National Institute for Health and Care Excellence

Suspected cancer: recognition and referral

[B] Technical appendices for dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone and age and serum CA125 thresholds for detection of suspected ovarian cancer in adults

NICE guideline NG12

Technical data underpinning diagnostic review B

April 2026

Final

NICE National Institute for Health and Care Excellence®

FINAL

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Contents

Appendix A Review protocols

Review question 1

Review protocol for diagnostic review of the dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone in adults

Field	Content
Review title	Dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone for detection of suspected ovarian cancer in adults.
Review question	What is the diagnostic accuracy of dual testing with serum CA125 and ultrasound scan for the detection of suspected ovarian cancer compared to serum CA125 alone in adults for referral via a suspected cancer pathway?
Objective	This review aims to compare the accuracy of dual testing with serum CA125 and ultrasound scan* compared to serum CA125 alone to refer adults via a suspected cancer pathway when presenting with symptoms that suggest ovarian cancer in primary care. *CA125 and ultrasound are arranged in primary care before referral to a suspected cancer pathway. As dual testing, the tests are often not done simultaneously, and both must be requested/completed before onward referral can take place.
Searches	The following databases will be searched: • Clinical searches – Medline ALL, Embase, Epistemonikos, Cochrane CDSR • Economic searches - Medline ALL, Embase and INAHTA The principal search strategy will be developed in MEDLINE and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters

	• Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language. • Non-OECD countries Date limits: 2015 - present Search filters and classifiers: The following standard NICE filters will be used to limit results by study type: cost effectiveness studies / cost utility studies/ systematic reviews / diagnostic studies and cohort studies. The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final review.
Condition or domain being studied	Dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone in adults presenting with symptoms that suggest ovarian cancer in primary care.
Population	Inclusion: Adults (≥18 years old) presenting to primary care* with symptoms that suggest ovarian cancer. *When a paper includes populations from primary and secondary care and the data cannot be disaggregated if at least 80% of the population are from primary care the paper will be considered . Exclusion: Adults previously diagnosed with any type of cancer.
Intervention/Exposure/Test	Dual testing with serum CA125 and ultrasound scan in adults presenting with symptoms that suggest ovarian cancer in primary care that might trigger a referral via a suspected cancer pathway.
Reference standard	Cancer diagnosis within 12 months following standard care in adults presenting with symptoms that suggest ovarian cancer in primary care that might trigger further investigations such as ultrasound or trigger a referral via a suspected cancer pathway.

	Standard care according to CG122 is to measure serum CA125 with ultrasound initiated if serum CA125 is 35 IU/ml or greater.
Types of study to be included	Include published full-text papers: • Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies • Studies from OECD countries The number of papers identified for consideration for full paper review and data extraction will be reviewed and a process of prioritisation may be implemented where studies for example non-UK studies for reasons of more direct applicability and generalisability to the UK context or with prospective data are prioritised in order to manage resources to complete the review and to focus the review on the most pertinent data.
Other exclusion criteria	Inclusion: • All other study types • Full text papers • OECD countries - UK based studies will be prioritised, but publications from other OECD countries will be considered 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 • Studies where multivariate regression analysis was not conducted, or where important confounders were not adjusted for in the analysis, will be excluded. • Non-English language articles
Context	In May 2024, an exceptional surveillance review of the suspected cancer: recognition and referral guideline (NG12) and ovarian cancer: recognition and initial management guideline (CG122) highlighted the need for the recommendation on ovarian cancer in the NICE guideline on suspected cancer (1.5.7 and 1.5.8) to refer patients via the suspected cancer pathway according to CA125 test and ultrasound results, and in the NICE guideline on ovarian cancer (1.1.2.2 to 1.1.2.4). This guidance will update recommendation listed above

	and seek to provide dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone to inform primary care decision making when making a referral to the suspected cancer pathway in adults presenting with symptoms that suggest ovarian cancer in primary care.
Primary outcomes	Accuracy of dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone for ovarian cancer diagnosis within 12 months based on presentation symptoms that suggest ovarian cancer: • Sensitivity • Specificity • Positive predictive value • False negative rate The suggested thresholds for sensitivity and specificity are: • Sensitivity – upper 90, lower 10 • Specificity – upper 80, lower 50
Secondary outcomes	Not applicable
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding.

	One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • QUADAS-2 for diagnostic accuracy studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. For dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted when possible. If more than two studies report dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the likelihood of cancer diagnosis in the 12 months following CA125 test and ultrasound (compared to CA125 alone). The positive predictive value will form the basis of the risk estimate. A positive predictive value threshold of 3% or more for urgent cancer investigation will be used. Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metaDTA app (https://crsu.shinyapps.io/MetaDTA/). Cochrane Review Manager software may be used to help with visually displaying information. Sensitivity, specificity, positive predictive value and false negative rate with 95% CIs will be used as outcomes for diagnostic test accuracy. These diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. 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/"

<table>
<tr><td>Analysis of sub-groups</td><td colspan="3">Evidence will be stratified by:
Not applicable
Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:
• Groups identified in the equality and health inequalities assessment (EHIA) as outlined in the scope including:
○ socioeconomic and geographical factors
○ age
○ ethnicity
○ disabilities
○ people for whom English is not their first language or who have other communication needs.
○ trans people
○ non-binary people
Where evidence is stratified or sub-grouped 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.</td></tr>
<tr><td rowspan="7">Type and method of review</td><td>☐</td><td colspan="2">Intervention</td></tr>
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<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
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<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
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<tr><td>Anticipated completion date</td><td colspan="3">01/10/2025</td></tr>
<tr><td rowspan="3">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☒</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☒</td></tr>
</table>

	Formal screening of search results against eligibility criteria	☐	☒
	Data extraction	☐	☒
	Risk of bias (quality) assessment	☐	☒
	Data analysis	☐	☒
Named contact	**5a. Named contact** NICE **5b Named contact e-mail** SuspectedCancer@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
Review team members	• Robby Richey – Topic lead • Steven Barnes – Technical advisor • James Jagroo – Senior technical analysts • Armina Paule - Technical analyst • Eric Slade - Health economist • Amy Finnegan - Information specialist • Jon Littler – Project manager		
Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
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: Project information | Suspected Cancer: recognition and referral (update) | Guidance | NICE	
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.	
Keywords	CA125 thresholds, ultrasound, ovarian cancer, suspected ovarian cancer referral.	
Details of existing review of same topic by same authors	This is a new review question that will update recommendation on CA125 test and ultrasound in 1.5.7 and 1.5.8 in Suspected cancer: recognition and referral guideline and 1.1.2.2 to 1.1.2.4 in Ovarian cancer: recognition and initial management guideline and introducing dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone to be used to refer adults presenting with symptoms that suggest ovarian cancer in primary care via suspected cancer pathway.	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

Abbreviations: CA125: cancer antigen 125; CDSR: Cochrane Database of Systematic Reviews; CI: confidence interval; EHIA: Equality and Health Inequalities Impact Assessment; Embase: Excerpta Medica dataBASE; EPPI: Evidence for Policy & Practice Information; GRADE: Grading of Recommendations Assessment, Development and Evaluation; INAHTA: International Network of Agencies for Health Technology Assessment; Medline: Medical Literature Analysis and Retrieval System; MetaDTA:meta-analysis of diagnostic test accuracy studies; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; ROBIS: Risk of Bias in Systematic Reviews.

Review question 2

Review protocol for diagnostic review of the age and serum CA125 thresholds for detection of suspected ovarian cancer in adults

Field	Content
Review title	Age and serum CA125 thresholds for detection of suspected ovarian cancer in adults.
Review question	What is the diagnostic accuracy of different age thresholds and different serum CA125 thresholds for the detection of suspected ovarian cancer in adults for referral via a suspected cancer pathway?
Objective	Recommendation on serum CA125 thresholds relating to symptoms that suggest ovarian cancer in primary care currently stratify by one age threshold (aged 50 or over). This review aims to compare the accuracy of different age thresholds and different CA125 thresholds used to refer adults via a suspected cancer pathway when presenting with symptoms that suggest ovarian cancer in primary care.
Searches	The following databases will be searched: • Clinical searches – Medline ALL, Embase, Epistemonikos, Cochrane CDSR • Economic searches - Medline ALL, Embase and INAHTA The principal search strategy will be developed in MEDLINE and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language. • Non-OECD countries Date limits: 2015 - present Search filters and classifiers: The following standard NICE filters will be used to limit results by study type: cost effectiveness

	studies / cost utility studies/ systematic reviews / diagnostic studies and cohort studies. The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final review.
Condition or domain being studied	Different age thresholds and different serum CA125 thresholds in adults presenting with symptoms that suggest ovarian cancer in primary care.
Population	Inclusion: Adults (≥18 years old) presenting to primary care* with symptoms that suggest ovarian cancer. *When a paper includes populations from primary and secondary care and the data cannot be disaggregated if at least 80% of the population are from primary care the paper will be considered and not excluded based on 'population'. Exclusion: • Adults previously diagnosed with any type of cancer.
Intervention/Exposure/Test	Age thresholds and CA125 thresholds in adults presenting with symptoms that suggest ovarian cancer in primary care that might trigger a referral via a suspected cancer pathway.
Reference standard	Cancer diagnosis within 12 months following a CA125 test for suspected cancer.
Types of study to be included	Include published full-text papers: • Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies The number of papers identified for consideration for full paper review and data extraction will be reviewed and a process of prioritisation may be implemented where studies for example non-UK studies for reasons of more direct applicability and generalisability to the UK context or with prospective data are prioritised in order to manage resources to complete the review and to focus the review on the most pertinent data.
Other exclusion criteria	• All other study types • 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 • Studies where multivariate regression analysis was not conducted, or where important confounders were not adjusted for in the analysis, will be excluded. • Non-English language articles
Context	In May 2024, an exceptional surveillance review of the suspected cancer: recognition and referral guideline (NG12) and ovarian cancer: recognition and initial management guideline (CG122) highlighted the need for the recommendation on ovarian cancer in the NICE guideline on suspected cancer (1.5.6, 1.5.7 and 1.5.9) to refer patients via the suspected cancer pathway according to age categories and CA125 test results, and in the NICE guideline on ovarian cancer (1.1.2). This guidance will update recommendation listed above and seek to provide age thresholds to inform primary care decision making when making a referral to the suspected cancer pathway in adults presenting with symptoms that suggest ovarian cancer in primary care.
Primary outcomes	Accuracy of age thresholds and CA125 thresholds for ovarian cancer diagnosis within 12 months based on presentation symptoms that suggest ovarian cancer: • Sensitivity • Specificity • Positive predictive value • False negative rate The suggested thresholds for sensitivity and specificity are: • Sensitivity – upper 90, lower 10 • Specificity – upper 80, lower 50
Secondary outcomes	Not applicable
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required.

	Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • QUADAS-2 for diagnostic accuracy studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. For each reported age and CA125 thresholds the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted when possible. If more than two studies report a given age and CA125 thresholds, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the likelihood of cancer diagnosis in the 12 months following CA125 test associated with each age threshold. The positive predictive value will form the basis of the risk estimate. A positive predictive value threshold of 3% or more for cancer investigation will be used. Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metaDTA app (https://crsu.shinyapps.io/MetaDTA/). Cochrane Review Manager software may be used to help with visually displaying information.

	Sensitivity, specificity, positive predictive value and false negative rate with 95% CIs will be used as outcomes for diagnostic test accuracy. These diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. 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/"	
Analysis of sub-groups	Evidence will be stratified by: • Age groups • CA125 thresholds Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: • Groups identified in the equality and health inequalities assessment (EHIA) as outlined in the scope including: o socioeconomic and geographical factors o age o ethnicity o disabilities o people for whom English is not their first language or who have other communication needs. o trans people o non-binary people Where evidence is stratified or sub-grouped 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.	
Type and method of review	☐	Intervention
	☒	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery

<table>
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<tr><td>Piloting of the study selection process</td><td>☐</td><td>☒</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☒</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☒</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☒</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☒</td></tr>
<tr><td>Named contact</td><td colspan="3">5a. Named contact
NICE

5b Named contact e-mail
SuspectedCancer@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE)</td></tr>
<tr><td>Review team members</td><td colspan="3">• Robby Richey – Topic lead
• Steven Barnes – Technical advisor
• James Jagroo – Senior technical analysts
• Armina Paule - Technical analyst
• Eric Slade - Health economist
• Amy Finnegan - Information specialist
• Jon Littler – Project manager</td></tr>
<tr><td>Funding sources/sponsor</td><td colspan="3">This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.</td></tr>
<tr><td>Conflicts of interest</td><td colspan="3">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</td></tr>
</table>

	committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
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: Project information | Suspected Cancer: recognition and referral (update) | Guidance | NICE	
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.	
Keywords	Age thresholds, CA125 thresholds, ovarian cancer, suspected ovarian cancer referral.	
Details of existing review of same topic by same authors	This is a new review question that will update recommendation on CA125 thresholds in 1.5.6, 1.5.7 and 1.5.9 in Suspected cancer: recognition and referral guideline and 1.1.2 in Ovarian cancer: recognition and initial management guideline and introducing age thresholds to be used to refer adults presenting with symptoms that suggest ovarian cancer in primary care via suspected cancer pathway.	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

Abbreviations: CA125: cancer antigen 125; CDSR: Cochrane Database of Systematic Reviews; CI: confidence interval; EHIA: Equality and Health Inequalities Impact Assessment; Embase: Excerpta Medica dataBASE; EPPI: Evidence for Policy & Practice Information; GRADE: Grading of Recommendations

Assessment, Development and Evaluation; INAHTA: International Network of Agencies for Health Technology Assessment; Medline: Medical Literature Analysis and Retrieval System MetaDTA:meta-analysis of diagnostic test accuracy studies; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; ROBIS: Risk of Bias in Systematic Reviews.

Economic review protocol

ID	Field	Content
1.	Review title	1.1 Dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone for detection of suspected ovarian cancer in adults. 1.2 Age and serum CA125 thresholds for detection of suspected ovarian cancer in adults.
2.	Objective	To identify economic studies for the review question on dual testing with serum CA125 and ultrasound scan, and also the use of age-based CA125 thresholds for referral via suspected cancer pathway.
3.	Inclusion criteria	Populations, interventions and comparators must be as specified in the effectiveness review protocol. Relevant comparative economic study design: cost–utility analysis as these are most relevant to NICE's decision making. Decision analytic model-based or within-trial economic analyses OECD countries. Healthcare and personal social services cost perspective. Studies published from 2015 onwards – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs. High-quality studies in line with the NICE reference case (recent UK NHS/PSS cost-utility analyses using the QALY as the measure of outcome) are the most applicable to NICE decision making. Not all studies meeting the inclusion criteria will therefore necessarily be used in decision-making - see Review strategy below for details.
4.	Exclusion criteria	Conference posters or abstract only studies – these do not provide sufficient information for quality assessment. Studies published before 2015 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs. Studies from non-OECD countries – these are considered unlikely to be applicable to the UK NHS setting due to substantial differences in healthcare delivery and unit costs.

		Non-comparative economic analyses including cost-of-illness studies. Letters, editorials or commentaries, study protocols or reviews of economic evaluations (recent reviews will be ordered and the bibliographies will be checked for relevant individual economic studies, which will then be ordered and checked for eligibility). Non-English language papers. Studies considering exclusively intervention costs, e.g. medicine acquisition costs, without considering wider healthcare costs associated with the management of ovarian cancer. Studies comparing costs of branded vs generic forms of the same medicine. Studies only focussing on productivity losses or gains.
5.	Search strategy	An economic study search will be undertaken using question-specific terms. For search details see appendix B below.
6.	Review strategy	Studies meeting the inclusion and exclusion criteria will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist in appendix H of Developing NICE guidelines: the manual. The NICE economic evaluation checklist assesses: Applicability to the NICE guideline decision making context with consideration of the NICE reference case relevant to the guideline. Recent UK studies that use the NICE reference case methods are the most applicable when considering cost effectiveness. Methodological limitations. The aim is to present the best available economic evidence to inform committee decision-making in the context of the guideline, the current UK NHS setting and NICE methods. Therefore, the health economist may not present all studies that meet inclusion criteria. If recent high quality, UK cost-utility analyses are available for a question, it is often not deemed informative to present studies that are less applicable or lower quality such as older UK analyses or analyses from other countries. A similar principle is deemed to apply more generally when considering applicability and methodological limitations. Some specific examples are given below: If multiple versions of a model are available for the UK and other countries it is usually reasonable to only present the UK version. If multiple versions of the same UK model are available, it is usually reasonable to present only the most recent.

		If there has been a NICE MTA or guideline model that informs current NHS practice it is usually reasonable not to present older studies, unless they address a different subpopulation or other specific issue. If a UK model that includes all interventions in the decision space is available it may be reasonable not to present studies that only include individual or fewer interventions, if the analysis is sufficiently applicable and of good methodological quality. Quality and relevance of effectiveness data used in the economic analysis: the more closely the clinical effectiveness data used in the economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. Hierarchy of economic evaluation evidence based on quality assessment 'Directly applicable' and 'Minor limitations' (only recent UK CUAs can get this rating). Usually presented and used in decision-making. Directly or partially applicable combined with minor or potentially serious limitations (other than 1). Discretion over whether these are presented and used in decision-making, depending on the availability of more relevant evidence. 'Not applicable' or 'Very serious limitations'. Typically, not presented and not used in decision-making. The health economist will decide based on the relative applicability and quality of the available evidence for each question, in discussion with the guideline committee if required. All decisions will be transparently reported in the evidence report. Studies that are presented to the committee and used in decision-making when formulating recommendations will be included in the summary tables and will have an evidence extraction. Other studies may not be presented to the committee in detail but will be listed, with the reason for not being presented to the committee and thus not used in decision-making being provided. Committee members can review and query the decision not to present studies with the health economist and will be provided with full details of these studies where requested.

Appendix B Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches. The MEDLINE strategies below were quality assured (QA) by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The population and intervention lines have been adapted from the following sources:

Davenport, C et al (2022) Menopausal status, ultrasound and biomarker tests in combination for the diagnosis of ovarian cancer in symptomatic women. Cochrane Database of systematic review.

Ovarian Cancer: the recognition and initial management of ovarian cancer – evidence review (2011) NICE guideline CG122

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters

- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of 01 January 2015 to 18 August 2025 was applied, as stated in the review protocol.

Search filters and classifiers

Effectiveness searches

Cohort filter:

The terms used for cohort studies are standard NICE practice that have been developed in house.

Diagnosis filter:

The Medline and Embase searches were limited to diagnosis evidence using the optimal filter. Additional terms were added to the filter.

Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from MEDLINE: analytical survey. *BMJ*. 2004;328:1040-2.

OECD countries filter:

The MEDLINE and Embase searches were limited to evidence from Organisation for Economic Co-operation and Development (OECD) member states using the validated NICE filter.

The OECD countries filters were used without modification:

Ayiku, L., Hudson, T., Williams, C., Levay, P., & Jacob, C. (2021). The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. *Journal of the Medical Library Association*, 109(4), 583–589.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

> Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

- The search developed was a combined search, covering the evidence review for both CA125 and Age and CA125 and Ultrasound and corresponding economic reviews.
- No reruns were performed for this search.

Clinical searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	19/08/2025	Wiley	Issue 8 of 12, August 2025	5
Embase	19/08/2025	Ovid	1974 to 2025 August 14	4623
Epistemonikos	19/08/2025	https://www.epistemonikos.org/	n/a	104
MEDLINE ALL	19/08/2025	Ovid	1946 to August 18, 2025	2182

Search strategy history

Database name: Cochrane CDSR

Searches

#1 MeSH descriptor: [Ovarian Neoplasms] explode all trees 3511

#2 MeSH descriptor: [Adnexal Diseases] explode all trees 7357

#3 MeSH descriptor: [Genital Neoplasms, Female] explode all trees 9483

#4 MeSH descriptor: [Peritoneal Neoplasms] this term only 584

#5 MeSH descriptor: [Pelvic Neoplasms] this term only 201

#6 ((ovar* or adnexa* or fallopian or peritoneal* or peritoneum* or pelvic or pelvis or sertoli-leydig or oviduct or uterine or uterus or tubal) NEAR/3 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or fibrosarcoma* or rhabdomyosarcoma* or myosarcoma* or

Searches

rhabdosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or androblastom* or arrhenoblastom* or adenoma* or lesion* or oncolo*)):ti,ab 13029

#7 ((grad* or germ-cell* or epithelial or stromal or serous* or mucinous or borderline or border-line or suspect* or suspicious*) NEAR/3 ovar*):ti,ab 2723

#8 (HGSOC or LGSOC or HGOC or LGOC or HGSC or LGSC):ti,ab 170

#9 {or #1-#8} 22430

#10 MeSH descriptor: [CA-125 Antigen] this term only 260

#11 (CA125 or CA-125 or cancer-antigen-125 or MUC16 or MUC-16 or mucin-16 or mucin16):ti,ab 1380

#12 {or #10-#11} 1412

#13 #9 AND #12 with Cochrane Library publication date Between Jan 2015 and Aug 2025, in Cochrane Reviews 5

Database name: Embase

Searches

1 exp ovary tumor/ (208955)

2 exp adnexa disease/ (337177)

3 exp female genital tract tumor/ (473762)

4 exp peritoneum tumor/ (41949)

5 exp pelvis tumor/ (966337)

6 ((ovar* or adnexa* or fallopian or peritoneal* or peritoneum* or pelvic or pelvis or sertoli-leydig or oviduct or uterine or uterus or tubal) adj3 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or fibrosarcoma* or rhabdomyosarcoma* or myosarcoma* or rhabdosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or androblastom* or arrhenoblastom* or adenoma* or lesion* or oncolo*)).ti,ab. (286767)

7 ((grad* or germ-cell* or epithelial or stromal or serous* or mucinous or borderline or border-line or suspect* or suspicious*) adj3 ovar*).ti,ab. (48979)

8 (HGSOC or LGSOC or HGOC or LGOC or HGSC or LGSC).ti,ab. (5698)

9 or/1-8 (1184976)

10 CA 125 antigen/ (26612)

11 (CA125 or CA-125 or cancer-antigen-125 or MUC16 or MUC-16 or mucin-16 or mucin16).ti,ab. (21328)

12 or/10-11 (32187)

13 9 and 12 (22999)

14 Case control study/ (240590)

15 cross-sectional study/ (754529)

16 Longitudinal study/ (252581)

17 Retrospective study/ (1880204)

Searches

18 comparative study/ (1127742)
19 Prospective study/ (1001700)
20 Randomized controlled trials/ (298420)
21 19 not 20 (989522)
22 Cohort analysis/ (1427959)
23 cohort analy$.tw. (24799)
24 (Cohort adj (study or studies)).tw. (596154)
25 (Case control$ adj (study or studies)).tw. (195235)
26 (cross sectional adj (study or studies)).tw. (436499)
27 case series.tw. (175399)
28 prospective.tw. (1345424)
29 retrospective.tw. (1537714)
30 or/14-18,21-29 (6330459)
31 sensitiv*.tw. (2355251)
32 diagnostic accuracy.sh. (350881)
33 diagnostic.tw. (1449484)
34 ((likelihood adj ratio*) or lr or plr or nlr).ti,ab. (96380)
35 or/31-34 (3738452)
36 30 or 35 (9294294)
37 13 and 36 (10958)
38 37 and (2015* or 2016* or 2017* or 2018* or 2019* or 202*).dc,dd. (6884)
39 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or

Searches

exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1932590)

40 exp "organisation for economic co-operation and development"/ (3548)

41 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (4070193)

42 european union/ (33927)

43 developed country/ (37234)

44 or/40-43 (4106808)

45 39 not 44 (1761542)

46 38 not 45 (6643)

47 46 not conference*.db,pt,su. (4810)

48 limit 47 to english language (4666)

49 48 not (letter or editorial).pt. (4635)

50 animal/ or nonhuman/ or exp Animal Experiment/ or exp Experimental Animal/ or animal model/ or exp Rodent/ (10852399)

51 (rat or rats or mouse or mice or rodent*).ti. (1730314)

52 50 or 51 (10882359)

53 52 not human/ (7684070)

54 49 not 53 (4623)

