Suspected cancer: recognition and referral guideline

Review protocol review question 3 Dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone for detection of suspected ovarian cancer in adults

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone for detection of suspected ovarian cancer in adults.
2.	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?
3.	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.
4.	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.
5.	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.

6.	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.
7.	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.
8.	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..
9.	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.
10.	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
11.	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.
12.	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
13.	Secondary outcomes	Not applicable
14.	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.
15.	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.
16.	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/"
17.	Analysis of sub-groups	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.		
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	20/08/2025		
22.	Anticipated completion date	01/10/2025		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐

		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE **5b Named contact e-mail** SuspectedCancer@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	• Robby Richey – Topic lead • Steven Barnes – Technical advisor • James Jagroo – Senior technical analyst • Armina Paule - Technical analyst • James Hawkins - Health economist • Amy Finnegan - Information specialist		

		• Jon Littler – Project manager
26.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	[Give the citation and link for the published protocol, if there is one.]
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	CA125 thresholds, ultrasound, ovarian cancer, suspected ovarian cancer referral.

33.	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.
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk