077	2.427	6.848	1.41	0.26
Suszynska 2019	NBN	medium	y	any	20	7050	NA	NA	2.166	1.346	3.488	0.77	0.24
Suszynska 2019	NF1	low	n	any	0	37	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	PALB2	medium	y	any	30	7099	NA	NA	2.134	1.42	3.207	0.76	0.21
Suszynska 2019	PMS2	low	y	any	7	3822	NA	NA	0.707	0.292	1.716	-0.35	0.45
Suszynska 2019	PTEN	very low	y	any	2	3177	NA	NA	5.473	1.257	23.82	1.70	0.75
Suszynska 2019	RAD50	low	y	any	4	2992	NA	NA	0.42	0.157	1.125	-0.87	0.50
Suszynska 2019	RAD51C	high	y	any	21	3791	NA	NA	4.241	2.562	7.022	1.44	0.26
Suszynska 2019	RAD51D	low	y	any	19	3258	NA	NA	7.276	4.028	13.14	1.98	0.30
Suszynska 2019	SLX4	very low	n	any	0	1992	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	SMAD4	very low	n	any	0	638	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	STK11	very low	n	any	0	1213	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	TP53	very low	y	any	11	3736	NA	NA	5.046	2.407	10.58	1.62	0.38
Suszynska 2019	VHL	very low	n	any	0	514	NA	NA	NA	NA	NA	NA	NA
Suszynska 2019	XRCC2	very low	n	any	0	175	NA	NA	NA	NA	NA	NA	NA
Dicks 2017	FANCM	high	y	HGSOC	29	3107	13	3368	2.5	1.3	5	0.92	0.35
Dicks 2017	FANCM	high	y	any	35	4578	13	3368	2.1	1.1	3.9	0.74	0.32
Kurian 2017	BRCA2	high	y	any	199	5020	681	64649	5.26	4.38	6.31	1.66	0.09
Kurian 2017	BRCA1	high	y	any	255	5020	521	64649	11.8	9.99	14	2.47	0.09
Kurian 2017	CHEK2	medium	y	any	24	5020	434	64649	0.86	0.56	1.33	-0.15	0.22
Kurian 2017	ATM	high	y	any	43	5020	362	64649	1.69	1.19	2.4	0.52	0.18
Kurian 2017	PALB2	medium	y	any	21	5020	212	64649	1.6	0.98	2.6	0.47	0.25
Kurian 2017	PMS2	low	y	any	21	5020	189	64649	1.57	0.94	2.6	0.45	0.26
Kurian 2017	BRIP1	high	y	any	36	5020	161	64649	2.62	1.72	3.98	0.96	0.21
Kurian 2017	MSH6	medium	y	any	24	5020	146	64649	1.92	1.19	3.1	0.65	0.24
Kurian 2017	NBN	medium	y	any	17	5020	115	64649	1.85	1.05	3.24	0.62	0.29
Kurian 2017	BARD1	very low	y	any	4	5020	84	64649	0.59	0.21	1.68	-0.53	0.53
Kurian 2017	MSH2	low	y	any	13	5020	110	64649	2.04	1.08	3.84	0.71	0.32

study	gene	prev_grp	include	oc_type	n_cases	total_cases	n_controls	total_controls	or	or_ci_low	or_ci_high	log_or	se_log_or
Kurian 2017	RAD51C	high	y	any	32	5020	72	64649	4.98	3.09	8.04	1.61	0.24
Kurian 2017	MLH1	very low	y	any	9	5020	86	64649	3.11	1.47	6.59	1.13	0.38
Kurian 2017	APC	very low	y	any	1	5020	70	64649	0.36	0.05	2.77	-1.02	1.04
Kurian 2017	CDKN2A	very low	n	any	2	5020	42	64649	0.56	0.12	2.53	-0.58	0.77
Kurian 2017	RAD51D	low	y	any	9	5020	40	64649	4.78	2.13	10.7	1.56	0.41
Kurian 2017	CDH1	very low	n	any	1	5020	28	64649	0.63	0.08	4.93	-0.46	1.05
Kurian 2017	TP53	very low	y	any	1	5020	16	64649	0.66	0.05	8.68	-0.42	1.31
Kurian 2017	MUTYH	very low	n	any	1	5020	33	64649	0.4	0.05	3.26	-0.92	1.07
Kurian 2017	PTEN	very low	y	any	0	5020	9	64649	NA	NA	NA	NA	NA
Kurian 2017	BMPR1A	very low	n	any	0	5020	6	64649	NA	NA	NA	NA	NA
Kurian 2017	P14ARF	very low	n	any	0	5020	6	64649	NA	NA	NA	NA	NA
Kurian 2017	STK11	very low	n	any	2	5020	2	64649	41.9	5.55	315	3.74	1.03
Kurian 2017	SMAD4	very low	n	any	0	5020	2	64649	NA	NA	NA	NA	NA
Kurian 2017	CDK4	very low	n	any	0	5020	0	64649	NA	NA	NA	NA	NA
Song 2019 OCAC	PALB2	medium	y	any	11	13288	6	18936	2.1	0.74	5.94	0.74	0.53
Song 2019 OCAC	PALB2	medium	y	HGSOC	6	6174	6	18936	3.48	1.1	11.1	1.25	0.59
Song 2019 Biobank	PALB2	medium	y	any	3	856	11	9685	3.12	0.87	11.2	1.14	0.65
Song 2019 Biobank	PALB2	medium	y	HGSOC	1	362	11	9685	2.49	0.32	19.4	0.91	1.05