Database name: Epistemonikos

Searches

(title:(((ovar* OR adnexa* OR fallopian OR peritoneal* OR peritoneum* OR pelvic OR pelvis OR sertoli-leydig OR oviduct OR uterine OR uterus OR tubal) AND (cancer* OR carcinoma* OR malignan* OR neoplas* OR tumour* OR tumor* OR mass OR masses OR cyst* OR adenocarcin* OR sarcoma* OR choriocarcinoma* OR chorioncarcinoma* OR dysgerminoma* OR seminoma* OR teratoma* OR teratocarcinoma* OR cystadenocarcin* OR fibrosarcoma* OR rhabdomyosarcoma* OR myosarcoma* OR rhabdosarcoma* OR leiomyosarcoma* OR carcinosarcoma* OR granulosa* OR metasta* OR meta-sta* OR androblastom* OR arrhenoblastom* OR adenoma* OR lesion* OR oncolo*)) OR ((grad* OR grad* OR germ-cell* OR epithelial OR stromal OR serous* OR mucinous OR borderline OR border-line OR suspect* OR suspicious*) AND ovar*) OR (HGSOC OR LGSOC OR HGOC OR LGOC OR HGSC OR LGSC)) OR abstract:(((ovar* OR adnexa* OR fallopian OR peritoneal* OR peritoneum* OR pelvic OR pelvis OR sertoli-leydig OR oviduct OR

Searches

uterine OR uterus OR tubal) AND (cancer* OR carcinoma* OR malignan* OR neoplas* OR tumour* OR tumor* OR mass OR masses OR cyst* OR adenocarcin* OR sarcoma* OR choriocarcinoma* OR chorioncarcinoma* OR dysgerminoma* OR seminoma* OR teratoma* OR teratocarcinoma* OR cystadenocarcin* OR fibrosarcoma* OR rhabdomyosarcoma* OR myosarcoma* OR rhabdosarcoma* OR leiomyosarcoma* OR carcinosarcoma* OR granulosa* OR metasta* OR meta-sta* OR androblastom* OR arrhenoblastom* OR adenoma* OR lesion* OR oncolo*)) OR ((grad* OR grad* OR germ-cell* OR epithelial OR stromal OR serous* OR mucinous OR borderline OR border-line OR suspect* OR suspicious*) AND ovar*) OR (HGSOC OR LGSOC OR HGOC OR LGOC OR HGSC OR LGSC))) AND (title:((CA125 OR CA-125 OR cancer-antigen-125 OR MUC16 OR MUC-16 OR mucin-16 OR mucin16)) OR abstract:((CA125 OR CA-125 OR cancer-antigen-125 OR MUC16 OR MUC-16 OR mucin-16 OR mucin16)))

Limit: Publication year 2015 –2025

Limit: publication type: Systematic reviews

Total: 104

Database name: Medline ALL

Searches

1 exp Ovarian Neoplasms/ (102089)

2 exp adnexal diseases/ (158190)

3 exp Genital Neoplasms, Female/ (273701)

4 Peritoneal Neoplasms/ (18442)

5 Pelvic Neoplasms/ (7655)

6 ((ovar* or adnexa* or fallopian or peritoneal* or peritoneum* or pelvic or pelvis or sertoli-leydig or oviduct or uterine or uterus or tubal) adj3 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or fibrosarcoma* or rhabdomyosarcoma* or myosarcoma* or rhabdosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or androblastom* or arrhenoblastom* or adenoma* or lesion* or oncolo*)).ti,ab. (200982)

7 ((grad* or germ-cell* or epithelial or stromal or serous* or mucinous or borderline or border-line or suspect* or suspicious*) adj3 ovar*).ti,ab. (31431)

8 (HGSOC or LGSOC or HGOC or LGOC or HGSC or LGSC).ti,ab. (2749)

9 or/1-8 (423575)

10 CA-125 Antigen/ (5734)

11 (CA125 or CA-125 or cancer-antigen-125 or MUC16 or MUC-16 or mucin-16 or mucin16).ti,ab. (12875)

12 or/10-11 (13780)

13 9 and 12 (9373)

Searches

14 exp Case-Control Studies/ (1626530)

15 exp Cohort Studies/ (2778452)

16 Cross-Sectional Studies/ (554033)

17 Comparative Study.pt. (1957250)

18 (case adj (control or series)).tw. (295893)

19 (cohort adj (study or studies)).tw. (409300)

20 cohort analy$.tw. (15455)

21 longitudinal.tw. (384133)

22 prospective.tw. (823054)

23 retrospective.tw. (926471)

24 cross sectional.tw. (644831)

25 or/14-24 (6011438)

26 (sensitiv: or predictive value:).mp. or accurac:.tw. (2924693)

27 ((likelihood adj ratio*) or lr or plr or nlr).ti,ab. (65795)

28 diagnos*.ti. (758643)

29 or/26-28 (3557692)

30 25 or 29 (8754936)

31 13 and 30 (5482)

32 31 and (2015* or 2016* or 2017* or 2018* or 2019* or 202*).ed,dt. (2434)

33 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/

Searches

or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1445395)

34 "organisation for economic co-operation and development"/ (689)

35 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3692751)

36 european union/ (18589)

37 developed countries/ (21861)

38 or/34-37 (3709725)

39 33 not 38 (1351612)

40 32 not 39 (2357)

41 limit 40 to english language (2290)

42 limit 41 to (letter or historical article or comment or editorial or news or case reports) (105)

43 41 not 42 (2185)

44 43 not overall.pt. (2185)

45 animals/ or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ (7741131)

46 (rat or rats or mouse or mice or rodent*).ti. (1537780)

47 (45 or 46) not humans/ (5456614)

48 44 not 47 (2182)

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	21/08/2025	Ovid	1974 to 2025 August 19	138
International HTA Database	21/08/2025	https://database.inahta.org/	n/a	4

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
MEDLINE	21/08/2025	Ovid	1946 to August 19, 2025	59

Search strategy history

Database name: Embase

Searches

1 exp ovary tumor/ (209023)

2 exp adnexa disease/ (337289)

3 exp female genital tract tumor/ (473934)

4 exp peritoneum tumor/ (41961)

5 exp pelvis tumor/ (966691)

6 ((ovar* or adnexa* or fallopian or peritoneal* or peritoneum* or pelvic or pelvis or sertoli-leydig or oviduct or uterine or uterus or tubal) adj3 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or fibrosarcoma* or rhabdomyosarcoma* or myosarcoma* or rhabdosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or androblastom* or arrhenoblastom* or adenoma* or lesion* or oncolo*)).ti,ab. (286873)

7 ((grad* or germ-cell* or epithelial or stromal or serous* or mucinous or borderline or border-line or suspect* or suspicious*) adj3 ovar*).ti,ab. (49002)

8 (HGSOC or LGSOC or HGOC or LGOC or HGSC or LGSC).ti,ab. (5701)

9 or/1-8 (1185408)

10 CA 125 antigen/ (26614)

11 (CA125 or CA-125 or cancer-antigen-125 or MUC16 or MUC-16 or mucin-16 or mucin16).ti,ab. (21336)

12 or/10-11 (32195)

13 9 and 12 (23005)

14 13 and (2015* or 2016* or 2017* or 2018* or 2019* or 202*).dc,dd. (12763)

15 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or

Searches

grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1933911)

16 exp "organisation for economic co-operation and development"/ (3553)

17 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (4072091)

18 european union/ (33945)

19 developed country/ (37239)

20 or/16-19 (4108718)

21 15 not 20 (1762748)

22 14 not 21 (12434)

23 22 not conference*.db,pt,su. (9086)

24 limit 23 to english language (8801)

25 24 not (letter or editorial).pt. (8581)

26 animal/ or nonhuman/ or exp Animal Experiment/ or exp Experimental Animal/ or animal model/ or exp Rodent/ (10859340)

27 (rat or rats or mouse or mice or rodent*).ti. (1731184)

28 26 or 27 (10889301)

29 28 not human/ (7687710)

30 25 not 29 (8540)

31 Health economics/ (37575)

32 exp health care cost/ (376540)

33 exp Fee/ (47092)

Searches

34 exp Budget/ (37168)

35 Funding/ (83256)

36 budget*.ti,ab. (53718)

37 cost*.ti. (215194)

38 (economic* or pharmaco?economic*).ti. (86104)

39 (price* or pricing*).ti,ab. (83648)

40 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (348682)

41 (financ* or fee or fees).ti,ab. (277316)

42 (value adj2 (money or monetary)).ti,ab. (4651)

43 or/31-42 (1221294)

44 30 and 43 (138)

Database name: International HTA

Searches

#1 "ovarian neoplasms"[mhe] 148

#2 "adnexal diseases"[mhe] 165

#3 "genital neoplasms female"[mhe] 386

#4 "peritoneal neoplasms"[mh] 57

#5 "pelvic neoplasms"[mh] 5

#6 ((ovar* or adnexa* or fallopian or peritoneal* or peritoneum* or pelvic or pelvis or "sertoli-leydig" or oviduct or uterine or uterus or tubal) AND (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or fibrosarcoma* or rhabdomyosarcoma* or myosarcoma* or rhabdosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or "meta-sta"* or androblastom* or arrhenoblastom* or adenoma* or lesion* or oncolo*)) 304

#7 ((grad* or "germ-cell"* or epithelial or stromal or serous* or mucinous or borderline or "border-line" or suspect* or suspicious*) AND ovar*) 50

#8 hgsoc or lgsoc or hgoc or lgoc or hgsc or lgsc 0

#9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 541

#10 "ca-125 antigen"[mh] 3

#11 (ca125 or "ca-125" or "cancer-antigen"-125 or muc16 or "muc-16" or "mucin-16" or mucin16) 51

#12 #11 OR #10 52

#13 #12 AND #9 12

Limit Publication year 2015 - 2025 4

Database name: Medline ALL

Searches

1 exp Ovarian Neoplasms/ (102089)

2 exp adnexal diseases/ (158190)

3 exp Genital Neoplasms, Female/ (273701)

4 Peritoneal Neoplasms/ (18442)

5 Pelvic Neoplasms/ (7655)

6 ((ovar* or adnexa* or fallopian or peritoneal* or peritoneum* or pelvic or pelvis or sertoli-leydig or oviduct or uterine or uterus or tubal) adj3 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or mass or masses or cyst* or adenocarcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or cystadenocarcin* or fibrosarcoma* or rhabdomyosarcoma* or myosarcoma* or rhabdosarcoma* or leiomyosarcoma* or carcinosarcoma* or granulosa* or metasta* or meta-sta* or androblastom* or arrhenoblastom* or adenoma* or lesion* or oncolo*)).ti,ab. (201002)

7 ((grad* or germ-cell* or epithelial or stromal or serous* or mucinous or borderline or border-line or suspect* or suspicious*) adj3 ovar*).ti,ab. (31433)

8 (HGSOC or LGSOC or HGOC or LGOC or HGSC or LGSC).ti,ab. (2750)

9 or/1-8 (423596)

10 CA-125 Antigen/ (5734)

11 (CA125 or CA-125 or cancer-antigen-125 or MUC16 or MUC-16 or mucin-16 or mucin16).ti,ab. (12877)

12 or/10-11 (13782)

13 9 and 12 (9374)

14 13 and (2015* or 2016* or 2017* or 2018* or 2019* or 202*).ed,dt. (3866)

15 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or

Searches

"saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1445402)

16 "organisation for economic co-operation and development"/ (689)

17 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3692760)

18 european union/ (18589)

19 developed countries/ (21861)

20 or/16-19 (3709734)

21 15 not 20 (1351619)

22 14 not 21 (3771)

23 limit 22 to english language (3646)

24 limit 23 to (letter or historical article or comment or editorial or news or case reports) (597)

25 23 not 24 (3049)

26 25 not overall.pt. (3049)

27 animals/ or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ (7741145)

28 (rat or rats or mouse or mice or rodent*).ti. (1537862)

29 (27 or 28) not humans/ (5456704)

30 26 not 29 (3035)

31 Economics/ (27551)

32 Value of life/ (5846)

33 exp "Costs and Cost Analysis"/ (281021)

34 exp Economics, Hospital/ (26259)

35 exp Economics, Medical/ (14464)

36 Economics, Nursing/ (4013)

37 Economics, Pharmaceutical/ (3169)

38 exp "Fees and Charges"/ (31721)

39 exp Budgets/ (14390)

40 budget*.ti,ab. (40334)

41 cost*.ti. (159567)

42 (economic* or pharmaco?economic*).ti. (68746)

Searches

43 (price* or pricing*).ti,ab. (61194)

44 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (251302)

45 (financ* or fee or fees).ti,ab. (189021)

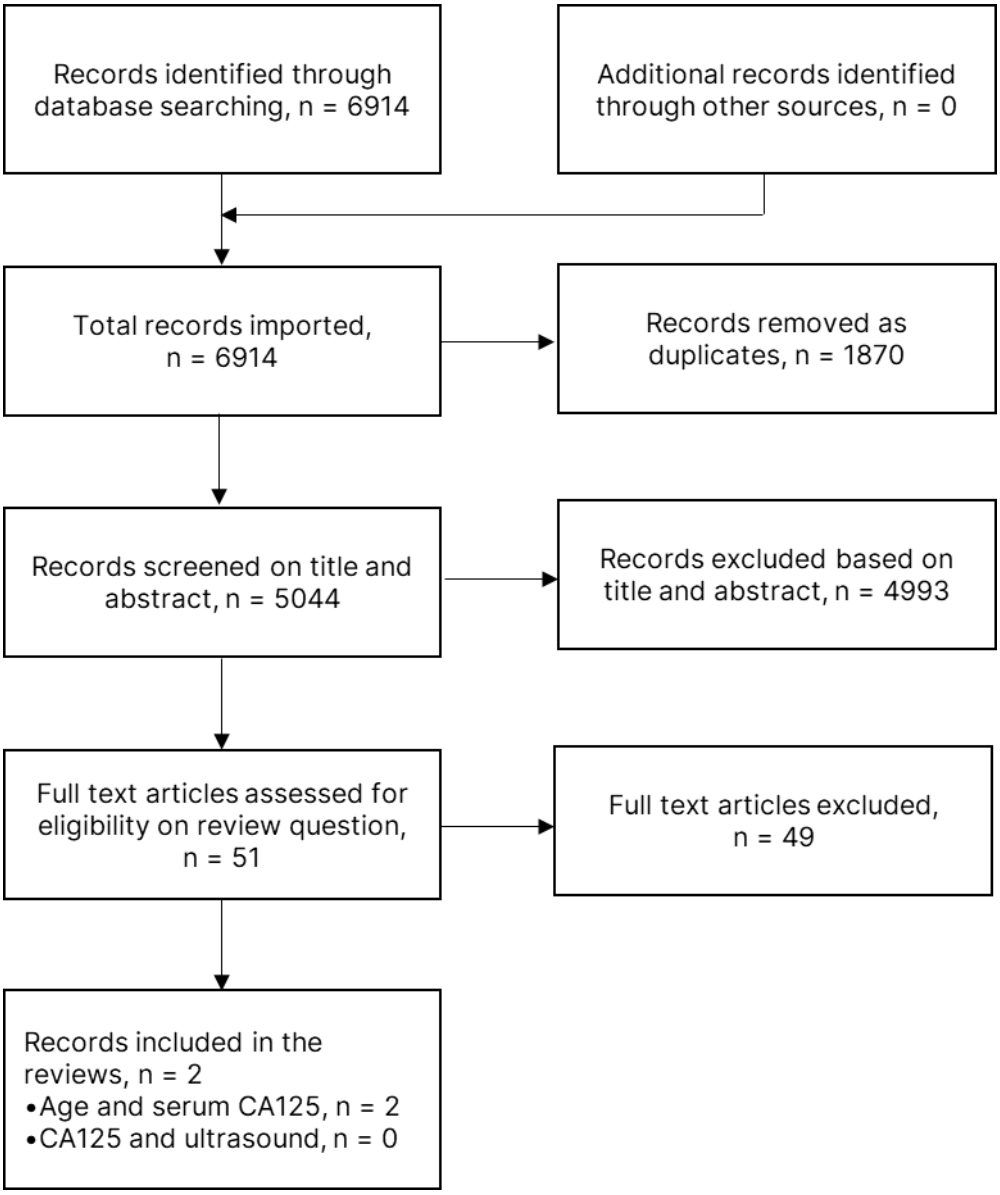
46 (value adj2 (money or monetary)).ti,ab. (3466)

47 or/31-46 (831256)

48 30 and 47 (59)

Appendix C Study selection

Figure 1 Diagnostic evidence study selection



Appendix D Diagnostic evidence

Arendse, 2025

Bibliographic Reference	Arendse, K.D.; Walter, F.M.; Abel, G.; Rous, B.; Hamilton, W.; Crosbie, E.J.; Funston, G.; CA125 and age-based models for ovarian cancer detection in primary care: a population-based external validation study; medRxiv; 2025

Table 1: Arendse 2025 study details

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location - UK (England) Setting - Primary care Study dates - 1 May 2011 to 31 December 2017 Sources of funding - Cancer Research UK [C8640/A23385] - The National Institute of Health Research (NIHR) [PR-PRU-1217-21601]
Inclusion criteria	- Women with a valid code for CA125 measurement in Clinical Research Practice Datalink (CPRD) - CA125 entries recorded in standard equivalent units: U/ml, IU/ml, KU/L, or KIU/L
Exclusion criteria	Women: - <18 years old at first CA125 test - with a CA125 test within 12 months prior to the first CA125 test taken during the study period - had a previous diagnosis of any ovarian cancer (including borderline ovarian tumours) - CA125 entries were deemed invalid if the value was missing or ≤0
Number of participants	N = 342278 women
Length of follow-up	12 months
Loss to follow-up	None
Index test(s)	Serum biomarker cancer antigen 125 (CA125) cut-off ≥35 U/ml for age groups <50 years old and ≥50 years old
Reference standard (s)	Invasive ovarian cancer recorded in the National Cancer Registration and Analysis Service (NCRAS) within 12 months of the index CA125 test
Additional comments	The study used routinely collected coded data. The study used linked data from the CPRD Aurum dataset and the NCRAS. The analysis was performed using the Ovatools prediction model, developed using CA125 results and age data from over 50,000 women tested in English primary care. The Ovatools models, developed via

	logistic regression, used continuous CA125 and age with restricted cubic splines to account non-linear relationships between variables. Invasive ovarian cancer was defined (per International Classification of Diseases (ICD)-10 codes by World Health Organization (WHO)/International Federation of Gynaecology and Obstetrics (FIGO)) as: - Ovarian malignancy - Fallopian tube malignancy - Primary peritoneal malignancy Outcome excluded borderline ovarian tumours and neoplasms of uncertain behaviour of the ovary.

Abbreviations: CA125: cancer antigen 125; ICD: International Classification of Diseases.

Population characteristics

Characteristic	**Study (N = 342278)**
Mean age (SD) Median (IQR)	53 (44 to 66)
Number of patients - <50 years Sample size	n = 143298; % = 41.9
Number of patients - ≥50 years Sample size	n = 198980; % = 58.1
Raised CA125, (≥35 U/ml) No of events	n = 23742; % = 6.94
Cancer incidence - Invasive ovarian cancer No of events	n = 2143; % = 0.63
Cancer incidence - Borderline ovarian cancer No of events	n = 513; % = 0.15
Deprivation quintiles based on the Townsend Deprivation score - Quintile 1 (least deprived) Number of patients (%) Custom value	83628 (24.4)
Deprivation quintiles based on the Townsend Deprivation score - Quintile 2 Number of patients (%) Custom value	75611 (22.1)
Deprivation quintiles based on the Townsend Deprivation score - Quintile 3 Number of patients (%) Custom value	66688 (19.5)

Characteristic	Study (N = 342278)
Deprivation quintiles based on the Townsend Deprivation score - Quintile 4 Number of patients (%) Custom value	57796 (16.9)
Deprivation quintiles based on the Townsend Deprivation score - Quintile 5 (most deprived) Number of patients (%) Custom value	58184 (17)
Deprivation quintiles based on the Townsend Deprivation score - Missing Number of patients (%) Custom value	371 (0.11)
Ethnicity - White or White British Number of patients (%) Custom value	289186 (84.5)
Ethnicity - Asian or Asian British Number of patients (%) Custom value	17711 (5.2)
Ethnicity - Mixed Number of patients (%) Custom value	14261 (4.2)
Ethnicity - Black or Black British Number of patients (%) Custom value	11290 (3.3)
Ethnicity - Other Number of patients (%) Custom value	5876 (1.7)
Ethnicity - Missing Number of patients (%) Custom value	3954 (1.2)

Abbreviations: CA125: cancer antigen 125; IQR: interquartile range.

Risk of bias

Critical Appraisal - QUADAS-2

Question	Answer
Risk of Bias	Low *(Index test was interpreted with full knowledge of the reference standard results; however, index test is objective so decreases the likelihood of bias. Reference standard was interpreted with full knowledge of the index test results; however, reference standard is objective so decreases the likelihood of bias.)*

Question	Answer
Directness	Directly applicable *(The analysis was performed using the Ovatools prediction model.)*

Funston, 2020

Bibliographic Reference	Funston, Garth; Hamilton, Willie; Abel, Gary; Crosbie, Emma J; Rous, Brian; Walter, Fiona M; The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: A population-based cohort study.; PLoS medicine; 2020; vol. 17 (no. 10); e1003295

Table 2: Funston 2020 study details

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location - UK (England) Setting - Primary care Study dates - 1 May 2011 to 31 December 2014 Sources of funding - Cancer Research UK [C8640/A23385] - The National Institute of Health Research (NIHR) School of Primary Care Research [FR17424]
Inclusion criteria	- Women with a code for CA125 measurement in primary care - CA125 entries documented in standard equivalent units: U/ml, IU/ml, KU/L, or KIU/L
Exclusion criteria	Women: - <18 years old at first CA125 test - registered at GP practices not “up-to-standard” on data quality by the Clinical Practice Research Datalink (CPRD) at first CA125 test - with a record of ovarian cancer in the National Cancer Registration and Analysis Service (NCRAS) on or before the CA125 test date - with a CA125 test within 12 months prior to the first CA125 test taken during the study period - CA125 values with spurious cutoffs (245, 420, 455 U/ml) or with no cutoff provided
Number of participants	N = 50780 women

Length of follow-up	12 months
Loss to follow-up	None
Index test(s)	Serum biomarker cancer antigen 125 (CA125) cut-off ≥35 U/ml for age groups <50 years old and ≥50 years old
Reference standard (s)	Diagnosis of ovarian cancer (ICD-10, NCRAS) within 12 months after the initial CA125 test
Additional comments	The study used routinely collected coded data. The study used linked data from the CPRD GOLD dataset and the NCRAS. Ovarian cancer was defined (per International Federation of Gynaecology and Obstetrics (FIGO)/World Health Organization (WHO)) as: - Ovarian malignancy - Fallopian tube malignancy - Peritoneal malignancy - Neoplasm of uncertain behaviour of the ovary Outcome included borderline ovarian tumours.

Abbreviations: CA125: cancer antigen 125.

Population characteristics

Characteristic	**Study (N = 50780)**
Mean age (SD) mean (range) Custom value	56 (18–102)
Number of patients - <50 years Sample size	n = 19694; % = 38.8
Number of patients - ≥50 years Sample size	n = 31086; % = 61.2
Raised CA125, (≥35 U/ml) No of events	n = 3468; % = 6.8
Raised CA125, - <50 years No of events	n = 1482; % = 7.5
Raised CA125, - ≥50 years No of events	n = 1986; % = 6.4
Ovarian cancers No of events	n = 456; % = 0.9
Ovarian cancers - <50 years No of events	n = 80; % = 0.4
Ovarian cancers - ≥50 years	n = 376; % = 1.2

Characteristic	Study (N = 50780)
No of events	
Non-ovarian cancer No of events	n = 1321; % = 2.6
Non-ovarian cancer - <50 years No of events	n = 161; % = 0.8
Non-ovarian cancer - more or equal 50 years No of events	n = 1160; % = 3.7

Abbreviations: CA125: cancer antigen 125; SD: Standard deviation.

