Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2025, 15(11), 1827-1840
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

# Clinical Utility of Cancer Antigen 125 in the Evaluation of Suspected Ovarian Cancer: Evidence and Diagnostic Pathways

**Sonali Gupta[1], Rupali Banzal[2], Ravindra H. Mahajan[3], Arul Prakash Pandian James[4]**

[1]Department of Gynaecology, University Hospitals of Coventry and Warwickshire, Coventry, UK
[2]Department of Gynaecology, University Hospitals of Leicester, Leicester, UK
[3]Department of Orthopaedics, George Eliot Hospital NHS Trust, Nuneaton, UK
[4]Department of Chronic Pain Medicine, George Eliot Hospital NHS Trust, Nuneaton, UK
Email: sonaligupta494@gmail.com

**How to cite this paper:** Gupta, S., Banzal, R., Mahajan, R.H. and James, A.P.P. (2025) Clinical Utility of Cancer Antigen 125 in the Evaluation of Suspected Ovarian Cancer: Evidence and Diagnostic Pathways. *Open Journal of Obstetrics and Gynecology*, **15**, 1827-1840.
https://doi.org/10.4236/ojog.2025.1511152

**Received:** September 27, 2025
**Accepted:** October 31, 2025
**Published:** November 3, 2025

Copyright © 2025 by author(s) and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/

Open Access

## Abstract

**Background:** Ovarian cancer remains the most lethal gynaecological malignancy, with survival closely linked to stage at diagnosis. Cancer antigen 125 (CA 125) is a long-established biomarker that, when interpreted within clinical context, aids early identification of women at risk. **Objective:** This narrative review evaluates the biological basis, diagnostic performance, and contemporary clinical role of CA 125 in the evaluation of suspected ovarian cancer, integrating evidence across primary and secondary care and summarising cost-effectiveness and emerging adjuncts. **Methods:** A narrative synthesis was conducted using PubMed, Web of Science, and guideline databases to March 2025. Studies describing CA 125 performance, transvaginal ultrasound (TVUS) integration, or validated risk algorithms (RMI, ROMA, ROCA) were prioritised. Evidence from population cohorts, meta-analyses, and national guidance (NICE NG12, CG122, NG241) was reviewed. **Results:** CA 125 shows pooled sensitivity of ~78% and specificity of ~87% in secondary-care populations with adnexal masses but markedly lower positive predictive value in primary care (≈10% at ≥35 U/mL). Combining CA 125 with TVUS or composite indices such as the Risk of Malignancy Index improves triage accuracy. Population screening using CA 125—alone or with ROCA—does not reduce ovarian-cancer mortality and is not cost-effective. In high-risk women declining or deferring risk-reducing salpingo-oophorectomy, ROCA-based surveillance may be a cost-effective interim option. Emerging markers (HE4) and artificial-intelligence-based ultrasound classifiers enhance discrimination but require prospective validation. **Conclusions:** CA 125 remains integral to symptom-led diagnostic pathways when combined with structured imaging and risk al-

gorithms. Its limitations—reduced sensitivity in early-stage disease and non-specific elevation in benign states—preclude population screening but support selective use for triage, early referral, and multidisciplinary management.

**Keywords**

Ovarian Cancer, CA 125, Transvaginal Ultrasound, Risk of Malignancy Index (RMI), ROMA, ROCA, NICE Guidelines, Biomarker, Artificial Intelligence

## 1. Introduction

Ovarian cancer is a formidable public health challenge and remains the most lethal gynaecological malignancy. Survival is closely linked to stage at diagnosis, with significantly better outcomes in early disease, which underlines the critical importance of timely detection [1]. Presentation is often insidious because symptoms such as abdominal bloating, early satiety, pelvic discomfort, and urinary frequency are common and non-specific. This symptom ambiguity contributes to delays across primary and secondary care, so simple, reliable, and accessible diagnostic tools are essential to aid earlier identification [2].

Multiple efforts have evaluated population screening, but large trials have not demonstrated a reduction in ovarian cancer mortality. As a result, national and international bodies do not recommend general population screening for ovarian cancer [3]. Despite this, cancer antigen 125 (CA 125) remains a vital component of the diagnostic process for women who present with symptoms suggestive of ovarian malignancy and is incorporated into guideline-endorsed pathways, including those of the National Institute for Health and Care Excellence [4] [5].

Cancer antigen 125 is an imperfect marker. Elevation is not cancer-specific and occurs in numerous benign and physiological states, while not all ovarian cancers, particularly early-stage and certain non-serous histotypes, raise the marker. Consequently, interpretation requires a clinical context and the integration of structured transvaginal ultrasound and formalised risk assessment models, such as the Risk of Malignancy Index, to support appropriate triage and referral to specialist multidisciplinary care [6]-[9].

This narrative review examines the biological basis and limitations of cancer antigen 125, critically evaluates its diagnostic performance across care settings, and positions the marker within contemporary, guideline-based diagnostic pathways. The overarching aim is to clarify when and how cancer antigen 125 adds value in the evaluation of suspected ovarian cancer and to highlight practical strategies that minimise harm from false positives while expediting referral of women at genuine risk.

## 2. Review

*Biological basis of cancer antigen* 125

Cancer antigen 125, also known as MUC16, is a high molecular weight transmembrane glycoprotein encoded by the MUC16 gene located on chromosome 19p13.2. It was first identified in 1981 through the development of the monoclonal antibody OC125, which reacted with an ovarian cancer cell line, leading to the discovery of cancer antigen 125 as a tumour-associated antigen [10]. Structurally, MUC16 is characterised by a large, heavily glycosylated extracellular domain, a single-pass transmembrane region, and a cytoplasmic tail. The extensive glycosylation contributes to its function and stability, particularly in shielding epithelial surfaces from environmental insults and modulating immune responses. Cancer antigen 125 is normally expressed on the surface of mesothelial cells lining the peritoneal, pleural, and pericardial cavities, as well as other coelomic epithelium-derived tissues, suggesting a physiological role in lubrication and defence of serosal membranes [11].

In the context of epithelial ovarian cancer, particularly high-grade serous carcinoma, cancer antigen 125 is markedly overexpressed and aberrantly shed into the peritoneal cavity and bloodstream. This process enables its detection in serum, forming the basis for its use in clinical diagnostics. Mechanistically, cancer antigen 125 contributes to tumour progression by facilitating peritoneal metastasis. It enhances adhesion between ovarian cancer cells and the mesothelial lining of the peritoneum, a critical step in the dissemination of tumour cells within the abdominal cavity. Additionally, the bulky and glycosylated extracellular region of cancer antigen 125 may serve as a physical barrier against immune surveillance, thereby promoting immune evasion and aiding in tumour cell survival and immune suppression within the tumour microenvironment [12].

From a clinical perspective, serum cancer antigen 125 levels are elevated in approximately eighty percent of women with advanced-stage epithelial ovarian cancer [13]. However, its utility as a screening biomarker is limited by reduced sensitivity in early-stage disease, with elevated levels observed in only around fifty percent of International Federation of Gynecology and Obstetrics stage I cases [14]. This disparity significantly reduces the effectiveness of cancer antigen 125 as a standalone tool for early detection. Moreover, expression is histotype-dependent. While serous subtypes of ovarian cancer typically produce high levels of cancer antigen 125, other histological variants such as mucinous, clear cell, and germ cell tumours may not express the antigen at detectable levels. This leads to potential false-negative results and highlights the heterogeneity of ovarian cancer biology [15].

Adding to its complexity, cancer antigen 125 is not specific to malignancy. It is frequently elevated in a variety of benign and physiological conditions, particularly among premenopausal women. For instance, menstruation, pregnancy, and ovulation can all transiently raise cancer antigen 125 levels. Pathological states such as endometriosis, pelvic inflammatory disease, benign ovarian cysts, and fibroids are also common causes of elevation in the absence of malignancy. Beyond gynaecological disorders, cancer antigen 125 levels may increase in systemic and

inflammatory conditions such as hepatic cirrhosis, peritonitis, pleuritis, and congestive heart failure. These numerous confounding variables greatly diminish specificity, especially in primary care or general screening populations where the pre-test probability of ovarian cancer is low [16].

In conclusion, cancer antigen 125 is a biomarker deeply intertwined with the biology of epithelial ovarian cancer. Its discovery has significantly influenced the diagnostic and monitoring landscape for this malignancy. Nevertheless, its limited sensitivity in early-stage disease, lack of tumour specificity, and variable expression across histological subtypes restrict standalone utility. Understanding the molecular biology and expression profile of cancer antigen 125 is crucial for appreciating both its clinical value and its limitations. As such, cancer antigen 125 should not be viewed in isolation but rather as one component of a multimodal diagnostic strategy-integrated with clinical assessment, imaging studies, and validated risk assessment tools such as the risk of malignancy index or the risk of ovarian malignancy algorithm. Ongoing research into novel biomarkers and panels aims to build upon its legacy, with the goal of improving early detection and outcomes for women affected by ovarian cancer.

*Diagnostic performance of cancer antigen 125*

Overview of Clinical Utility: The clinical application of cancer antigen 125 as a diagnostic biomarker for ovarian cancer has been extensively explored. Numerous systematic reviews and meta-analyses have assessed performance, particularly in secondary and tertiary care settings where women often present with adnexal masses. In an early comprehensive review, Myers and colleagues reported pooled sensitivity and specificity of seventy-eight percent in detecting ovarian malignancy among women referred for further assessment [17]. A subsequent meta-analysis by Medeiros and colleagues corroborated these findings, reporting sensitivity of eighty percent and specificity of seventy-five percent, underscoring robustness across studies [18]. These figures are clinically meaningful; however, they are derived from enriched populations with higher prevalence and therefore have limited generalisability to primary care.

Limitations in Primary Care: Performance is substantially compromised in low-prevalence environments such as primary care, where women may present with vague, non-specific symptoms rather than overt pelvic masses. In this context, the positive predictive value-the likelihood that a positive test reflects true disease-is low. In a large United Kingdom population-based cohort, among symptomatic women with elevated cancer antigen 125 the positive predictive value for ovarian cancer was only around one percent, highlighting the challenge of relying on this marker in undifferentiated populations [2]. False positives can result in unnecessary investigations, specialist referrals, patient anxiety, and even surgery, contributing to healthcare burden and potential morbidity.

Evidence gap note: Direct pooled accuracy for the full, two-step primary-care CA125→TVUS pathway is not available; we therefore present in **Table 1**, primary-care CA125 accuracy and a validated secondary-care proxy (RMI) [3] [19].

**Table 1.** Setting-specific test performance relevant to UK pathways.

| Setting/Test | Threshold | Sensitivity | Specificity | PPV | NPV | Source |
|---|---|---|---|---|---|---|
| Primary care: CA125 alone (symptomatic women in UK general practice; n ≈ 50,780) | ≥35 U/mL | 77.0% | 93.8% | 10.1% | 99.8% | Funston *et al.*, PLOS Med 2020 [2] |
| Secondary care proxy for CA125 + TVUS: RMI (integrates CA125, menopausal status, ultrasound morphology), pooled | RMI-I ≥ 200 - 250 | ≈78% | ≈87% | Varies with prevalence | Varies with prevalence | Ngu *et al.*, Cancers 2022 [19] |
| Illustrative PPV/NPV for RMI at typical prevalences | — | — | — | 10% prev → 40.0%; 30% prev → 72.0% | 10% prev → 97.3%; 30% prev → 90.2% | Derived from pooled Se/Sp |

Role in Combination with Transvaginal Ultrasound: To mitigate these limitations, cancer antigen 125 is often combined with transvaginal ultrasound. This dual-modality approach enhances diagnostic accuracy and improves risk stratification. When both cancer antigen 125 and transvaginal ultrasound are abnormal, the likelihood of malignancy rises significantly. Conversely, when both tests are normal, the negative predictive value can exceed ninety-nine point nine percent, providing strong reassurance and avoiding over-investigation of benign conditions [2] [17].

Structured Diagnostic Algorithms—Risk of Malignancy Index and Risk of Ovarian Malignancy Algorithm: Rather than relying on a single biomarker, structured tools integrate multiple parameters. The risk of malignancy index combines the cancer antigen 125 concentration, ultrasound findings, and menopausal status to yield a risk score and is widely endorsed in United Kingdom clinical guidance (including National Institute for Health and Care Excellence NG12) for triaging women with suspected ovarian cancer and determining the need for referral to a specialist gynaecological oncology centre [4]. The risk of ovarian malignancy algorithm incorporates cancer antigen 125 and human epididymis protein four levels, alongside menopausal status, and has shown promise in distinguishing benign from malignant adnexal masses. Although less commonly used in the United Kingdom, it is gaining traction elsewhere due to enhanced discriminatory capacity [8].

Clinical Interpretation and Recommendations: Across secondary-care studies, RMI (pooled sensitivity ≈ 78%, specificity ≈ 87%) and ROMA (HE4 + CA125 + menopausal status) generally outperform CA125 alone; ROMA often yields higher sensitivity at comparable specificity—especially in premenopausal women—while contemporary head-to-head work indicates the ultrasound-based IOTA ADNEX model can exceed both for overall discrimination and net benefit [19]-[21].

Given limited specificity and sensitivity in certain contexts, cancer antigen 125 should not be used in isolation as a diagnostic tool. It functions best as one component of a multimodal strategy, where interpretation is informed by clinical context, imaging results, and formal risk assessment. An elevated cancer antigen 125

should prompt further evaluation rather than immediate surgical intervention. The National Institute for Health and Care Excellence recommends that women with elevated cancer antigen 125 and abnormal imaging be referred via a two-week suspected cancer pathway [4]. Algorithmic approaches help minimise unnecessary procedures while ensuring that patients with genuine malignancies receive timely care.

*Current National Institute for Health and Care Excellence guidelines and clinical pathways*

Evaluation of suspected ovarian cancer in the United Kingdom is governed by structured guidance from the National Institute for Health and Care Excellence, which aims to standardise investigation, improve early detection, and reduce unnecessary interventions. The guidance (NG12) outlines a tiered approach beginning in primary care with symptom recognition and progressing through biochemical testing, imaging, and risk stratification tools, ultimately leading to urgent referral when warranted [4].

Symptom recognition is the cornerstone of initial assessment. Clinicians should remain alert to possible ovarian cancer in any woman-particularly those over fifty years-who presents with persistent, non-specific abdominal or pelvic symptoms. These include abdominal distension or bloating, early satiety or reduced appetite, pelvic or abdominal pain, and increased urinary urgency or frequency. Symptoms should occur frequently (more than twelve times per month) and be persistent to justify further investigation; this threshold filters transient or functional symptoms and improves specificity [4]. Caution is advised when diagnosing new-onset irritable bowel syndrome in women over fifty without excluding gynaecological malignancy, since irritable bowel syndrome rarely presents de novo in this age group [4].

The first-line investigation is a serum cancer antigen 125 test, which is widely accessible in primary care. A threshold of greater than or equal to 35 international units per millilitre is considered abnormal and should prompt further evaluation [4]. Interpretation must be contextual: elevations occur in benign conditions including menstruation, endometriosis, pelvic inflammatory disease, fibroids, liver cirrhosis, and peritonitis, limiting specificity. Conversely, a normal cancer antigen 125 does not exclude ovarian cancer, especially in early-stage disease or in non-serous histological subtypes [4].

If cancer antigen 125 is elevated, the next recommended step is transvaginal ultrasound of the pelvis. Transvaginal ultrasound provides superior resolution for adnexal masses compared with abdominal ultrasound, allowing detailed morphological assessment of features such as solid areas, papillary projections, multiloculated cysts, bilateral involvement, ascites, and vascularity-features that may suggest malignancy [5]. Scan findings contribute to formalised risk assessment and inform subsequent investigation or referral.

To aid decision-making, the risk of malignancy index is advocated. It is calculated as cancer antigen 125 × ultrasound score × menopausal status score, where

the ultrasound score is 0 (no suspicious features), 1 (one suspicious feature), or 3 (two or more suspicious features), and the menopausal status score is 1 if premenopausal or 3 if postmenopausal. A risk of malignancy index of greater than or equal to 250 indicates high malignancy risk and triggers urgent two-week referral to a specialist multidisciplinary team at a recognised gynaecological oncology centre [5]. Surgery for suspected ovarian cancer should be undertaken by subspecialists in gynaecological oncology, which improves surgical outcomes and survival [22]. When cancer antigen 125 is elevated but transvaginal ultrasound findings are normal, consider other causes of elevation. If no alternative explanation is evident, repeat cancer antigen 125 testing after four to six weeks to assess trends; a rising level should prompt additional imaging, such as computed tomography of the abdomen and pelvis, or secondary-care referral for further evaluation [4]. A single raised cancer antigen 125 alone is not sufficient to warrant immediate referral or surgery; a stepwise, evidence-based approach integrates laboratory, imaging, and clinical data to prioritise women with malignancy while avoiding unnecessary escalation in those with benign disease [4] [5].

*Screening role and limitations of cancer antigen* 125

Cost-effectiveness: In the general population, modelling alongside UKCTOCS indicates that CA125-based strategies (including ROCA) are not cost-effective without a confirmed mortality benefit. In contrast, ROCA-based surveillance in BRCA1/2 carriers who defer RRSO appears cost-effective in the NHS (ALDO). For secondary-care triage of adnexal masses, economic studies suggest that adding serum biomarkers to high-quality ultrasound offers limited incremental value relative to ultrasound-centred strategies [5] [23]-[25].

Limitations in Early Detection: Despite widespread diagnostic use, application for screening asymptomatic populations-particularly for early detection-remains constrained. Insufficient sensitivity for early-stage disease, especially International Federation of Gynecology and Obstetrics stage I epithelial ovarian cancer, is the core limitation. In this subset, cancer antigen 125 is elevated in only approximately fifty percent of cases [14]. Thus, half of early-stage cancers may be missed when relying on a single threshold. Early detection strongly influences survival, with five-year survival for stage I disease exceeding ninety percent versus less than thirty percent for advanced stages [26].

Pathobiology helps explain underperformance: early tumours are small, nonserous histotypes (mucinous, clear cell, endometrioid) may not secrete detectable levels, and peritoneal spread that contributes to elevation is typically absent [15]. Temporal variability means levels may rise late in the tumour's course; early neoplasms may fall below the established threshold of greater than or equal to 35 international units per millilitre. Menstrual phase, hormonal status, and comorbidities add variability and reduce reliability for screening. Serial monitoring and algorithm-based interpretation-such as the risk of ovarian cancer algorithm-improve characteristics slightly, especially in high-risk groups, but do not overcome poor sensitivity for stage I disease [27]. In the United Kingdom Collaborative Trial

of Ovarian Cancer Screening, although multimodal screening improved stage shift, the lack of mortality benefit was attributed in part to insufficient early detection.

Specificity Challenges and False Positives: The lack of specificity further restricts screening utility. Physiological fluctuations (for example, menstruation and early pregnancy) and benign gynaecological conditions (endometriosis, pelvic inflammatory disease, fibroids, benign ovarian cysts) can elevate cancer antigen 125 [16] [28]. Non-gynaecological conditions such as liver cirrhosis, peritoneal tuberculosis, congestive heart failure, pleural effusions, and peritonitis also raise levels; chronic hepatic dysfunction may impair clearance and spuriously increase values [28]. In low-prevalence screening populations the positive predictive value is markedly reduced, leading to large numbers of false positives, unnecessary imaging (including transvaginal ultrasound and computed tomography), and occasional diagnostic laparoscopy or laparotomy, with associated risks. Psychological impacts include anxiety and reduced quality of life. In the United Kingdom Collaborative Trial of Ovarian Cancer Screening, cancer antigen 125-based screening improved stage at diagnosis but resulted in substantial over-diagnosis and overtreatment in benign conditions [3].

Evidence from Large-scale Trials: The role of cancer antigen 125 in screening has been shaped by major trials, notably the United Kingdom Collaborative Trial of Ovarian Cancer Screening. This multicentre randomised controlled trial enrolled more than 202,000 postmenopausal women between 2001 and 2005 across thirteen National Health Service centres in England, Wales, and Northern Ireland [27]. Participants were randomised to no screening, multimodal screening (annual serum cancer antigen 125 interpreted with the risk of ovarian cancer algorithm and transvaginal ultrasound if abnormal), or ultrasound screening alone. Multimodal screening produced a statistically significant stage shift towards earlier disease [27] but did not significantly reduce disease-specific mortality at a median follow-up of 16.3 years (hazard ratio 0.94, 95 percent confidence interval 0.88 - 1.02; $p = 0.10$) [3]. A pre-specified analysis excluding prevalent cases suggested a possible mortality reduction of up to twenty percent after seven to ten years, but this lacked statistical power and consistency to change practice [3]. The United States Prostate, Lung, Colorectal and Ovarian trial likewise showed no mortality benefit with fixed-threshold cancer antigen 125 or ultrasound screening, with additional limitations such as control-arm contamination [29]. Collectively, these findings underpin recommendations against routine population-based screening [30].

Current Clinical Recommendations: Across guideline bodies-the United States Preventive Services Task Force, the American College of Obstetricians and Gynecologists, and the National Institute for Health and Care Excellence-the consensus is to avoid population screening with cancer antigen 125, alone or with ultrasound, in average-risk, asymptomatic women [4] [30] [31]. Harms include false positives, unnecessary imaging and surgery, psychosocial distress, and oppor-

tunity costs that may divert resources from higher-value care [32]. In high-risk individuals, risk-reducing surgery remains the recommended strategy; surveillance may be considered when surgery is declined or deferred, with counselling that monitoring is not equivalent to prevention [33].

*Role in High-risk Populations*

Despite limitations in the general population, cancer antigen 125 may have a role in surveillance of women at high risk, such as carriers of germline BRCA1 and BRCA2 pathogenic variants or those with strong family histories suggestive of hereditary breast and ovarian cancer syndrome. Annual or semi-annual surveillance with cancer antigen 125 and transvaginal ultrasound has been proposed as a risk-management strategy, but survival benefit remains limited. For confirmed carriers, risk-reducing salpingo-oophorectomy after childbearing-typically by thirty-five to forty years for BRCA1 and forty to forty-five years for BRCA2-significantly reduces ovarian and breast cancer incidence; surveillance is an adjunct for those who decline or defer surgery.

*Age and Cancer Antigen* 125 *Interpretation*

High-risk carriers (BRCA1/2 and selected DNA-repair genes): NICE NG241 (2024) recommends risk-reducing bilateral salpingo-oophorectomy after gene- and age-specific thresholds (e.g., BRCA1 ≥ 35 y; BRCA2 ≥ 40 y). For those who defer or decline surgery, surveillance should be framed as short-term management: serial 4-monthly CA125 with an algorithm (e.g., ROCA) within a specialist service, with regular review to re-discuss surgery; surveillance does not reduce incidence and is not an alternative to RRSO. The NHS ALDO prospective study reported feasible delivery, down-staging of detected cancers and favourable cost-effectiveness versus no surveillance, informing the guidance [21] [34].

Age strongly modifies post-test probability: In women over fifty years, a cancer antigen 125 concentration above the conventional threshold of 35 units per millilitre carries a markedly higher risk of malignancy than in younger women. In a primary-care cohort, the risk of ovarian cancer following a raised result was approximately fifteen percent in older women versus about three percent in women under fifty years [2]. Baseline values tend to decrease with age, particularly after menopause [35]. Consequently, a mildly elevated result can be more concerning in a seventy-year-old than in a thirty-year-old. The cancer antigen 125 level corresponding to a three percent probability of ovarian cancer (the National Institute for Health and Care Excellence threshold for urgent investigation) varied by age-from 104 units per millilitre at forty years to 32 units per millilitre at seventy years [2]. Serial measurement and trend-based approaches such as the risk of ovarian cancer algorithm, which incorporate age and trajectories, may detect rising patterns within the reference range, although these methods are largely confined to research or specialist settings [36].

*Alternative biomarkers and future directions*

Dynamic, age-adjusted thresholds: Rather than a single fixed 35 U/mL cut-off, the Risk of Ovarian Cancer Algorithm (ROCA) models an individual's longitudi-

nal CA125 trajectory with age/menopausal status to estimate short-term risk and trigger imaging when the rate-of-rise is suspicious. Large trials (UKCTOCS) showed stage shift but no mortality reduction in population screening; accordingly, population screening is not recommended. However, NICE NG241 (2024) advises serial CA125 interpreted with an algorithm (e.g., ROCA) only for high-risk carriers who defer risk-reducing salpingo-oophorectomy, delivered within specialist familial ovarian cancer services [3] [21].

Human epididymis protein four: This glycoprotein is overexpressed in serous and endometrioid epithelial ovarian cancers and is rarely elevated in benign gynaecological conditions, offering greater specificity than cancer antigen 125 in some settings [7]. In comparative studies, human epididymis protein four outperformed cancer antigen 125 in distinguishing malignant from benign adnexal masses, particularly among postmenopausal women [9].

Risk of ovarian malignancy algorithm: By combining human epididymis protein four, cancer antigen 125, and menopausal status, this algorithm classifies women into low- or high-risk categories and has demonstrated higher sensitivity and specificity than cancer antigen 125 alone across multiple validation cohorts [8] [9]. Adoption is limited by assay variability, cost, and access to human epididymis protein four testing.

Circulating tumour deoxyribonucleic acid: Tumour-derived deoxyribonucleic acid fragments in blood offer a non-invasive route to detection. Early studies suggest utility for recurrence monitoring and potentially for early diagnosis, though sensitivity for early-stage disease remains under evaluation [37].

Micro-ribonucleic acid profiling: Specific circulating micro-ribonucleic acid signatures show high diagnostic accuracy for distinguishing ovarian cancer from benign conditions, including in early-stage disease [38].

Proteomic profiling: High-throughput proteomics can identify complex protein patterns associated with malignancy, with integrative proteogenomic studies mapping signatures across ovarian cancer subtypes [15].

Artificial intelligence and machine learning: Data-driven models that integrate clinical risk factors, biomarkers, and imaging can generate personalised risk scores and may outperform traditional statistical models, but require prospective validation before clinical implementation [39].

Recent AI studies show promising performance for adnexal-mass classification using ultrasound deep learning/radiomics, and multimodal models that integrate CA125/HE4 can improve specificity compared with imaging alone; nevertheless, IOTA ADNEX remains a strong benchmark and prospective, multi-centre external validation is required before routine adoption [21] [40]-[42].

## 3. Conclusions

Cancer antigen 125 remains integral to the evaluation of women with suspected ovarian cancer when it is interpreted within clinical context and combined with structured transvaginal ultrasound and validated risk models. Used this way, it

supports triage, standardises referral to specialist multidisciplinary teams, and helps avoid unnecessary intervention in women with benign disease. Its limitations are well defined: reduced sensitivity in early-stage disease, lack of tumour specificity across many benign and physiological states, and variable expression by histotype. These constraints explain why population screening with cancer antigen 125, alone or with ultrasound, is not recommended. In practice, the greatest clinical value arises in symptom-led pathways that incorporate age-aware interpretation, repeat testing when appropriate, and a stepwise approach to escalation that prioritises patient safety and resource stewardship.

Limitations: The evidence base shows spectrum effects between primary- and secondary-care cohorts; CA125 assays and ultrasound expertise vary across studies; no pooled accuracy exists for the complete two-step CA125→TVUS pathway in primary care; evidence for emerging biomarkers (e.g., HE4/ROMA) is moderate/heterogeneous; and dynamic/AI models need external validation and impact studies before widespread implementation.

Future improvements in early detection will likely come from a multimodal strategy rather than reliance on a single biomarker. Human epididymis protein four and risk algorithms that integrate multiple inputs can refine pre-test and post-test probabilities in selected settings, while emerging molecular diagnostics, proteomic panels, and artificial-intelligence-assisted models may further enhance discrimination. These innovations require robust prospective validation and demonstration of patient-centred benefit, including earlier diagnosis, less morbidity, and improved survival, before widespread adoption. For individuals at high genetic risk, risk-reducing surgery remains the most effective intervention, with surveillance reserved for those who decline or defer definitive risk reduction.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

[1] Matulonis, U.A., Sood, A.K., Fallowfield, L., Howitt, B.E., Sehouli, J. and Karlan, B.Y. (2016) Ovarian Cancer. *Nature Reviews Disease Primers*, **2**, Article No. 16061. https://doi.org/10.1038/nrdp.2016.61

[2] Funston, G., Hamilton, W., Abel, G., Crosbie, E.J., Rous, B. and Walter, F.M. (2020) The Diagnostic Performance of CA125 for the Detection of Ovarian and Non-Ovarian Cancer in Primary Care: A Population-Based Cohort Study. *PLOS Medicine*, **17**, e1003295. https://doi.org/10.1371/journal.pmed.1003295

[3] Menon, U., Gentry-Maharaj, A., Burnell, M., Singh, N., Ryan, A., Karpinskyj, C., *et al.* (2021) Ovarian Cancer Population Screening and Mortality after Long-Term Follow-Up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A Randomised Controlled Trial. *The Lancet*, **397**, 2182-2193. https://doi.org/10.1016/s0140-6736(21)00731-5

[4] National Institute for Health and Care Excellence (NICE) (2025) Suspected Cancer: Recognition and Referral (NG12). https://www.nice.org.uk/guidance/ng12

[5] National Institute for Health and Care Excellence (NICE) (2011) Ovarian Cancer:

Recognition and Initial Management (CG122). https://www.nice.org.uk/guidance/cg122

[6] Jacobs, I., Oram, D., Fairbanks, J., Turner, J., Frost, C. and Grudzinskas, J.G. (1990) A Risk of Malignancy Index Incorporating CA 125, Ultrasound and Menopausal Status for the Accurate Preoperative Diagnosis of Ovarian Cancer. *BJOG: An International Journal of Obstetrics & Gynaecology*, **97**, 922-929. https://doi.org/10.1111/j.1471-0528.1990.tb02448.x

[7] Moore, R.G., McMeekin, D.S., Brown, A.K., DiSilvestro, P., Miller, M.C., Allard, W.J., *et al.* (2009) A Novel Multiple Marker Bioassay Utilizing HE4 and CA125 for the Prediction of Ovarian Cancer in Patients with a Pelvic Mass. *Gynecologic Oncology*, **112**, 40-46. https://doi.org/10.1016/j.ygyno.2008.08.031

[8] Moore, R.G., Miller, M.C., Disilvestro, P., Landrum, L.M., Gajewski, W., Ball, J.J., *et al.* (2011) Evaluation of the Diagnostic Accuracy of the Risk of Ovarian Malignancy Algorithm in Women with a Pelvic Mass. *Obstetrics & Gynecology*, **118**, 280-288. https://doi.org/10.1097/aog.0b013e318224fce2

[9] Sandri, M.T., Bottari, F., Franchi, D., Boveri, S., Candiani, M., Ronzoni, S., *et al.* (2013) Comparison of HE4, CA125 and ROMA Algorithm in Women with a Pelvic Mass: Correlation with Pathological Outcome. *Gynecologic Oncology*, **128**, 233-238. https://doi.org/10.1016/j.ygyno.2012.11.026

[10] Bast, R.C., Feeney, M., Lazarus, H., Nadler, L.M., Colvin, R.B. and Knapp, R.C. (1981) Reactivity of a Monoclonal Antibody with Human Ovarian Carcinoma. *Journal of Clinical Investigation*, **68**, 1331-1337. https://doi.org/10.1172/jci110380

[11] Yin, B.W.T. and Lloyd, K.O. (2001) Molecular Cloning of the CA125 Ovarian Cancer Antigen: Identification as a New Mucin, MUC16. *Journal of Biological Chemistry*, **276**, 27371-27375. https://doi.org/10.1074/jbc.m103554200

[12] Felder, M., Kapur, A., Gonzalez-Bosquet, J., Horibata, S., Heintz, J., Albrecht, R., *et al.* (2014) MUC16 (CA125): Tumor Biomarker to Cancer Therapy, a Work in Progress. *Molecular Cancer*, **13**, Article No. 129. https://doi.org/10.1186/1476-4598-13-129

[13] Jacobs, I. and Bast, R.C. (1989) The CA 125 Tumour-Associated Antigen: A Review of the Literature. *Human Reproduction*, **4**, 1-12. https://doi.org/10.1093/oxfordjournals.humrep.a136832

[14] Charkhchi, P., Cybulski, C., Gronwald, J., Wong, F.O., Narod, S.A. and Akbari, M.R. (2020) CA125 and Ovarian Cancer: A Comprehensive Review. *Cancers*, **12**, Article 3730. https://doi.org/10.3390/cancers12123730

[15] Zhang, H., Liu, T., Zhang, Z., Payne, S.H., Zhang, B., McDermott, J.E., *et al.* (2016) Integrated Proteogenomic Characterization of Human High-Grade Serous Ovarian Cancer. *Cell*, **166**, 755-765. https://doi.org/10.1016/j.cell.2016.05.069

[16] Hirsch, M., Duffy, J., Davis, C., Nieves Plana, M. and Khan, K. (2016) Diagnostic Accuracy of Cancer Antigen 125 for Endometriosis: A Systematic Review and Meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, **123**, 1761-1768. https://doi.org/10.1111/1471-0528.14055

[17] Myers, E.R., Bastian, L.A., Havrilesky, L.J., Kulasingam, S.L., Terplan, M.S., Cline, K.E., Gray, R.N. and McCrory, D.C. (2006) Management of Adnexal Mass. *Evidence report/Technology Assessment*, No. 130, 1-145. https://pubmed.ncbi.nlm.nih.gov/17854238/

[18] Medeiros, L.R., Rosa, D.D., da Rosa, M.I. and Bozzetti, M.C. (2009) Accuracy of CA 125 in the Diagnosis of Ovarian Tumors: A Quantitative Systematic Review. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **142**, 99-105. https://doi.org/10.1016/j.ejogrb.2008.08.011

[19] Ngu, S.F., Chai, Y.K., Choi, K.M., Leung, T.W., Li, J., Kwok, G.S.T., *et al.* (2022) Diagnostic Performance of Risk of Malignancy Algorithm (ROMA), Risk of Malignancy Index (RMI) and Expert Ultrasound Assessment in a Pelvic Mass Classified as Inconclusive by International Ovarian Tumour Analysis (IOTA) Simple Rules. *Cancers*, **14**, Article 810. https://doi.org/10.3390/cancers14030810

[20] Sundar, S., Agarwal, R., Davenport, C., Scandrett, K., Johnson, S., Sengupta, P., *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**, 1371-1386. https://doi.org/10.1016/s1470-2045(24)00406-6

[21] National Institute for Health and Care Excellence (NICE) (2024) Ovarian Cancer: Identifying and Managing Familial and Genetic Risk (NG241). https://www.nice.org.uk/guidance/ng241

[22] Moss, E., Taylor, A., Andreou, A., Ang, C., Arora, R., Attygalle, A., *et al.* (2024) British Gynaecological Cancer Society (BGCS) Ovarian, Tubal and Primary Peritoneal Cancer Guidelines: Recommendations for Practice Update 2024. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **300**, 69-123. https://doi.org/10.1016/j.ejogrb.2024.06.025

[23] Menon, U., McGuire, A.J., Raikou, M., Ryan, A., Davies, S.K., Burnell, M., *et al.* (2017) The Cost-Effectiveness of Screening for Ovarian Cancer: Results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *British Journal of Cancer*, **117**, 619-627. https://doi.org/10.1038/bjc.2017.222

[24] Kearns, B., Chilcott, J., Whyte, S., Preston, L. and Sadler, S. (2016) Cost-Effectiveness of Screening for Ovarian Cancer amongst Postmenopausal Women: A Model-Based Economic Evaluation. *BMC Medicine*, **14**, Article No. 200. https://doi.org/10.1186/s12916-016-0743-y

[25] Piovano, E., Cavallero, C., Fuso, L., Viora, E., Ferrero, A., Gregori, G., *et al.* (2017) Diagnostic Accuracy and Cost-effectiveness of Different Strategies to Triage Women with Adnexal Masses: A Prospective Study. *Ultrasound in Obstetrics & Gynecology*, **50**, 395-403. https://doi.org/10.1002/uog.17320

[26] Cancer Research UK (2025) Ovarian Cancer Survival Statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer

[27] Menon, U., Ryan, A., Kalsi, J., Gentry-Maharaj, A., Dawnay, A., Habib, M., *et al.* (2015) Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared with a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. *Journal of Clinical Oncology*, **33**, 2062-2071. https://doi.org/10.1200/jco.2014.59.4945

[28] Medscape, L.B. (2025) CA125: Reference Range, Interpretation, Collection and Panels. https://emedicine.medscape.com/article/2087557-overview?form=fpf

[29] Buys, S.S. (2011) Effect of Screening on Ovarian Cancer Mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA*, **305**, 2295-2303. https://doi.org/10.1001/jama.2011.766

[30] US Preventive Services Task Force (2018) Screening for Ovarian Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*, **319**, 588-594.

[31] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Gynecology (2016) Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. *Obstetrics and Gynecology*, **128**, e210-e226. https://doi.org/10.1097/AOG.0000000000001768

[32] Andrykowski, M.A., Boerner, L.M., Salsman, J.M. and Pavlik, E. (2004) Psychological Response to Test Results in an Ovarian Cancer Screening Program: A Prospective, Longitudinal Study. *Health Psychology*, **23**, 622-630. https://doi.org/10.1037/0278-6133.23.6.622

[33] Rebbeck, T.R., Lynch, H.T., Neuhausen, S.L., Narod, S.A., van't Veer, L., Garber, J.E., *et al.* (2002) Prophylactic Oophorectomy in Carriers of *BRCA*1 or *BRCA*2 Mutations. *New England Journal of Medicine*, **346**, 1616-1622. https://doi.org/10.1056/nejmoa012158

[34] Philpott, S., Raikou, M., Manchanda, R., Lockley, M., Singh, N., Scott, M., *et al.* (2022) The Avoiding Late Diagnosis of Ovarian Cancer (ALDO) Project; a Pilot National Surveillance Programme for Women with Pathogenic Germline Variants in *BRCA*1 and *BRCA*2. *Journal of Medical Genetics*, **60**, 440-449. https://doi.org/10.1136/jmg-2022-108741

[35] Pauler, D.K., Menon, U., McIntosh, M., Symecko, H.L., Skates, S.J. and Jacobs, I.J. (2001) Factors Influencing Serum CA125II Levels in Healthy Postmenopausal Women. *Cancer Epidemiology*, *Biomarkers & Prevention*, **10**, 489-493. https://pubmed.ncbi.nlm.nih.gov/11352859/

[36] Skates, S.J. (2003) Calculation of the Risk of Ovarian Cancer from Serial CA-125 Values for Preclinical Detection in Postmenopausal Women. *Journal of Clinical Oncology*, **21**, 206s-210. https://doi.org/10.1200/jco.2003.02.955

[37] Cohen, J.D., Li, L., Wang, Y., Thoburn, C., Afsari, B., Danilova, L., *et al.* (2018) Detection and Localization of Surgically Resectable Cancers with a Multi-Analyte Blood Test. *Science*, **359**, 926-930. https://doi.org/10.1126/science.aar3247

[38] Yokoi, A., Matsuzaki, J., Yamamoto, Y., Yoneoka, Y., Takahashi, K., Shimizu, H., *et al.* (2018) Integrated Extracellular MicroRNA Profiling for Ovarian Cancer Screening. *Nature Communications*, **9**, Article No. 4319. https://doi.org/10.1038/s41467-018-06434-4

[39] Dochez, V., Caillon, H., Vaucel, E., Dimet, J., Winer, N. and Ducarme, G. (2019) Biomarkers and Algorithms for Diagnosis of Ovarian Cancer: CA125, HE4, RMI and ROMA, a Review. *Journal of Ovarian Research*, **12**, Article No. 28. https://doi.org/10.1186/s13048-019-0503-7

[40] Chen, H., Yang, B., Qian, L., Meng, Y., Bai, X., Hong, X., *et al.* (2022) Deep Learning Prediction of Ovarian Malignancy at US Compared with O-RADS and Expert Assessment. *Radiology*, **304**, 106-113. https://doi.org/10.1148/radiol.211367

[41] Du, Y., Guo, W., Xiao, Y., Chen, H., Yao, J. and Wu, J. (2024) Ultrasound-Based Deep Learning Radiomics Model for Differentiating Benign, Borderline, and Malignant Ovarian Tumours: A Multi-Class Classification Exploratory Study. *BMC Medical Imaging*, **24**, Article No. 89. https://doi.org/10.1186/s12880-024-01251-2

[42] Wang, Z., Luo, S., Chen, J., Jiao, Y., Cui, C., Shi, S., *et al.* (2024) Multi-modality Deep Learning Model Reaches High Prediction Accuracy in the Diagnosis of Ovarian Cancer. *iScience*, **27**, Article ID: 109403. https://doi.org/10.1016/j.isci.2024.109403