National Institute for Health and Care Excellence

Suspected cancer: recognition and referral

[A] Diagnostic review 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

Evidence underpinning recommendations 1.5.6 to 1.5.9 and 1.5.11 and research recommendation

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Draft for consultation

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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

1 Review question

Review question 1

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?

Review question 2

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?

1.1.1 Summary of the protocol

Table 1: Summary of the dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone in adults protocol

Population	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.
Index 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.

Diagnosis of interest	Different age thresholds and different serum CA125 thresholds in adults presenting with symptoms that suggest ovarian cancer in primary care.
Study type	• Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies •
Other	• Only studies from OECD countries will be included

Abbreviations: CA125: cancer antigen 125.

Table 2: Summary of the age and serum CA125 thresholds for detection of suspected ovarian cancer in adults protocol

Population	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.
Index 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.
Diagnosis of interest	Different age thresholds and different serum CA125 thresholds in adults presenting with symptoms that suggest ovarian cancer in primary care.
Study type	• Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies • Studies from OECD countries

Abbreviations: CA125: cancer antigen 125.

For the full protocol see appendix A in the technical appendices document.

1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol and in appendix J in the technical appendices document.

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

1.1.2.1 Search methods

The searches for the effectiveness evidence were run on 19/08/2025. The following databases were searched: Cochrane CDSR (Wiley), Embase (Ovid) and Medline ALL (Ovid). Limits were applied to remove animal papers, non-English language papers and conference abstracts. Filters were used to limit to OECD countries, diagnostic and cohort studies. A date limit was applied from January 2015 to August 2025.

The searches for the cost effectiveness evidence were run on 21/08/2025. The following databases were searched Embase (Ovid), International Health Technology Assessment Database (INAHTA), Medline ALL (Ovid). Limits were applied to remove animal papers, non-English language papers and conference abstracts. Filters were used to limit to cost effectiveness studies. A date limit was applied from January 2015 to August 2025.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in appendix B.

1.1.3 Diagnostic evidence

1.1.3.1 Included studies

Study selection

A systematic search was carried out to identify potentially relevant studies as detailed in appendix J in the technical appendices document /the methods document. See appendix B in the technical appendices document for the literature search strategy. The study selection process is presented as a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram in appendix C in the technical appendices document.

Review question 1

No studies were identified that met the criteria specified in the review protocol for the dual testing with serum CA125 and ultrasound scan compared to serum CA125 alone review appendix A.

Review question 2

Two studies were included. For a summary of included studies see Table 3**Error! Reference source not found.** and for full references see the list of included studies (section 1.1.11.1).

Evidence was presented in all ages (Arendse 2025 and Funston 2020) and in the following age subgroups: <50 years (Arendse 2025 and Funston 2020), ≥50 years (Arendse 2025 and Funston 2020), 18-89 years (Arendse 2025), 18-49 years (Arendse 2025), 50-89 years (Arendse 2025), 50-59 years (Arendse 2025), 60-69 years (Arendse 2025), 70-79 years (Arendse 2025), 80-89 years (Arendse 2025).

1.1.3.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion, are given in appendix I.

1.1.4 Summary of studies included in the diagnostic evidence

Review question 1

No evidence was identified that met the inclusion criteria for this review.

Review question 2

Table 3 Summary of studies included in the diagnostic evidence

Study details	Setting/Location/Funding	Population	Index test	Reference standard	Outcomes	Risk of bias
Arendse et al., 2025 N=342278 Study type: retrospective cohort Time between tests: not applicable	Setting: primary care Location: UK Funding source: Cancer Research UK [C8640/A23385] NIHR [PR-PRU-1217-21601]	≥18 years old women with a valid code for CA125 measurement in CPRD Target condition: suspected ovarian cancer	• Serum biomarker CA125 cut-off ≥35 U/ml for all age groups • ≥46U/ml and ≥123U/ml for 18 - 49 years old • ≥26U/ml and ≥57U/ml	Invasive ovarian cancer recorded in the NCRAS within 12 months of the index CA125 test	Sensitivity Specificity PPV FNR	Low

Study details	Setting/Location/Funding	Population	Index test	Reference standard	Outcomes	Risk of bias
			for 50 - 59 years old • ≥22U/ml and ≥37U/ml for 60 - 69 years old • ≥22U/ml and ≥41U/ml for 70 - 79 years old • ≥26U/ml and ≥58U/ml for 80 - 89 years old			
Funston et al., 2020 N=50780 Study type: retrospective cohort	Setting: primary care Location: UK Funding source: Cancer Research UK [C8640/A23385] NIHR School of Primary Care Research [FR17424]	≥18 years old women with a code for CA125 measurement in primary care Target condition: suspected ovarian cancer	Serum biomarker cancer antigen CA125 cut-off ≥35 U/ml	Diagnosis of ovarian cancer (ICD-10, NCRAS) within 12 months after the initial CA125 test	Sensitivity Specificity PPV FNR	Low

Study details	Setting/Location/Funding	Population	Index test	Reference standard	Outcomes	Risk of bias
Time between tests: not applicable						

Abbreviations: CA125: cancer antigen 125; CPRD: Clinical Research Practice Datalink; ICD: International Classification of Diseases; NCRAS: National Cancer Registration and Analysis Service; NIHR: The National Institute of Health Research; PPV: positive predictive value; FNR: false negative rate

See appendix D for full evidence tables.