Risk of bias

Critical Appraisal - QUADAS-2

Question	Answer
Risk of Bias	Low *(Index test was interpreted with full knowledge of the reference standard results; however, index test is objective so decreases the likelihood of bias. Reference standard was interpreted with full knowledge of the index test results; however, reference standard is objective so decreases the likelihood of bias.)*
Directness	Directly applicable *(Authors assumed that CA125-tested women were symptomatic as the only indication for CA125 testing in English primary care is a presentation with a symptom of possible ovarian cancer.)*

Appendix E Forest plots

Review question 1

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

Review question 1

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

Appendix F GRADE summary

Table 3: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults <50 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[1] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	143298	≥35U/ml	Sensitivity 75.3 (70, 80) Specificity 92.5 (92.3, 92.6)	2 (1.8, 2.3)	24.7 (20, 30)	Not serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity
1 (Funston 2020)	Retrospective cohort	19694	≥35U/ml	Sensitivity 72.5 (56.1, 85.4) Specificity 92.6 (92.2, 93)	2 (1.3, 2.8)	27.5 (14.6, 43.9)	Not serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.
Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the papers. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

2. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

Table 4: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults ≥50 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[1] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	198980	≥35U/ml	Sensitivity 86.5 (84.8, 88) Specificity 94.3 (94.2, 94.4)	12.5 (11.9, 13.1)	13.5 (12, 15.2)	Not serious	Serious[2]	Not serious	Serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity
1 (Funston 2020)	Retrospective cohort	31086	≥35U/ml	Sensitivity 86.5 (82.2, 90) Specificity 94.4 (94.2, 94.7)	13.8 (12.4, 15.4)	13.5 (10, 17.8)	Not serious	Serious[2]	Not serious	Serious for sensitivity[3] Not serious for specificity	LOW for sensitivity MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the papers. This figure has been multiplied by 100 to convert it into a % for ease of understanding.
2. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.
3. Serious imprecision because 95% CI crosses 1 decision making thresholds (for sensitivity, thresholds are 0.10 and 0.90).

Table 5: Diagnostic evidence summary: serum CA125 for detection of ovarian cancer[1] in adults <50 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[2] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Funston 2020)	Retrospective cohort	19694	≥35U/ml	Sensitivity 62.5 (51, 73.1)	3.4 (2.5, 4.4)	37.5 (26.9, 49)	No serious	Serious[3]	Not serious	Not serious for sensitivity	MODERATE for sensitivity
				Specificity 92.7 (92.3, 93.1)						Not serious for specificity	MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. Outcome included borderline ovarian tumours.
2. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.
3. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

Table 6: Diagnostic evidence summary: serum CA125 for detection of ovarian cancer[1] in adults ≥50 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[2] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Funston 2020)	Retrospective cohort	31086	≥35U/ml	Sensitivity 80.1 (75.7, 84) Specificity 94.5 (94.3, 94.8)	15.2 (13.6, 16.8)	19.9 (16, 24.3)	No serious	Serious[3]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. Outcome included borderline ovarian tumours.

2. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

3. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

Table 7: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults all ages (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[1] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	342278 (18 – 89 years old)	≥35U/ml	Sensitivity 84.9 (83.8, 86.4) Specificity 93.6 (93.5, 93.6)	7.7 (7.3, 8.0)	15.1 (13.6, 16.2)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity
1 (Funston 2020)	Retrospective cohort	50780	≥35U/ml	Sensitivity 84.9 (80.8, 88.5) Specificity 93.7 (93.5, 93.9)	8.8 (7.8, 9.8)	15.1 (11.5, 19.2)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

2. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

Table 8: Diagnostic evidence summary: serum CA125 for detection of ovarian cancer[1] in adults all ages (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[2] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	342278 (18 – 89 years old)	≥35U/ml	Sensitivity 78.6 (77.0, 80.2) Specificity 93.6 (93.5, 93.7)	8.8 (8.4, 9.2)	21.4 (19.8, 23)	No serious	Serious[3]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity
1 (Funston 2020)	Retrospective cohort	50780	≥35U/ml	Sensitivity 77 (72.8, 80.8) Specificity 93.8 (93.6, 94)	10.1 (9.1, 11.2)	23 (19.2, 27.2)	No serious	Serious[3]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.
Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. Outcome included borderline ovarian tumours.

2. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

3. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

Table 9: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults 18 - 49 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[1] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	143298	≥46U/ml	Sensitivity 67.9 (62.3, 73.2) Specificity 95.8 (95.7 95.9)	3.2 (2.8, 3.7)	32.1 (26.8, 37.7)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity
1 (Arendse 2025)	Retrospective cohort	143298	≥123U/ml	Sensitivity 48.8 (43.0, 54.6) Specificity 99.1 (99.1, 99.2)	10.7 (9.1, 12.5)	51.2 (45.4, 57)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

2. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

Table 10: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults 50 - 89[1] years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[2] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	198980	≥35U/ml	Sensitivity 86.2 (84.6, 87.8)	12.8 (12.2, 13.4)	13.8 (12.2, 15.4)	No serious	Serious[3]	Not serious	Not serious for sensitivity	MODERATE for sensitivity
				Specificity 94.6 (94.5, 94.7)						Not serious for specificity	MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. Age group 50-89 excludes everyone above 89, who are likely to be included in the ≥50 age group. Excluding the participants aged above 89 years old lead to marginal difference from the results reported in Table 4.

2. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

3. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

Table 11: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults 50 - 59 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[1] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	77697	≥35U/ml	Sensitivity 80.5 (76.3, 84.3) Specificity 95.7 (76.3, 84.3)	8.8 (7.9, 9.7)	19.5 (15.7, 23.7)	No serious	Serious[2]	Not serious	Not serious for sensitivity Serious for specificity[3]	MODERATE for sensitivity LOW for specificity
1 (Arendse 2025)	Retrospective cohort	77697	≥26U/ml	Sensitivity 84.8 (80.9, 88.2) Specificity 91.6 (91.4, 91.8)	5.0 (4.5, 5.5)	15.2 (11.8, 19.1)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity
1 (Arendse 2025)	Retrospective cohort	77697	≥57U/ml	Sensitivity 72.3 (67.7, 76.6)	16.7 (14.9, 18.5)	27.7 (23.4, 32.3)	No serious	Serious[2]	Not serious	Not serious for sensitivity	MODERATE for sensitivity

				Specificity 98.1 (98.0, 98.2)						Not serious for specificity	MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

2. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

3. Serious imprecision because 95% CI crosses 1 decision making thresholds (for specificity, thresholds are 0.50 and 0.80).

Table 12: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults 60 - 69 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[1] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	57257	≥35U/ml	Sensitivity 86.9 (83.9, 89.5)	18.5 (17.1, 19.9)	13.1 (10.5, 16.1)	No serious	Serious[2]	Not serious	Not serious for sensitivity	MODERATE for sensitivity
				Specificity 95.9 (95.8, 96.1)						Not serious for specificity	MODERATE for specificity

1 (Arendse 2025)	Retrospective cohort	57257	≥22U/ml	Sensitivity 92.4 (90.0 94.4) Specificity 89.3 (89.0, 89.5)	8.4 (7.7, 9.1)	7.6 (5.6, 10)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity
1 (Arendse 2025)	Retrospective cohort	57257	≥37U/ml	Sensitivity 86.6 (83.6, 89.2) Specificity 96.2 (96.1, 96.4)	19.7 (18.2, 21.3)	13.4 (10.8, 16.4)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

2. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

Table 13: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults 70 - 79 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%)	FNR[1] (%)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty

					(95% CI)	**(95% CI)**					
1 (Arendse 2025)	Retrospective cohort	40624	≥35U/ml	Sensitivity 87.7 (84.6, 90.3) Specificity 93.6 (93.4, 93.8)	15.5 (14.2, 16.8)	12.3 (9.7, 15.4)	No serious	Serious[2]	Not serious	Serious[3] for sensitivity Not serious for specificity	LOW for sensitivity MODERATE for specificity
1 (Arendse 2025)	Retrospective cohort	40624	≥22U/ml	Sensitivity 93.5 (91.0 95.4) Specificity 84.7 (84.4, 85.1)	7.6 (6.9, 8.2)	6.5 (4.6, 9)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity
1 (Arendse 2025)	Retrospective cohort	40624	≥41U/ml	Sensitivity 86.4 (83.2, 89.2) Specificity 94.9 (94.6, 95.1)	18.3 (16.8, 19.9)	13.6 (10.8, 16.8)	No serious	Serious[2]	Not serious	Not serious for sensitivity Not serious for specificity	MODERATE for sensitivity MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

2. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

3. Serious imprecision because 95% CI crosses 1 decision making thresholds (for sensitivity, thresholds are 0.10 and 0.90).

Table 14: Diagnostic evidence summary: serum CA125 for detection of invasive ovarian cancer in adults 80 - 89 years old (sensitivity analysis)

No of studies	Study design	Sample size	CA125 threshold	Effect size (%) (95% CI)	PPV (%) (95% CI)	FNR[1] (%) (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Arendse 2025)	Retrospective cohort	23402	≥35U/ml	Sensitivity 90.6 (88.6, 93.9)	9.2 (8.1, 10.4)	9.4 (6.1, 11.4)	No serious	Serious[2]	Not serious	Serious[3] for sensitivity	LOW for sensitivity
				Specificity 88.6 (88.1, 89.0)						Not serious for specificity	MODERATE for specificity
1 (Arendse 2025)	Retrospective cohort	23402	≥26U/ml	Sensitivity 92.2 (88.1, 95.1)	6.1 (5.3, 6.9)	7.8 (4.9, 11.9)	No serious	Serious[2]	Not serious	Serious[2] for sensitivity	LOW for sensitivity
				Specificity 81.8 (81.2, 82.3)						Not serious for specificity	MODERATE for specificity
1 (Arendse 2025)	Retrospective cohort	23402	≥58U/ml	Sensitivity 83.1 (78.0, 87.5)	15.0 (13.2, 16.9)	16.9 (12.5, 22)	No serious	Serious[2]	Not serious	Not serious for sensitivity	MODERATE for sensitivity

				Specificity 94.0 (93.6, 94.3)						Not serious for specificity	MODERATE for specificity

Abbreviations: CA125: cancer antigen 125; CI: confidence interval; FNR: false negative rate; PPV: positive predictive value.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

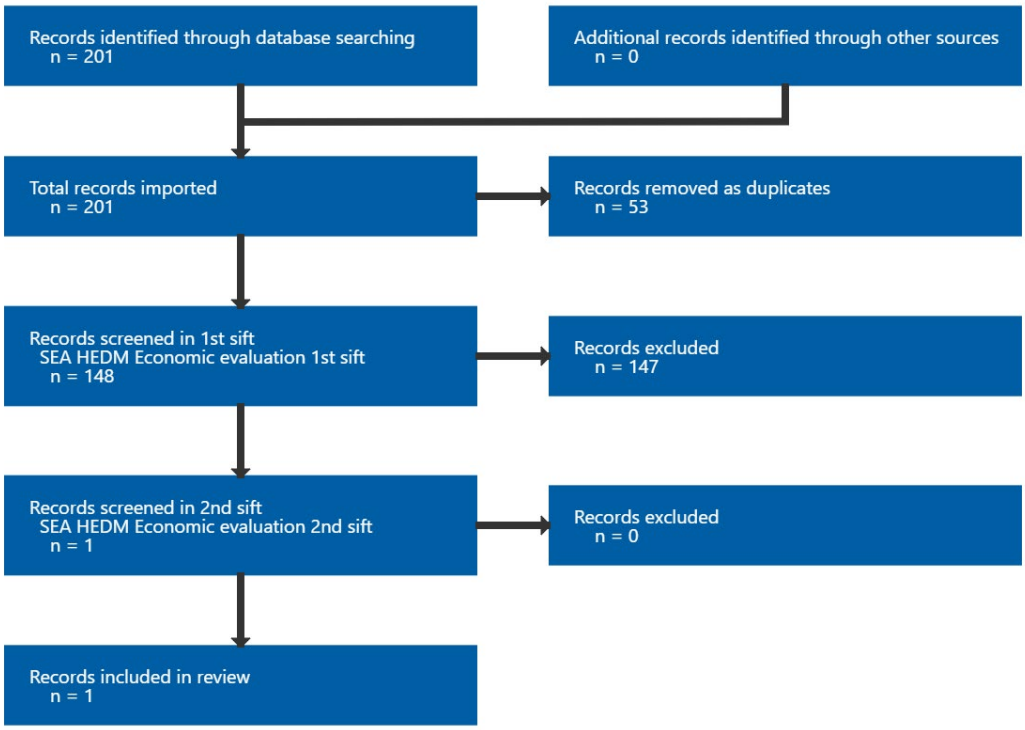
1. FNR is calculated as follows: FNR = (1-sensitivity) to avoid using derived values as the 2x2 table was not reported in the paper. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

2. Downgraded once for serious inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

3. Serious imprecision because 95% CI crosses 1 decision making thresholds (for sensitivity, thresholds are 0.10 and 0.90).

Appendix G Economic evidence study selection

Figure 2: Economic evidence study selection flow chart



Appendix H Economic evidence tables

Sequential and concurrent pathways using age-based CA125 thresholds versus standard primary care pathway for detecting ovarian cancer in women presenting with suspected cancer in primary care

Table 15: Wu 2025 study details

Section	Details for Wu, 2025
Study details	**Economic analysis type:** Cost-utility analysis. **Analysis design:** Decision analytic model with a primary-care diagnostic decision tree plus a cohort Markov model. **Country setting:** UK **Perspective:** NHS **Time horizon/Follow-up:** Lifetime (to age 110) **Treatment duration:** NA (diagnostic pathway evaluation) **Discount rate per year:** Costs: 3.5%; Outcomes: 3.5%
Interventions	**Pathway 1:** CA125 test; if CA125 ≥ 35 U/mL, then pelvic/transvaginal ultrasound (USS) – standard care **Pathway 2:** Ovarian cancer (OC) risk estimated using Ovatools (that uses age and CA125); if OC risk < 1%: no further investigation; 1 to < 3%: USS; ≥ 3%: urgent suspected cancer referral. **Pathway 3:** Uses age-specific CA125 thresholds equivalent to Ovatools ~1% (USS) and ~3% (urgent referral) OC risk cut-points. **Pathway 4:** Concurrent CA125 and ultrasound, with referral if either test is abnormal. The abnormal CA125 threshold was defined in various ways, including Ovatools OC risk ≥ 3%, its equivalent age-adjusted CA125 threshold, or CA125 ≥ 35 U/ml. Two and 3 are equivalent with 2 using OC risk and 3 using equivalent age-based CA125 levels.
Population	**Population:** Women (N=276,827) presenting to primary care with suspected ovarian cancer symptoms **Baseline characteristics** Mean age = 54.6 years (SD 15.8) < 50 years: N=112,081, invasive OC within 1 year: 0.2%; of staged cases, 46% late stage (III–IV) ≥ 50 years: N=164,746, invasive OC within 1 year: 1.05%; of staged cases, 72% late stage (III–IV) Ethnicity: White 89.9%, Asian 5.7%, Black 3.4%, Mixed/Other 1.0%
Costs included	**Original currency & cost year:** 2022 British pounds **Cost components incorporated:** GP face-to-face, GP phone, nurse time, CA125 test, USS test, outpatient consultations, inpatient care costs, add-ons for referrals without an eventual cancer diagnosis (outpatient consultation, a CA125 test and a USS), missed diagnoses (repeat diagnostic process in primary care), benign surgery, i.e., false-positive referrals who undergo surgery.

Section	Details for Wu, 2025
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** -Diagnostic endpoints after CA125: true positive OC (detected & referred), false negative OC (missed), true negative, false positive (no OC but referred). - Stage shift for additional true positives (proportion of cases moving from late to early stage). - Benign surgery among referred non-cancer cases, i.e., false-positive referrals who undergo surgery. - Cancer and non-cancer death.
Data Sources	**Effectiveness data:** - CA125 and Ovatools sensitivities/specificities by age from a parallel CPRD-based study. - USS diagnostic accuracy from evidence used in NICE CG122. - Stage-shift (late-to-early) effect when cancers are detected earlier (relative reduction in late-stage incidence derived from UKCTOCS). - Survival using flexible parametric models for cancer death by site including OC, lower GI, uterine, lung, pancreatic, other using CPRD linked data with age, stage, ethnicity, deprivation. **Baseline / epidemiological data:** - CPRD primary care records for women who had CA125 and/or USS between April 2013 – December 2017 was used to identify the study population, CA125 testing and baseline characteristics (age, ethnicity, deprivation). - Hospital Episode Statistics data for inpatient and diagnostic imaging data. - National Cancer Registration and Analysis Service (NCRAS) for cancer diagnoses, stage at diagnosis. - Death registration data for mortality outcomes. - Office for National Statistics (ONS) mortality tables for age-, sex-, and cause-specific mortality rates for non-cancer deaths beyond 8 years. **Quality-of-life weights:** EQ-5D utilities predicted from UK Biobank **Costs and/or resource use:** National sources including Unit Costs of Health and Social Care 2022 manual and NHS England National Schedule of NHS Costs 2021/2022
Results: costs	**Lifetime** incremental Women < 50 years (2 - 1): –£33,354 (savings) (3 - 1): –£33,455 (savings) (4 - 3): £258,083 to £334,595 (depending on how abnormal CA125 was defined) Women ≥ 50 years (2 - 1): £34,894 (3 - 1): £39,327 (4 - 3): £283,225 to £304,856 (depending on how abnormal CA125 was defined)
Results: health outcomes	**Lifetime** incremental (QALYs) Women < 50 years (2 - 1): –0.97 (reduction) (3 - 1): –0.95 (reduction) (4 - 3): 0.3 to 2.44 (depending on how abnormal CA125 was defined)

Section	Details for Wu, 2025
	Women ≥ 50 years (2 - 1): 1.48 (3 - 1): 1.53 (4 - 3): 1.86 to 2.23 (depending on how abnormal CA125 was defined)
Results: cost effectiveness	**Incremental cost-effectiveness ratios:** Women < 50 years 2 vs 1: £34,350 cost saving per QALY lost 3 vs 1: £35,348 cost saving per QALY lost 4 vs 3: extendedly dominated[1] to £137,123 per QALY gained. Women ≥ 50 years 2 vs 1: £23,610 per QALY gained 3 vs 1: £25,712 per QALY gained 4 vs 3: extendedly dominated[1] to £358,960 per QALY gained
Results: Uncertainty	Sensitivity analyses were not reported for women < 50 years and focused only on 2 or 3 versus 1, with 2 and 3 being equivalent with one utilising OC risk and the other equivalent age-based CA125 levels. **Deterministic:** Women ≥ 50 years • Raising the moderate-risk threshold for USS from 1.0% to 1.2–1.4% brings ICER below £20k; at ~1.5% it is ~£10k; further increases up to 2% can yield benefits with cost savings (age-based CA125 dominant). Changing the high-risk (≥3%) referral threshold has minor impact. At OC risk of 1.4% age-based CA125 thresholds were: 50 – 59 years: 31 U/ml or greater, 60 – 69 years: 24 IU/ml or greater, 70 – 79 years: 25 IU/ml or greater, and 80+: 31 IU/ml or greater. • Late-stage risk reduction (stage-shift) (base-case: RR 0.836 [95% CI: 0.737 – 0.950], i.e. have about a 16.4% lower risk of being diagnosed at late stage compared to usual care): Smaller reduction increases ICER; larger reduction decreases ICER (can fall <£20k/QALY). • Excluding the long-term QoL improvement after benign gynaecological surgery (base-case: immediate disutility of –0.04 in the year of surgery, +0.008 per year thereafter), pathway using age-based CA125 thresholds looked less cost effective without this benefit. • Discounting (base-case: 3.5%): Using 1.5% for costs & QALYs reduces ICER (improves cost effectiveness). • Including effects on other cancers (lower GI, uterine, lung, pancreatic) improves cost effectiveness. • USS test characteristics/costs: Higher USS sensitivity (base-case: 85%, varied by ±5%) or higher USS (base-case: £204, £64-210 sensitivity analyses) costs tend to worsen ICER but not very sensitive due to it being undertaken on a smaller subset of people. **Probabilistic:** Cost-effectiveness acceptability: Women ≥ 50 years At an ICER of £23,610/QALY and above, pathway using age-based CA125 thresholds have higher probability of being cost effective (vs current practice).

Section	Details for Wu, 2025
Health inequalities assessment	Ethnicity and deprivation were included as covariates in the survival and cost models used to predict long-term outcomes and costs, but there is no subgroup cost-effectiveness analysis or explicit equity impact assessment.
Comments	**Source of funding:** National Institute for Health and Care Research (NIHR) School for Primary Care Research. Additional support: NIHR Advanced Fellowship (NIHR300650) and NIHR Manchester Biomedical Research Centre (NIHR203308) for one author; Cancer Research UK through the CanTest Collaborative (grant C8640/A23385) **Other:** Concurrent CA125 and USS pathways were also modelled, however, these were not cost effective.
Rating: Applicability	Partially applicable. The model focused on invasive ovarian cancer detection only. Generally, CA125 is less sensitive to borderline tumours. These cancers are usually diagnosed at an earlier stage, often incidentally and have a much better prognosis. Also, the current practice NICE “CA125 first, then ultrasound” pathway was aimed to pick up invasive cancers. Modelled pathways assumed that USS could be largely undertaken within primary care. Otherwise, all other applicability criteria were met including UK study, QALYs and UK NHS perspective.
Rating: Quality/ limitations	Minor limitations Well conducted study with no limitations identified. Some inputs were based on assumptions; however, the impact on the ICER was assessed using extensive sensitivity analyses.

Abbreviations: Abbreviations: UK = United Kingdom; NHS = National Health Service; NA = Not applicable; CA125 = Cancer antigen 125; U/ml = Units per millilitre; USS = Ultrasound scan; OC = Ovarian cancer; N = Number; SD = Standard deviation; GP = General practitioner; QALY = Quality-adjusted life year; CPRD = Clinical Practice Research Datalink; GI = Gastrointestinal; NCRAS = National Cancer Registration and Analysis Service; ONS = Office for National Statistics; EQ-5D = EuroQol five dimensions questionnaire; k = Thousand; RR = Relative risk; CI = Confidence interval; ICER = Incremental cost-effectiveness ratio; QoL = Quality of life; NIHR = National Institute for Health and Care Research; PPV = Positive predictive value

1. An extendedly dominated option is an option that is less efficient than a combination of other available options. There exists a more efficient mix of alternatives that achieves the same or greater health benefit at a lower or equal cost per QALY.

Appendix I Excluded studies

Diagnostic

Table 16: Studies excluded from the diagnostic review

Study	Code [Reason]
(2002) Ovarian Cancer Screening Pilot Trial in High Risk Women. clinicaltrials.gov	- Publication date *Study (pilot) was published before 2015.*
(2004) Specialized Program Of Research Excellence (SPORE) In Ovarian Cancer/Cancer Genetics Network Collaborative Ovarian Cancer Screening Pilot Trial In High Risk Women. clinicaltrials.gov	- Publication date *Study (pilot) was published before 2015.*
(2011) Blood Test for Ovarian Cancer Associated Auto Antibodies. clinicaltrials.gov	- Not a relevant study design *experiment protocol*
(2019) The Use of a New Biomarker, HE4, in Combination With Simple Ultrasound Rules in the Prediction of Malignancy in a Pelvic Mass Detected on Ultrasound. clinicaltrials.gov	- Country *Study conducted in Hong Kong.*
(2024) Discriminating Borderline from Stage I Invasive Ovarian Cancer (BIOC): a Prospective Multicenter Diagnostic Biomarker Study. clinicaltrials.gov	- Full text paper not available *Study is not completed. Expected completion between 2028 and 2029. Study aims to enrol patients with borderline ovarian tumours and with stage I invasive ovarian cancer from multiple hospitals and gynaecology ultrasound departments where they will receive pre-surgical blood sampling and clinical evaluations.*
Abdalla, Nabil, Bachanek, Michal, Trojanowski, Seweryn et al. (2013) Diagnostic value of ultrasound indicators of neoplastic risk in preoperative differentiation of adnexal masses. Journal of ultrasonography 13(53): 145-54	- Population *Population is people admitted to the secondary care with adnexal mass and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Ashmore, Ayisha A, Gnanachandran, Chellappah, Luqman, Iqra et al. (2021) One-stop clinic for patients with suspected ovarian cancer: results from a retrospective outcome study of the referral pathway. BMC women's health 21(1): 429	- Outcome to be predicted do not match that specified in the protocol *Outcomes report age groups and histological outcome based on Ca-125 and not a diagnostic accuracy of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Aydin, D S, Turkyilmaz, E, Goksedef, B P et al. (2017) 1,138 women with adnexal mass: pathologic findings according to age.	- Population *Population is patients who operated for suspected adnexal masses and not adults*