1.1.5 Summary of diagnostic evidence

Review question 1

No studies were identified that met the inclusion criteria for this review.

Review question 2

Sensitivity is the proportion of those with the target condition who test positive for the condition and Specificity is the proportion of those without the target condition who test negative for the condition. The interpretation for the diagnostic ability of each index test was based on the agreed clinical decision-making thresholds. Sensitivity and specificity were rated as high, moderate or low based on the following:

- High: Point estimate is greater than or equal to the upper clinical decision-making threshold (≥90% for sensitivity and ≥80% for specificity).

- Moderate: Point estimate greater than or equal to the lower clinical decision-making threshold but lower than the upper clinical decision-making threshold (≥10% to <90% for sensitivity and ≥50% to <80% for specificity).
- Low: Point estimate is less than the lower clinical decision-making threshold (<10% for sensitivity and <50% for specificity).

A test with high sensitivity will classify more people as having the disease, thereby being good at ruling out the condition in people with a negative test result. A test with high specificity will classify fewer people as having the disease, thereby being good at ruling in the condition in people with a positive test result.

A minimum of 3 studies is required to estimate the parameters needed for bivariate meta-analysis. As only 2 studies have been included no meta-analysis was carried out.

Table 4: Summary of findings for diagnostic accuracy of serum CA125 for detecting of invasive ovarian cancer in adults <50 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detecting of invasive ovarian cancer in adults <50 years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (% range of point estimates) (95% CI)**	**PPV (%) (95% CI)**	**FNR[1] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
2* Arendse et al 2025; Funston et al 2020	Diagnostic accuracy (invasive ovarian cancer in adults <50 years old or not)	162992	≥35U/ml	Sensitivity: 72.5 to 75.3 [Arendse 75.3 (70, 80) and Funston 72.5 (56.1, 0.85.4)]	Arendse 2025: 2 (1.8, 2.3) Funston 2020: 2	Arendse 2025: 24.7 (20, 30) Funston 2020:	MODERATE	Moderate sensitivity. Test will rule out 24.7% to 27.5% of people who have the condition
				Specificity: 92.5 to 92.6			MODERATE	High specificity. Test will rule in 7.4% to

				[Arendse 92.5 (92.3, 92.6) and Funston 92.6 (92.2, 93)]	(1.3, 2.8)	27.5 (14.6, 43.9)		7.5% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 5: Summary of findings for diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults ≥50 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults ≥50 years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (% range of point estimates) (95% CI)**	**PPV (%) (95% CI)**	**FNR[1] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
2* Arendse et al 2025; Funston et al 2020	Diagnostic accuracy (invasive ovarian cancer in adults ≥50 years old or not)	230066	≥35U/ml	Sensitivity: 86.5 [Arendse 86.5 (84.8, 88) and Funston 86.5 (82.2, 90)]	Arendse 2025: 12.5 (11.9, 13.1) Funston 2020: 13.8	Arendse 2025: 13.5 (12, 15.2) Funston 2020: 13.5	LOW	Moderate sensitivity. Test will rule out 13.5% of people who have the condition
				Specificity: 94.3 to 94.7 [Arendse 94.3 (94.2, 94.4) and			MODERATE	High specificity. Test will rule in 5.3% to 5.7% of people who

				Funston 94.4 (94.2, 94.7)]	(12.4, 15.4)	(10, 17.8)		do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 6: Summary of findings for diagnostic accuracy of serum CA125 for detection of ovarian cancer[1] in adults <50 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detection of ovarian cancer[1] in adults <50 years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (%) (95% CI)**	**PPV (%) (95% CI)**	**FNR[2] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
1* Funston et al 2020	Diagnostic accuracy (ovarian cancer in adults <50 years old or not)	19694	≥35U/ml	Sensitivity: 62.5 (51, 73.1)	3.4 (2.5, 4.4)	37.5 (26.9, 49)	MODERATE	Moderate sensitivity. Test will rule out 37.5% of people who have the condition
				Specificity: 92.7 (92.3, 93.1)			MODERATE	High specificity. Test will rule in 7.3% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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 papers. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 7: Summary of findings for diagnostic accuracy of serum CA125 for detection of ovarian cancer[1] in adults ≥50 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detection of ovarian cancer[1] in adults ≥50 years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (%) (95% CI)**	**PPV (%) (95% CI)**	**FNR[2] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
1* Funston et al 2020	Diagnostic accuracy (ovarian cancer in adults ≥50 years old or not)	31086	≥35U/ml	Sensitivity: 80.1 (75.7, 84)	15.2 (13.6, 16.8)	19.9 (16, 24.3)	MODERATE	Moderate sensitivity. Test will rule out 19.9% of people who have the condition
				Specificity: 94.5 (94.3, 94.8)			MODERATE	High specificity. Test will rule in 5.5% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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 papers. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 8: Summary of findings for diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults all ages

Diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults all ages								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (% range of point estimates) (95% CI)**	**PPV (%) (95% CI)**	**FNR[1] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
2* Arendse et al 2025; Funston et al 2020	Diagnostic accuracy (invasive ovarian cancer in adults all ages or not)	393058	≥35U/ml	Sensitivity: 84.9 [Arendse 84.9 (83.8, 86.4) and Funston 84.9 (80.8, 88.5)]	Arendse 2025: 7.7 (7.3, 8.0) Funston 2020: 8.8 (7.8, 9.8)	Arendse 2025: 15.1 (13.6, 16.2) Funston 2020: 15.1 (11.5, 19.2)	MODERATE	Moderate sensitivity. Test will rule out 15.1% of people who have the condition
				Specificity: 93.6 to 93.7 [Arendse (93.5, 93.6) and Funston 93.7 (93.5, 0.93.9)]			MODERATE	High specificity. Test will rule in 6.3% to 6.4% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 9: Summary of findings for diagnostic accuracy of serum CA125 for detection of ovarian cancer[1] in adults all ages

Diagnostic accuracy of serum CA125 for detection of ovarian cancer[1] in adults all ages								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (% range of point estimates) (95% CI)**	**PPV (%) (95% CI)**	**FNR[2] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
2* Arendse et al 2025; Funston et al 2020	Diagnostic accuracy (ovarian cancer in adults all ages or not)	393058	≥35U/ml	Sensitivity: 77 to 78.6 [Arendse 78.6 (77.0, 80.2) and Funston 77 (72.8, 80.8)]	Arendse 2025: 8.8 (8.4, 9.2) Funston 2020: 10.1 (9.1, 11.2)	Arendse 2025: 21.4 (19.8, 23) Funston 2020: 23 (19.2, 27.2)	MODERATE	Moderate sensitivity. Test will rule out 21.4% to 23% of people who have the condition
				Specificity: 93.6 to 93.8 [Arendse 93.6 (93.5, 93.7) and Funston 93.8 (93.6, 94)			MODERATE	High specificity. Test will rule in 6.2% to 6.4% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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 papers. This figure has been multiplied by 100 to convert it into a % for ease of understanding.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 10: Summary of findings for diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 18 – 49 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 18 – 49 years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (%) (95% CI)**	**PPV (%) (95% CI)**	**FNR[1] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 18 – 49 years old or not)	143298	≥46U/ml	Sensitivity 67.9 (62.3, 73.2)	3.2 (2.8, 3.7)	32.1 (26.8, 37.7)	MODERATE	Moderate sensitivity. Test will rule out 32.1% of people who have the condition
				Specificity 95.8 (95.7 95.9)			MODERATE	High specificity. Test will rule in 4.2% of people who do not have the condition
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 18 – 49 years old or not)	143298	≥123U/ml	Sensitivity 48.8 (43.0, 54.6)	10.7 (9.1, 12.5)	51.2 (45.4, 57)	MODERATE	Moderate sensitivity. Test will rule out 51.2% of people who have the condition
				Specificity 99.1 (99.1, 99.2)			MODERATE	High specificity. Test will rule in 0.9% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 11: Summary of findings for diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 50 – 89 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 50 – 89[1] years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (%) (95% CI)**	**PPV (%) (95% CI)**	**FNR[2] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 50 – 89 years old or not)	198980	≥35U/ml	Sensitivity 86.2 (84.6, 87.8)	12.8 (12.2, 13.4)	13.8 (12.2, 15.4)	MODERATE	Moderate sensitivity. Test will rule out 13.8% of people who have the condition
				Specificity 94.6 (94.5, 94.7)			MODERATE	High specificity. Test will rule in 5.4% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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 5.

2. 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.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 12: Summary of findings for diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 50 – 59 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 50 – 59 years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (%) (95% CI)**	**PPV (%) (95% CI)**	**FNR[1] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 50 – 59 years old or not)	77697	≥35U/ml	Sensitivity 80.5 (76.3, 84.3)	8.8 (7.9, 9.7)	19.5 (15.7, 23.7)	MODERATE	Moderate sensitivity. Test will rule out 19.5% of people who have the condition
				Specificity 95.7 (76.3, 84.3)			LOW	High specificity. Test will rule in 4.3% of people who do not have the condition
1*	Diagnostic accuracy (invasive ovarian cancer	77697	≥26U/ml	Sensitivity 84.8 (80.9, 88.2)	5.0 (4.5, 5.5)	15.2 (11.8, 19.1)	MODERATE	Moderate sensitivity. Test will rule out 15.2% of people who have the condition

Arendse et al 2025	in adults 50 – 59 years old or not)			Specificity 91.6 (91.4, 91.8)			MODERATE	High specificity. Test will rule in 8.4% of people who do not have the condition
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 50 – 59 years old or not)	77697	≥57U/ml	Sensitivity 72.3 (67.7, 76.6)	16.7 (14.9, 18.5)	27.7 (23.4, 32.3)	MODERATE	Moderate sensitivity. Test will rule out 27.7% of people who have the condition
				Specificity 98.1 (98.0, 98.2)			MODERATE	High specificity. Test will rule in 1.9% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

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.

Table 13: Summary of findings for diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 60 – 69 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 60 – 69 years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (%) (95% CI)**	**PPV (%) (95% CI)**	**FNR[1] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**

1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 60 – 69 years old or not)	57257	≥35U/ml	Sensitivity 86.9 (83.9, 89.5)	18.5 (17.1, 19.9)	13.1 (10.5, 16.1)	MODERATE	Moderate sensitivity. Test will rule out 13.1% of people who have the condition
				Specificity 95.9 (95.8, 96.1)			MODERATE	High specificity. Test will rule in 4.1% of people who do not have the condition
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 60 – 69 years old or not)	57257	≥22U/ml	Sensitivity 92.4 (90.0 94.4)	8.4 (7.7, 9.1)	7.6 (5.6, 10)	MODERATE	High sensitivity. Test will rule out 7.6% of people who have the condition
				Specificity 89.3 (89.0, 89.5)			MODERATE	High specificity. Test will rule in 10.7% of people who do not have the condition
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 60 – 69 years old or not)	57257	≥37U/ml	Sensitivity 86.6 (83.6, 89.2)	19.7 (18.2, 21.3)	13.4 (10.8, 16.4)	MODERATE	Moderate sensitivity. Test will rule out 13.4% of people who have the condition
				Specificity 96.2 (96.1, 96.4)			MODERATE	High specificity. Test will rule in 3.8% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 14: Summary of findings for diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 70 – 79 years old (sensitivity analysis)

Diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 70 – 79 years old								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (%) (95% CI)**	**PPV (%) (95% CI)**	**FNR[1] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 70 – 79 years old or not)	40624	≥35U/ml	Sensitivity 87.7 (84.6, 90.3)	15.5 (14.2, 16.8)	12.3 (9.7, 15.4)	LOW	Moderate sensitivity. Test will rule out 12.3% of people who have the condition
				Specificity 93.6 (93.4, 93.8)			MODERATE	High specificity. Test will rule in 6.4% of people who do not have the condition
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 70 – 79 years old or not)	40624	≥22U/ml	Sensitivity 93.5 (91.0 95.4)	7.6 (6.9, 8.2)	6.5 (4.6, 9)	MODERATE	High sensitivity. Test will rule out 6.5% of people who have the condition
				Specificity 84.7 (84.4, 85.1)			MODERATE	High specificity. Test will rule in 15.3% of

								people who do not have the condition
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 70 – 79 years old or not)	40624	≥41U/ml	Sensitivity 86.4 (83.2, 89.2)	18.3 (16.8, 19.9)	13.6 (10.8, 16.8)	MODERATE	Moderate sensitivity. Test will rule out 13.6% of people who have the condition
				Specificity 94.9 (94.6, 95.1)			MODERATE	High specificity. Test will rule in 5.1% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 15: Summary of findings for diagnostic accuracy of serum CA125 for detection of invasive ovarian cancer in adults 80 – 89 years old (sensitivity analysis)

Power								
Number of studies	**Outcome**	**Sample size**	**CA125 threshold**	**Effect estimate (%) (95% CI)**	**PPV (%) (95% CI)**	**FNR[1] (%) (95% CI)**	**Certainty**	**Interpretation of diagnostic ability**
1*	Diagnostic accuracy	23402	≥35U/ml	Sensitivity 90.6 (88.6, 93.9)			LOW	High sensitivity. Test will rule out 9.4% of

Arendse et al 2025	(invasive ovarian cancer in adults 80 – 89 years old or not)				9.2 (8.1, 10.4)	9.4 (6.1, 11.4)		people who have the condition
				Specificity 88.6 (88.1, 89.0)			MODERATE	High specificity. Test will rule in 11.4% of people who do not have the condition
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 80 – 89 years old or not)	23402	≥26U/ml	Sensitivity 92.2 (88.1, 95.1)	6.1 (5.3, 6.9)	7.8 (4.9, 11.9)	LOW	High sensitivity. Test will rule out 7.8% of people who have the condition
				Specificity 81.8 (81.2, 82.3)			MODERATE	High specificity. Test will rule in 18.2% of people who do not have the condition
1* Arendse et al 2025	Diagnostic accuracy (invasive ovarian cancer in adults 80 – 89 years old or not)	23402	≥58U/ml	Sensitivity 83.1 (78.0, 87.5)	15.0 (13.2, 16.9)	16.9 (12.5, 22)	MODERATE	Moderate sensitivity. Test will rule out 16.9% of people who have the condition
				Specificity 94.0 (93.6, 94.3)			MODERATE	High specificity. Test will rule in 6% of people who do not have the condition

CA125: cancer antigen 125; CI: confidence interval

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.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

See appendix F for full GRADE tables.

1.1.6 Economic evidence

1.1.6.1 Included studies

A single search was performed to identify published economic evaluations of relevance to both questions, including dual testing with serum CA125 and ultrasound scan, as well as age and serum CA125 thresholds for the detection of suspected ovarian cancer. See the literature search strategy in appendix B in the technical appendices document.

One economic study was identified that was applicable to the review question on age and serum CA125 thresholds. See economic study selection flow chart in appendix G in the technical appendices document.

One UK study compared sequential and concurrent pathways using age-based CA125 thresholds with the standard NHS primary care pathway for detecting invasive ovarian cancer in women presenting with suspected cancer in primary care (Wu, 2025). Characteristics of included economic study are summarised in Table 16. Full details of this study are provided in the economic evidence study extraction table in appendix H in the technical appendices document.

1.1.6.2 Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Table 16: Summary of characteristics of included study

Study details	Study design and type of analysis	Population	Interventions and comparators	Perspective	Primary outcome	Time horizon
Wu 2025 UK	Study design: Decision analytic model with a primary-care diagnostic decision tree plus a cohort Markov model Source of effectiveness data: Arendse 2025 (N=276,827)[1]	Women presenting to primary care with suspected ovarian cancer symptoms, mean age = 54.6 years (SD 15.8)	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: Like Pathway 2 but uses age-specific CA125 thresholds equivalent to Ovatools ~1% (USS) and ~3% (urgent referral) OC risk cut-points.	NHS	QALY	Lifetime (to age 110)

Study details	Study design and type of analysis	Population	Interventions and comparators	Perspective	Primary outcome	Time horizon
			Pathway 4: Concurrent CA125 and USS, 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.			

CA125: Cancer Antigen 125; N: Number; NHS: National Health Service; OC: Ovarian Cancer; QALY: Quality-adjusted life-year; SD: Standard Deviation; U/ml: Units per millilitre; UK: United Kingdom; USS: Ultrasound Scan

1 The sample for the cost effectiveness analysis was smaller. It was not reported why; however, the economic analysis used linkage to other datasets to estimate costs and QALYs and therefore was likely to have used the smaller sub-set of people that had complete linkage data.

1.1.7 Summary of economic evidence

See Table 17 for a summary of the economic evidence and appendix H in the technical appendices document for the economic evidence study extraction tables.

Table 17: Economic evidence summary table: sequential pathways using age-based CA125 thresholds versus standard care pathway for detection of suspected ovarian cancer

Study	Applicability and limitations	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty	Economic evidence statement
Wu 2025 (UK)	Partially applicable[1] Minor limitations[2]	Women < 50 years: Pathway 2 (vs SC): (£33,354) Pathway 3 (vs SC): (£33,455) Pathway 4 (vs 3): £259,095 to £334,595 Women ≥ 50 years: Pathway 2 (vs SC): £34,894	Women < 50 years: Pathway 2 (vs SC): (0.97) Pathway 3 (vs SC): (0.95) Pathway 4 (vs 3): 0.3 to 2.44 Women ≥ 50 years: Pathway 2 (vs SC): 1.48	Women < 50 years Pathway 2 (vs SC): £34,350 per QALY lost Pathway 3 (vs SC): £35,348 per QALY lost Pathway 4 (vs 3): extendedly dominated[3] to £137,123 per QALY gained depending on how abnormal CA125 was defined.	Women ≥ 50 years At an ICER of £23,610 per QALY and above, pathways 2 and 3 have higher probability of being cost effective (vs SC). Uncertainty analyses focused only on 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. Results also sensitive to assumptions on stage-shift, USS cost, benign surgery QoL assumptions,	Women < 50 years Compared to standard care age-based CA125 thresholds were cost effective at £20,000 per QALY threshold, since cost savings were sufficiently large enough to compensate for QALY losses. However, this means that fewer OCs are identified. Women ≥ 50 years In the base-case, ICERs of pathways 2 and 3 were above NICE's lower cost-effectiveness threshold of £20k/QALY. However, modelled pathways also

Study	Applicability and limitations	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty	Economic evidence statement
		Pathway 3 (vs SC): £39,327 Pathway 4 (vs 3): £283,225 to £304,856 Cost year: 2022	Pathway 3 (vs SC): 1.53 Pathway 4 (vs 3): 1.86 to 2.23	Women ≥ 50 years Pathway 2 (vs SC): £23,610 per QALY gained Pathway 3 (vs SC): £25,712 per QALY gained Pathway 4 (vs 3): extendedly dominated[3] to £358,960 per QALY gained depending on how abnormal CA125 was defined.	and including effects of other cancers.	included referrals for further investigations (USS) at moderate OC risk levels (<3%), which was outside the scope of this review. Sensitivity analyses showed that tightening the lower USS referral threshold from 1.0% to 1.2–1.4% lowered ICERs below £20k/QALY[4], and at ~1.5% the ICERs fell below £10k/QALY. This indicates that, at OC risk levels comparable to a PPV of 3% (the threshold for urgent referral for a suspected cancer pathway), the strategy would likely be as cost effective, and potentially more so.

CA125=Cancer Antigen 125; ICER=Incremental cost-effectiveness ratio; k=Thousand; PPV=Positive predictive value; QALY=Quality-adjusted life-year; QoL=Quality of life; UK=United Kingdom; USS=Ultrasound scan

1 Modelled pathways included referrals for further investigations (USS) at moderate ovarian cancer risk levels (1 to <3%), which were outside the scope of this review. Additionally, diagnostic accuracy estimates related to invasive ovarian cancer.

2 A well-conducted UK cost–utility analysis with no methodological limitations identified. While some model inputs were based on assumptions and uncertain data, extensive sensitivity analyses were undertaken.

3 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.

4 At ovarian cancer risk of 1.4% the equivalent 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.

1.1.8 Economic model

No original economic modelling was completed for this review question.

1.1.9 Committee discussion and interpretation of the evidence

There were two review questions for committee discussion, dual testing with serum CA125 and ultrasound scan for the detection of suspected ovarian cancer compared to serum CA125 and 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. No evidence was identified for the duel-testing question and the committee agreed to develop a research recommendation.

1.1.9.1 Is the problem a priority

The identification in primary care of those who need further tests or onward referral via a suspected cancer pathway is vital to ensure that both those who may have cancer get correctly referred and that those whose symptoms may have other causes are not referred unecessarily. Serum CA125 levels have been used as part of this referral pathway for ovarian cancer to identify where an ultrasound should be requested.

The NICE surveillance review that triggered this update (Surveillance review in May 2024), identified evidence that suggests that the positive predictive value of CA125 varies by age. This raised questions regarding the diagnostic value of CA125 at the ≥35U/ml threshold for use inovarian cancer detection given the low prevalence of ovarian cancer among symptomatic women, and the potential for many unnecessary tests to be performed, subsequently increasing demand on services and affecting women who are tested unecessarily for ovarian cancer risk. The surveillance review also discussed the use of duel testing with serum CA125 and ultrasound scan rather than the current sequential approach and recommended further exploration of the accuracy and utility on this.

1.1.9.2 Test accuracy and certainty in the test accuracy

There was no evidence found supporting a routine combined approach of serum CA125 testing together with ultrasound scan. The committee agreed

that they would not change the existing recommendation and developed a research recommendation.

Two retrospective cohort studies were included in the diagnostic review of the question regarding age and serum CA125 thresholds for detection of suspected ovarian cancer in adults. Although both studies (Arendse et al., 2025 and Funston et al., 2020) rely on routinely collected coded data, they use different underlying datasets. Arendse et al., (2025) used linked data from the Clinical Practice Research Datalink (CPRD) Aurum dataset and the National Cancer Registries and Analysis Service (NCRAS) and Funston et al., 2020 used linked data from the CPRD GOLD dataset and the NCRAS. CPRD Aurum and CPRD GOLD are separate datasets: Aurum contains data from practices using EMIS clinical systems, while GOLD uses data from InPS Vision GP software provider. Due to differences in structure and coding, they are not integrated.

The committee used the positive predictive value (PPV) of above 3% threshold for suspected ovarian cancer consistent with the original NICE guideline published in 2015. The committee agreed that they would prioritise sensitivity over specificity for this diagnostic test accuracy review. The committee considered the positive predictive value and false negative rate alongside sensitivity and specificity to allow them to understand the diagnostic test accuracy of CA125 results. The interpretation of sensitivity and specificity estimates was undertaken using the following parameters (see review protocol in appendix A).

The evidence was assessed with GRADE and was rated as moderate to low certainty. Evidence was downgraded predominatly due to inconsistency as meta-analyses could not be conducted (a minimum of 3 studies are needed to undertake bivariate meta-analysis) and inconsistency could not be assessed, so studies were downgraded accordingly to account for single study bias. The evidence was assessed for risk of bias and directness using the QUADAS-2 tool. The risk of bias was considered to be low for the included studies. One study (Arendse, 2025) looked at invasive ovarian cancer and the other study (Funston, 2020) invasive ovarian cancer and ovarian cancer including

borderline ovarian tumours. The evidence from both studies involved large sample sizes (50000 to over 300000) and was considered directly applicable as the studies used primary care data derived from the United Kingdom Clinical Practice Research Datalink from UK databases. The evidence was stratified by age and different thresholds for CA125. One study (Funston et al, 2020) examined CA125 cut-off ≥35 U/ml for <50 and ≥50 years old. One study (Arendse et al, 2025) additionally examined different CA125 threshold for 10-year age bands for ages 50 and above. The cost effectiveness analysis of the Wu et al (2025) study provided additional data for the CA125 thresholds for the 10-year age bands below 49, that was also presented to the committee.

Overall, for adults <50 years, serum CA125 of ≥35U/ml had a lower than 3% positive predictive value (PPV) meaning that it is below the threshold for further investigations. For those ≥50 years serum CA125 had a higher than 3% PPV for diagnosing invasive ovarian cancer in adults.

The committee discussed that the evidence showed that serum CA125 has lower sensitivity and worse diagnostic accuracy in younger women, raising concerns about the current recommendation which suggests referring any women with a serum CA125 threshold ≥35U/ml for abdominal or pelvic ultrasound.

The evidence provided further stratification by 10-year age bands for invasive ovarian cancer find ing that for those aged 50 and above the 3% PPV threshold (with adequate sensitivity) was met for levels of serum CA125 below the currently used 35IU/ml level. The evidence on 10-year age bands with different thresholds of the CA125 test showed quite clear ‘threshold - PPV’ gradient. The committee discussed these findings in conjunction with the related health economic analysis. This considered the clinical and economic evidence balancing diagnostic accuracy, increased referrals for ultrasounds and impact on outcomes and costs. The committee agreed updated thresholds for CA125 for 10-year age bands for those 50 and over.

The committee considered the evidence which stratified findings in 10-year cohorts for populations 49 years of age and below (18-29; 30-39 and 40-49)

which found that the PPV at the current serum CA125 level of ≥35U/ml was less than the 3% PPV.

For women aged 40 – 49, although the PPV did fall below the preferred threshold it did still demostrate moderate to high sensitivity. The committee considered this along side the concerns about late diagnosis with ovarian cancer and chose to retain the ≥35U/ml threshold for this group. For women aged under 40 both the PPV was lower and the sensitivity was poor. The committee agreed that the poor diagnostic performance of CA125 in this younger age group means that it is should not be used to base decisions on, and devloped a recommendation relating to the use of ultrasound in those aged under 40.

1.1.9.3 Values

The committee recognised that serum CA125 test is useful in the initial assessment of suspected ovarian cancer, but recognised the uncertainty in its value in informing suspected ovarian cancer referral decision in age groups <50 years of age. The evidence showed different serum CA125 thresholds across age groups >50 years of age to have mostly moderate sensitivity to reliably inform referral to ultrasound investigation. The committee acknowledged that people with serum CA125 levels not meeting the referral threshold, do not exclude ovarian cancer, particularly in early-stage disease and in people aged 39 years and under, and have developed recommendations that seek address this.

1.1.9.4 Balance of effects

The committee discussed the evidence and agreed that the prevalence of ovarian cancer in younger women influences the sensitivity of serum CA125, affecting how screening and investigation thresholds should be applied in younger women. The committee acknowledged that serum CA125 performs poorly in younger women, especially those under 40, and may be unhelpful or misleading in that group. The committee acknowledged that germ cell ovarian cancer, may be more common in young patients and is likely to be missed by serum CA125.

The committee discussed that lowering the serum CA125 thresholds for people aged 50 and above should increase case detection, and may create additional resource use. The committee noted that the economic evidence showed some age-based thresholds approach cost effectiveness only at specific values. The committee recommended setting the age-band thresholds based on the clinical and cost effectiveness. Though as the committee discussion identified that many GPs currently request both serum CA125 and an ultrasound at the same time there may not be the expected resource use increase.

The committee noted the existing recommendation about further assessment for those with a serum CA125 lower than the threshold or greater than the threshold but with a normal ultrasound. They agreed that this should be retained and updated to reflect the changed serum CA125 thresholds.

1.1.9.5 Resources and cost-effectiveness

Only one UK-based cost–utility analysis met the inclusion criteria (Wu 2025). This study assessed the cost–utility of age-based serum CA125 thresholds. The study was well conducted, using a large primary care dataset and robust modelling over a lifetime horizon from an NHS perspective. The analysis was partially applicable because it considered the detection of invasive ovarian cancer only. However, the current sequential pathway of serum CA125 ≥ 35 U/ml followed by ultrasound mainly aims to detect invasive epithelial ovarian cancers. The modelled pathways also assumed that ultrasound could be largely delivered in community settings. This does not reflect current service provision, with hospital radiology departments being the most common setting for diagnostic ultrasounds, although there is a growing number of community-based diagnostic hubs and some GP practices host ultrasound clinics.

The economic model assumed improved outcomes from stage shift in older women, where cancers previously diagnosed at a late stage would shift to an early stage because they were identified earlier as a result of age-based serum CA125 thresholds, which are generally lower than the current threshold for ultrasound referral. However, evidence from UKCTOCS suggests that

survival benefit due to stage shift is uncertain and the committee questioned assumptions on this. The impact of stage shift was tested extensively in sensitivity analyses, with the results being less favourable but overall the approach adopted was robust and conservative.

The committee discussed that all downstream effects of increased serum CA125 testing and ultrasound referrals, including outpatient and inpatient care, were sufficiently quantified in the model. Overall, the committee considered that this analysis had only minor methodological limitations and could be used to inform their recommendations.

The committee noted that, according to the economic model, in women aged 50 years and older, the age-based serum CA125 thresholds that had the most favourable diagnostic accuracy in the effectiveness review for this question and aligned with NICE's positive predictive value (PPV) criteria of 3% or more for suspected cancer referral had an incremental cost-effectiveness ratio (ICER) of £25,712 per QALY gained. This exceeded NICE's lower cost-effectiveness threshold of £20,000 per QALY gained and therefore was not cost effective. The committee also discussed that age-based serum CA125 thresholds are lower than the current practice threshold of serum CA125 ≥ 35 U/ml and would increase referrals substantially. They noted that services are currently struggling with capacity and this may create further capacity issues for ultrasound and downstream services. The economic analysis estimated that these thresholds would require £5.9 million of additional funding per year.