Study	Code [Reason]
European journal of gynaecological oncology 38(1): 102-105	*presenting to primary care with symptoms that suggest ovarian cancer.*
Bagde, N.D.; Bagde, M.N.; Lone, Z.A. (2020) Relationship between Serum Tumor Markers, CA-125, CEA, CA19-9, LDH, and betaHCG with Histopathology and Age in Women with Ovarian Tumors. Asia Pacific Journal of Cancer Biology 5(4): 167	- Country *Geography where study was conducted not disclosed. Judging from context it is likely not OECD.*
Barlow, Melissa, Down, Liz, Mounce, Luke T A et al. (2024) The diagnostic performance of CA-125 for the detection of ovarian cancer in women from different ethnic groups: a cohort study of English primary care data. Journal of ovarian research 17(1): 173	- Study does not contain any relevant index tests *Index test examines the association between patient ethnicity and ovarian cancer diagnosis following a CA-125 test and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Chen, J., Chang, C., Huang, H.-C. et al. (2015) Differentiating between borderline and invasive malignancies in ovarian tumors using a multivariate logistic regression model. Taiwanese Journal of Obstetrics and Gynecology 54(4): 398	- Country *Study conducted in Taiwan.*
Chen, Yong-Ning, Ma, Fei, Zhang, Ya-di et al. (2020) Ultrasound Features Improve Diagnostic Performance of Ovarian Cancer Predictors in Distinguishing Benign and Malignant Ovarian Tumors. Current medical science 40(1): 184-191	- Country *Study conducted in China.*
Crawford, S Michael and Evans, Colin (2018) Outcome of elevated CA125 values from primary care following implementation of ovarian cancer guidelines. Family practice 35(2): 199-202	- Study does not contain any relevant index tests *Index test reports CA125 values measured in accordance with NICE guidance and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Feng, Wei Lian, Xie, Xiu Jing, Jiang, Jian et al. (2025) Logistic regression analysis of ultrasound features for predicting borderline ovarian tumours in young women aged <= 40 year. Ginekologia polska	- Country *Study conducted in China.*
Filiz, Ahmet Arif; Kahyaoglu, Serkan; Atalay, Cemal Resat (2024) Comparison of International Ovarian Tumor Analysis ADNEX model and Ovarian-Adnexal Reporting and Data System with final histological diagnosis in adnexal masses: a retrospective study. Obstetrics & gynecology science 67(1): 86-93	- Study does not contain any relevant index tests *Index test focuses on the evaluation of the O-RADS and IOTA ADNEX model scores and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Fortner, Renee T, Vitonis, Allison F, Schock, Helena et al. (2017) Correlates of	- Study does not contain any relevant index tests

Study	Code [Reason]
circulating ovarian cancer early detection markers and their contribution to discrimination of early detection models: results from the EPIC cohort. Journal of ovarian research 10(1): 20	*Index test reports association between epidemiologic characteristics and CA125 and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Fung Kee Fung, M., Bryson, P., Johnston, M. et al. (2004) Screening Postmenopausal Women for Ovarian Cancer: A Systematic Review. Journal of Obstetrics and Gynaecology Canada 26(8): 717	- Publication date *Systematic review with all included studies published before 2015. Therefore, no studies checked against protocol.*
Funston, Garth, Abel, Gary, Crosbie, Emma J et al. (2021) Could Ovarian Cancer Prediction Models Improve the Triage of Symptomatic Women in Primary Care? A Modelling Study Using Routinely Collected Data. Cancers 13(12)	- Study does not contain any relevant index tests *Index test focuses on the diagnostic performance of two diagnostic prediction models and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Funston, Garth, Mounce, Luke Ta, Price, Sarah et al. (2021) CA125 test result, test-to-diagnosis interval, and stage in ovarian cancer at diagnosis: a retrospective cohort study using electronic health records. The British journal of general practice : the journal of the Royal College of General Practitioners 71(707): e465-e472	- Study does not contain any relevant index tests *Index test measures the associate between CA125 test result and three outcomes test-to-diagnosis interval, tumour morphology and stage in ovarian cancer at diagnosis and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Henderson, JT; Webber, EM; Sawaya, GF (2018) Screening for Ovarian Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 319(6): 595-606	- Population *Population is women participating in annual prevalence screening programme and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Henderson, JT; Webber, EM; Sawaya, GF (2018) Screening for Ovarian Cancer: An Updated Evidence Review for the U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews	- Population *Population is women participating in annual prevalence screening programme and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Hu, X.; Zhang, J.; Cao, Y. (2022) Factors associated with serum CA125 level in women without ovarian cancer in the United States: a population-based study. BMC Cancer 22(1): 544	- Study does not contain any relevant index tests *Index test examines the factors associated with CA125 level and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Janas, Lukasz, Stachowiak, Grzegorz, Glowacka, Ewa et al. (2024) The use of CA125, human epididymis protein 4 (HE4), risk of ovarian malignancy algorithm (ROMA), risk of malignancy index (RMI) and subjective assessment (SA) in	- Population *Population is women qualified for surgery due to pelvic mass and who had their blood samples taken and transvaginal ultrasound scans performed preoperatively and not adults presenting to primary care with symptoms that suggest ovarian cancer.*

Study	Code [Reason]
preoperative diagnosing of ovarian tumors. Ginekologia polska 95(5): 321-327	
Jha, S. and Singh, A. (2023) Enhancing Diagnostic Accuracy in Ovarian Tumour Assessment: A Combined Approach of IOTA Simple Rules and CA125. Eurasian Journal of Medicine and Oncology 7(4): 312	- Country *Study conducted in India.*
Jiang, Zhuolin, Pu, Wei, Luo, Xinyi et al. (2025) Integrating O-RADS US v2022, CEUS, and CA125 to enhance the diagnostic differentiation of ovarian masses: development of the OCC-US model. Cancer imaging : the official publication of the International Cancer Imaging Society 25(1): 96	- Country *Study conducted in China.*
Karadag, Burak, Kocak, M, Kayikcioglu, F et al. (2014) Risk for malignant and borderline ovarian neoplasms following basic preoperative evaluation by ultrasonography, ca125 level and age. Asian Pacific journal of cancer prevention : APJCP 15(19): 8489-93	- Population *Population is women who underwent surgical exploration for an adnexal mass and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Karakaya, Burcu Kisa, Ozgu, Emre, Kansu, Hatice Celik et al. (2017) Evaluation of Probably Benign Adnexal Masses in Postmenopausal Women. Revista brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia 39(5): 229-234	- Population *Population is women admitted to the secondary care with adnexal mass and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Karimi-Zarchi, M., Behtash, N., Mousavi, A. et al. (2018) A survey on the role of cancer antigen 125 (CA125), human epididymis protein 4 (HE4), risk of ovarian malignancy algorithm (ROMA), and risk of malignancy index (RMI) in pelvic mass. International Journal of Cancer Management 11(12): e79189	- Not a relevant study design *Literature review using computerised search in databases and Google Scholar with key words, not a systematic review.*
Kwong, Fong Lien Audrey, Kristunas, Caroline, Davenport, Clare et al. (2024) Symptom-triggered testing detects early stage and low volume resectable advanced stage ovarian cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society	- Outcome to be predicted do not match that specified in the protocol *Outcomes report stage, disease distribution, and complete cytoreduction rates and not a diagnostic accuracy of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Le, T., Fayadh, R.A., Menard, C. et al. (2008) Variations in Ultrasound Reporting on Patients Referred for Investigation of Ovarian Masses. Journal of Obstetrics and Gynaecology Canada 30(10): 902	- Publication date *Study was published before 2015.*

Study	Code [Reason]
Luzak, A, Schnell-Inderst, P, Bühn, S et al. (2016) Clinical effectiveness of cancer screening biomarker tests offered as self-pay health service: a systematic review. European journal of public health 26(3): 498-505	- Study does not contain any relevant index tests *Index test focuses on the clinical effectiveness of biomarkers that are offered as a self-pay healthcare service for cancer screening of asymptomatic individuals and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Mathis, J., Jellouli, M.A., Sabiani, L. et al. (2020) Ovarian cancer screening in the general Population. Hormone Molecular Biology and Clinical Investigation 41(3): 0038	- Study does not contain any relevant index tests *Literature review, not a systematic review.*
Menon, Usha, Talaat, Ahmed, Rosenthal, Adam N et al. (2014) Performance of ultrasound as a second line test to serum CA125 in ovarian cancer screening. BJOG : an international journal of obstetrics and gynaecology 121suppl7: 35-9	- Population *Population is women participating in annual prevalence screening programme and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Moro, F., Momi, M., Bertoldo, V. et al. (2024) External validation of ultrasound-based models for discrimination between benign and malignant adnexal masses in Italy: the prospective multicenter IOTA phase 6 study. medRxiv	- Duplicate reference *Duplicate of Moro et al. 2025 study.*
Moro, Francesca, Momi, Marina, Ledger, Ashleigh et al. (2025) External validation of ultrasound-based models for differentiating between benign and malignant adnexal masses: a nationwide prospective multicenter study (IOTA phase 6). American journal of obstetrics and gynecology	- Population *Population is patients with confirmed adnexal mass judged not to be physiological and selected to undergo surgery and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Nanez, Andrea, Stram, Douglas A, Garcia, Christine et al. (2021) Ovarian cancer surveillance in the clinical follow up of women with known BRCA1 or BRCA2 pathogenic variants in a large health care system. Gynecologic oncology 163(1): 134-141	- Population *Population is women with known BRCA1 or BRCA2 PV followed for at least one year from genetic testing and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Nicholson, Brian D, Lee, Mei-Man, Wijeratne, Dileep et al. (2019) Trends in Cancer Antigen 125 testing 2003-2014: A primary care population-based cohort study using laboratory data. European journal of cancer care 28(1): e12914	- Study does not contain any relevant index tests *Index test relates to patterns of CA125 testing over an 11-year period and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Patil, Nanda J, Mane, Avinash, Hulwan, Atul B et al. (2024) Evaluation of Serum Cancer Antigen (CA)-125 Levels as a Biomarker for Ovarian Lesions: Correlation With	- Study does not contain any relevant index tests *Index test examines the association between CA-125 levels and ovarian lesion*

Study	Code [Reason]
Histopathological Diagnosis and Clinical Outcomes. Cureus 16(7): e65342	*characteristics, diagnostic and prognostic implications of serum CA-125 levels in ovarian cancer management and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Piovano, E, Cavallero, C, Fuso, L et al. (2017) Diagnostic accuracy and cost-effectiveness of different strategies to triage women with adnexal masses: a prospective study. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 50(3): 395-403	- Population *Population is women with a clinical diagnosis of an adnexal mass who were candidates for surgery and not adults presenting to primary care with symptoms that suggest ovarian cancer.*
Radosa, M P, Vorwergk, J, Fitzgerald, J et al. (2014) Sonographic discrimination between benign and malignant adnexal masses in premenopause. Ultraschall in der Medizin (Stuttgart, Germany : 1980) 35(4): 339-44	- Publication date *Study was published before 2015.*
Sasamoto, Naoko, Babic, Ana, Rosner, Bernard A et al. (2019) Predicting Circulating CA125 Levels among Healthy Premenopausal Women. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 28(6): 1076-1085	- Study does not contain any relevant index tests *Index test focuses on the evaluation of factors associated with CA125 in premenopausal women and validation CA125 prediction models and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Shetty, J.; Reddy, G.; Pandey, D. (2017) Role of sonographic gray-scale pattern recognition in the diagnosis of adnexal masses. Journal of Clinical and Diagnostic Research 11(9): qc12	- Study does not contain any relevant index tests *Index test focuses on the efficacy of pattern recognition at predicting an accurate histological diagnosis of adnexal masses and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Sukanya, L. (2022) Risk of malignancy index (RMI) for prediction of malignancy in women with adnexal masses. International Journal of Research in Pharmaceutical Sciences 13(3): 339	- Not a relevant study design *Experiment protocol, not a primary study.*
Sundar, Sudha, Agarwal, Ridhi, Davenport, Clare et al. (2024) Risk-prediction models in postmenopausal patients with symptoms of suspected ovarian cancer in the UK (ROCkeTS): a multicentre, prospective diagnostic accuracy study. The Lancet. Oncology 25(10): 1371-1386	- Study does not contain any relevant index tests *Index test focuses on the accuracy of risk prediction models for diagnosing ovarian cancer and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*

Study	Code [Reason]
Sundar, Sudha; Neal, Richard D; Kehoe, Sean (2015) Diagnosis of ovarian cancer. BMJ (Clinical research ed.) 351: h4443	- Not a relevant study design *Clinical Review.*
Woolas, Robert, Young, Lisa, Brinkmann, Dirk et al. (2024) Exploration of Preliminary Objective Triage by Menopause Score and CA 125 Result Prior to Accelerating Fast-Track Booking for Suspected Ovarian Cancer-A Role for the Pathway Navigator?. Diagnostics (Basel, Switzerland) 14(5)	- Study does not contain any relevant index tests *Index test focuses on the hypothesis that multiplying the CA 125 value by menopausal status could offer an immediate triage before the imaging is available and not the identification of age and serum CA125 thresholds or dual testing with serum CA125 and ultrasound.*
Wu, Manli, Wang, Qingjuan, Zhang, Man et al. (2023) Does Combing O-RADS US and CA-125 Improve Diagnostic Accuracy in Assessing Adnexal Malignancy Risk in Women With Different Menopausal Status?. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 42(3): 675-685	- Country *Study conducted in China.*
Yu, Chunying, Dou, Ting, Liu, Yun et al. (2020) Clinical value of TV-CDS combined with serum tumor markers in diagnosis of ovarian cancer. Oncology letters 20(2): 2028-2034	- Country *Study conducted in China.*
Zhang, Wei; Wang, Liying; Xin, Zhongqiu (2018) Combination of serum CA19-9 and CA125 levels and contrast-enhanced ultrasound parametric data facilitates to differentiate ovarian serous carcinoma from ovarian malignant epithelial cancer. Medicine 97(16): e0358	- Country *Study conducted in China.*

Abbreviations: CA125: cancer antigen 125.

Economic

No economic study was reviewed at full text and excluded from this review.

Appendix J Methods

Development of the guideline

Guideline covers

The methods outlined here relate to the update of recommendations on:

- Ovarian cancer in the NICE guideline on suspected cancer: recognition and referral guideline (NG12) (Recommendations 1.5.7 and 1.5.8) which outline when to refer patients via the suspected cancer pathway according to CA125 test and ultrasound results, and NICE guideline on ovarian cancer: recognition and initial management guideline (CG122) (Recommendations 1.1.2.2 to 1.1.2.4). This guidance will update recommendation listed above and seek to provide dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone to inform primary care decision making when making a referral to the suspected cancer pathway in adults presenting with symptoms that suggest ovarian cancer in primary care.

- NICE guideline on suspected cancer: recognition and referral guideline (NG12) (Recommendations 1.5.6, 1.5.7 and 1.5.9) to refer patients via the suspected cancer pathway according to age categories and CA125 test results, and in the NICE guideline on ovarian cancer: recognition and initial management guideline (CG122) (Recommendation 1.1.2). This guidance will update recommendation listed above and seek to provide age thresholds to inform primary care decision making when making a referral to the suspected cancer pathway in adults presenting with symptoms that suggest ovarian cancer in primary care.

Guideline does not cover

The methods outlined here do not apply to any other recommendations in NICE guidelines on suspected cancer: recognition and referral guideline (NG12) or ovarian cancer: recognition and initial management guideline (CG122).

Methods – diagnostic

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.

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

Developing the review questions and outcomes

The 2 review questions developed for this guideline were based on the key areas identified in the guideline scope. They were drafted by the NICE guideline development team and refined and validated by the guideline committee.

The review questions were based on the following frameworks:

Population, index test(s), reference standard and outcome for reviews of diagnostic and predictive accuracy

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review.

Searching for evidence

Evidence was searched for each review question using the methods specified in Developing NICE guidelines: the manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee

members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. At least 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Data synthesis for diagnostic accuracy data

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The ‘raw’ 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline were as follows:

Sensitivity is the probability that the feature will be positive in a person with the condition.

- sensitivity = TP/(TP+FN)

Specificity is the probability that the feature will be negative in a person without the condition.

- specificity = TN/(FP+TN)

False negative rate (FNR) describes the proportion of actual positives that are incorrectly classified as negatives and describes how often a test fails to detect something. A high FNR means the test is missing a lot of actual cases.

- FNR = 1 - sensitivity

Positive predictive values describe the probability that a person with a positive feature has the disease.

- PPV = TP/ (TP+FP)

Meta-analysis of the findings was not undertaken as only 2 studies were included for this review. Meta-analysis should not be performed on 2 studies as a minimum of 3 studies is needed to estimate the 5 parameters needed for a bivariate meta-analysis (mean and variance of logit sensitivity, mean and variance of logit specificity, and the correlation between logit sensitivity and logit specificity).

Appraising the quality of evidence

Diagnostic accuracy studies

Individual diagnostic accuracy studies were quality assessed using the QUADAS-2 tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

GRADE for diagnostic accuracy evidence

Evidence from diagnostic accuracy studies was initially rated as high quality and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 17 below.

The choice of primary outcome for decision making was determined by the committee and GRADE assessments were undertaken based on these outcomes.

In all cases, the downstream effects of diagnostic accuracy on patient-important outcomes were considered. This was done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences were incorporated here in addition.

GRADE assessments were only undertaken for sensitivity and specificity where available but results for positive predictive values and false negative rates are also presented alongside those data.

The committee were consulted to set 2 clinical decision thresholds for each measure: the value above which a test would be recommended, and a second below which a test would be considered of no clinical use. These values were used to judge imprecision (see below).

If studies could not be pooled in a meta-analysis, GRADE assessments were undertaken for each study individually and reported as separate lines in the GRADE profile.

These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 17 Rationale for downgrading quality of evidence for diagnostic accuracy data

GRADE criteria	Reasons for downgrading quality
Risk of bias	• Not serious (don't downgrade): less than 50% overall weighting some concerns/high risk of bias • Serious (downgrade 1 level): more than 50% some concerns/high risk of bias • Very serious (downgrade 2 levels): more than 50% high risk of bias.
Indirectness	• Not serious (don't downgrade): less than 50% of overall weighting partially direct or indirect. • Serious (downgrade 1 level): more than 50% of overall weighting partially direct or indirect. • Very serious (downgrade 2 levels): more than 50% of overall weighting indirect.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. Where data was pooled it was checked visually to identify inconsistency. Where there are apparent differences in effect size due consideration was given to the appropriateness of pooling studies.
Imprecision	The most appropriate primary pair of measures (for example: sensitivity/specificity, likelihood ratio) were used

GRADE criteria	Reasons for downgrading quality
	as described this in the review protocol. And appropriate thresholds with were discussed with the guideline committee.
Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

Methods - economic evidence

Reviewing economic evidence

Identifying economic evidence

Systematic reviews of economic literature were conducted in all areas relevant for economic evaluation covered by these review protocols. Titles and abstracts of articles identified through the systematic economic literature searches were assessed for inclusion using predefined eligibility criteria reported in the economic review protocol(s) (provided in appendix A).

Once the screening of titles and abstracts was completed, full-text copies of potentially relevant articles were acquired for detailed assessment, applying the economic review protocol inclusion and exclusion criteria.

Details of economic evidence study selection are presented in appendix G.

Appraising the quality of economic evidence

The applicability and methodological quality of economic evidence derived either from published studies meeting the inclusion criteria or from new economic analysis conducted for the guideline was assessed using the

economic evaluations checklist specified in Developing NICE guidelines: the manual, appendix H. This process led to applicability and quality statements for each included study, made by the health economist, following the criteria shown in Table 18.

Table 18: Criteria for developing applicability and quality statements of economic evidence

Appraised element	Statement and criteria
Applicability	Directly applicable – the study meets all applicability criteria, or fails to meet 1 or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost effectiveness. Not applicable – the study fails to meet 1 or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Quality	Minor limitations – the study meets all quality criteria, or fails to meet 1 or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. Potentially serious limitations – the study fails to meet 1 or more quality criteria, and this could change the conclusions about cost effectiveness. Very serious limitations – the study fails to meet 1 or more quality criteria, and this is highly likely to change

Appraised element	Statement and criteria
	the conclusions about cost effectiveness. Such studies would usually be excluded from the review.

All studies that fully or partially met the applicability and quality criteria described in the methodology checklist were considered by the committee during the guideline development process.

Details on methods and results of economic studies that met inclusion criteria and were subsequently used in decision making are shown in economic evidence study extraction tables, provided in appendix H.

Characteristics and results (cost-effectiveness estimates) of economic studies used in decision making, including applicability and quality statements, have been summarised in economic evidence characteristics and summary tables, respectively, provided in the economic sections of evidence reviews.

New economic analysis

No new cost-effectiveness analysis was prioritised by the committee, as they were aware of a recently published UK-based economic evaluation relevant to these review questions

Cost effectiveness criteria

NICE's principles set out criteria that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if any of the following criteria applied (provided that the estimate was considered plausible):

the intervention dominated other relevant strategies (that is, it was both less costly in terms of overall resource use and more effective compared with all other relevant alternative strategies)

the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, then the reasons for this decision were provided and recorded, with reference to issues around the plausibility of the estimate or to other factors, for example the degree of uncertainty around the ICER, aspects that relate to uncaptured benefits and non-health factors, or aspects that relate to health inequalities, as set out in the NICE health technology evaluations manual.

When economic evidence was not available, the committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use and/or related UK NHS unit costs between options, alongside respective effectiveness evidence.

The committee's considerations of cost effectiveness are discussed explicitly in the section 'Committee discussion and interpretation of the evidence' under the subheading 'Resources and cost-effectiveness', in each evidence review.

Appendix K Research recommendations

Research recommendation

What is the diagnostic test accuracy and cost-effectiveness of dual vs. sequential CA125 and ultrasound testing for ovarian cancer in people presenting with symptoms of suspected cancer in primary care.

Why this is important

There is a lack of UK-based research on the diagnostic impact and cost-effectiveness of undertaking serum CA125 and ultrasound scan consecutively (dual testing) compared to sequentially (if the aged-based appropriate serum CA125 threshold had been reached, undertaking an ultrasound scan). A diagnostic test accuracy study would provide data to support recommendation development on what approach should be adopted in primary care when

making clinical decisions regarding suspected ovarian cancer risk in this population.

Rationale for research recommendation

Importance to the population

The committee highlighted that in practice ultrasound scans may be being ordered when serum CA125 is tested. This means that for ovarian cancer many ultrasound scans are not necessary. These unnecessary appointments are a potential cause of unnecessary stress and anxiety for those referred and may increase the burden on system resources. The committee also flagged the paucity of evidence in groups with protected or other characteristics. The committee highlighted that the equality and health inequalities assessment (EHIA) highlighted general issues regarding access to services and delayed diagnosis that may impact those with protected and other characteristics and highlighted the need for consideration of these groups when undertaken research.

Relevance to NICE guidance

No evidence was identified for this review question, so the committee could not update the recommendation. Evidence would enable a future committee to make recommendations to guide clinical practice in this area on whether dual testing with CA125 and ultrasound or the current sequential pathway in the guideline recommendations is the preferred approach

Relevance to the NHS

Updated recommendations would help to ensure the optimal decision making around those who attend primary care with symptoms that are suggestive of ovarian cancer.

Current evidence base

The evidence review that sought to answer the question “What is the diagnostic accuracy of dual testing with serum CA125 and ultrasound scan for

the detection of suspected ovarian cancer compared to serum CA125 alone in adults for referral via a suspected cancer pathway?" identified no studies.

Table 19 Research recommendation protocol outline

Population	Adults presenting to primary care with symptoms that suggest ovarian cancer
Index test	Dual testing with serum CA125 and ultrasound scan (abdominal and/or pelvic)
Reference standard	Cancer diagnosis within 12 months following standard care* in adults presenting with symptoms that suggest ovarian cancer in primary care that might trigger further investigations such as ultrasound or trigger a referral via a suspected cancer pathway. *Standard care according to is to measure serum CA125 with ultrasound initiated if serum CA125 is above the ages specified threshold.
Diagnosis of interest	Ovarian cancer diagnosis within 12 months based on presentation symptoms that suggest ovarian cancer assessed via: • Sensitivity (upper 90, lower 10) • Specificity (upper 80, lower 50) • Positive predictive value (PPV that would trigger a referral to the suspected cancer pathway is 3%) • False negative rate (Sub-group analysis of groups with protected or other characteristics where data is available)
Study type(s)	Prospective cohort study Retrospective cohort study Diagnostic accuracy study Cost-utility analysis