Therefore, the committee agreed to inform their recommendation using age-based serum CA125 thresholds that resulted in an ICER below £20,000 per QALY gained, were aligned with NICE's PPV criteria of 3% or more for suspected cancer referral and did not impose too much burden on the NHS. The recommended age-based serum CA125 thresholds resulted in an ICER of £12,593 per QALY gained when compared with the current fixed threshold of serum CA125 ≥ 35 U/ml irrespective of age. According to the economic analysis, this would still require approximately £2.45 million of additional funding per year. However, the committee highlighted that current clinical practice often diverges from the NICE guidance recommending sequential

serum CA125 testing and ultrasound referral, with many GPs requesting serum CA125 and ultrasound concurrently because of long waiting times.

The economic model also considered a strategy in which serum CA125 and ultrasound were undertaken concurrently and, if either test was abnormal, a referral was made for further investigations. However, this approach was not cost effective. When compared with sequential pathways using age-based serum CA125 thresholds, the concurrent strategy was extendedly dominated or with ICERs reaching as high as £358,960 per QALY gained depending on how referral thresholds were defined and the age group considered. The lack of cost effectiveness was mainly due to high ultrasound costs.

The committee discussed that recommending age-based serum CA125 thresholds may encourage GPs to change their practice and not request concurrent serum CA125 and ultrasounds but use sequential pathways. If implemented, this strategy may result in fewer ultrasounds being requested overall. In conclusion, the committee agreed that evidence supports recommending age-adjusted serum CA125 thresholds for women aged 50 years and older, balancing ovarian cancer detection, cost effectiveness and resource implications. But the overall resource imapct will depend on general practitioners' willingness to change their behaviour and adopt sequential age-based thresholds.

The economic evidence showed that in younger women (under 50 years), the use of age-based serum CA125 thresholds resulted in QALY losses but cost savings. The ICER for a strategy using age-based serum CA125 thresholds was £35,348 per QALY lost. This would be considered cost effective using NICE's cost-effectiveness thresholds because the cost savings (£35,348) exceed the value NICE assigns to a QALY gained (£20,000). In other words, the cost savings are large enough to offset the health loss, as they could fund more QALYs elsewhere than are being lost. However, the committee discussed the very poor diagnostic accuracy associated with age-based serum CA125 thresholds compared with the current fixed threshold, which are particularly sensitivity, meaning cancers would be missed. PPVs were also lower than NICE's PPV criteria of 3% or more for cancer referral. Raising

thresholds could reduce referrals but risks missing cancers, which the committee considered unacceptable. Therefore, the committee recommended that the current threshold should be retained in women aged 40 to 49 years but stressed an emphasis on clinical judgement. Given very poor diagnostic accuracy in those aged 39 years and under, a pragmatic approach may reduce inaccurate serum CA125 testing and the associated costs of managing false negative and false positive referrals but it may increase ultrasound activity. However, given the high prevalence of concurrent ultrasound in current practice, this is unlikely to create a large new demand. Overall, bacause of the low prevalence of ovarian cancer in these younger age groups, recommendations are not expected to have a significant resource impact.

1.1.9.6 Equity

The committee discussed concerns about the late diagnosis of ovarian cancer, with particular reference to those who are younger as ovarian cancer is rarer in those under 50 and symptoms may be attributed to other causes. They discussed that with the poor accuracy of serum CA125 in people under 40 that it was important to develop the additional recommendation for this group.

The committee acknowledged that clinicians working in deprived areas may consider using a lower threshold to refer because patients may present later and with more advanced disease.

1.1.9.7 Feasibility

The committee discussed that in primary care the request for a serum CA125 and an ultrasound scan may be done at the same visit with the aim of avoiding diagnostic delay. The committee noted that ultrasound availability and waiting times vary widely across regions and can be long, which encourages ordering both tests immediately rather than waiting for serum CA125 results alone. The committee discussed that the reasons for requesting the ultrasound in this way reflects that the ultrasound may be for the investigation of other possible patholgies that may be causing the

presenting symptoms. The committee discussed this approach to ordering serum CA125 and ultrasound and further discussed if changing serum CA125 thresholds may not substantially alter clinician behaviour.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.6 to 1.5.9 and 1.5.11, and the research recommendation on duel vs. sequential CA125 and ultrasound testing for ovarian cancer.

1.1.11 References

1.1.11.1 Diagnostic evidence

Arendse KD, Walter FM, Abel G et al. (2025) CA125 and age-based models for ovarian cancer detection in primary care: a population-based external validation study. : 1-9

Funston G, Hamilton W, Abel, G et al. (2020) The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: a population-based cohort study. Public Library of Science Medicine *17*(10): p.e1003295

1.1.11.2 Economic evidence

Wu R, Arendse KD, Hamdani T et al. (2025) Cost-effectiveness of CA125-and age-informed risk-based triage for ovarian cancer detection in primary care. British Journal of Cancer: 1-9