Ovarian cancer serum biomarker risk assessment testing

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Recent review date: 6/2026

Next review date: 10/2027

Policy contains: ovarian cancer, ovarian malignancy risk assessment, serum biomarker testing, ovarian cancer biomarker panel, adnexal mass, pelvic mass, preoperative risk stratification, gynecologic oncology referral, multivariate index assay.

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Coverage policy

Ovarian cancer serum biomarker risk assessment testing, including OVA1, the Risk of Ovarian Malignancy Algorithm/ROMA, Overa/OVA1 Next Generation, OvaWatch, and substantially similar serum biomarker algorithmic assays, are investigational/not clinically proven and, therefore, not medically necessary for the evaluation of adnexal or pelvic masses, including preoperative malignancy risk stratification, referral decision-making, selection of surgical setting, or surgical planning.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Ovarian cancer serum biomarker risk assessment testing uses multiple serum biomarkers and a proprietary algorithm to estimate the likelihood that an adnexal or pelvic mass is malignant. These tests are used after a mass has been identified, usually in the preoperative setting, as an adjunct to clinical assessment and imaging.

The proposed clinical role is risk stratification, not diagnosis. Test results are intended to classify an individual with an adnexal or pelvic mass into a higher-risk or lower-risk category to inform whether referral to a gynecologic oncologist or specialized surgical planning should be considered. The result does not establish histology, stage, resectability, or whether surgery is required (FDA Class II Special Controls Guidance, 2011; Federal Register final rule, 2011).

Standard evaluation of an adnexal or pelvic mass includes history, physical examination, pregnancy testing when applicable, transvaginal ultrasonography, cancer antigen 125 or other tumor markers when clinically indicated, and cross-sectional imaging when findings suggest disseminated disease or when ultrasonography is indeterminate. Guidelines also emphasize referral to a gynecologic oncologist for clinically suspicious lesions (American College of Obstetricians and Gynecologists, 2016; Glanc, 2017; National Comprehensive Cancer Network, 2026; Salvador, 2020).

The FDA classifies ovarian adnexal mass assessment score test systems as Class II devices under 21 CFR § 866.6050. These devices measure one or more serum or plasma proteins and use an algorithm to produce a single result estimating the likelihood that an adnexal pelvic mass is malignant in an individual for whom surgery is planned. The FDA has granted marketing authorization for three pre-surgical assays through distinct regulatory pathways: OVA1 was granted de novo classification (DEN090004; decision date September 11, 2009); ROMA received 510(k) clearance (K103358; cleared September 1, 2011); and Overa/OVA1 Next Generation received 510(k) clearance (K150588; cleared March 2016). The FDA Class II Special Controls Guidance and the Federal Register final rule require that these tests carry labeling stating they are adjuncts to independent clinical and radiologic evaluation and are not intended for ovarian cancer screening, stand-alone diagnosis, or determining whether surgery should proceed (Code of Federal Regulations, 2026; FDA, 2009 [DEN090004]; FDA, 2011 [K103358]; FDA, 2016 [K150588]; FDA Class II Special Controls Guidance, 2011; Federal Register final rule, 2011).

OvaWatch (Aspira Women’s Health) is described by the manufacturer as a noninvasive serum protein and clinical-data algorithm intended for women with adnexal masses initially evaluated as indeterminate or benign, to be used in conjunction with imaging and clinical assessment rather than as a stand-alone diagnostic, screening, or pre-surgical triage test. Its manufacturer-described intended-use population and clinical pathway therefore differ from the FDA-cleared pre-surgical assays (OVA1, ROMA, and Overa), which are labeled for women in whom surgery is already planned. The clinical-utility evidence for OvaWatch is addressed separately in the Findings section (Aspira Women’s Health, 2025).

Findings

The evidence base for ovarian cancer serum biomarker risk assessment testing in adnexal or pelvic mass evaluation is primarily diagnostic accuracy evidence rather than interventional evidence demonstrating improved management or outcomes. Accuracy studies commonly used postsurgical histology as the reference standard, which may preferentially include individuals already selected for operative management; studies that included nonsurgical management used clinical assessment, spontaneous resolution, or follow-up ranging from three to four months to one or two years. Major limitations include high or unclear risk of bias, high disease prevalence relative to community settings, inconsistent thresholds, incomplete reporting of presenting features, variable handling of borderline tumors, and limited data on calibration and clinical outcomes.

Diagnostic accuracy

A Cochrane diagnostic test accuracy review (Davenport 2022) included 59 studies, 32,059 women, and 9,545 cases of ovarian cancer. The review evaluated the Risk of Malignancy Index (RMI), the Risk of Ovarian Malignancy Algorithm (ROMA), the International Ovarian Tumor Analysis Logistic Regression Model 2 (LR2), and the Assessment of Different Neoplasias in the adnexa (ADNEX) model in individuals with a pelvic mass suspicious for ovarian cancer; the review did not directly evaluate OVA1, Overa, or OvaWatch. The reference standard was histologic confirmation or clinical follow-up (Davenport, 2022).

For premenopausal participants, the Risk of Ovarian Malignancy Algorithm had sensitivity 77.4% (95% confidence interval 72.7% to 81.5%) and specificity 84.3% (95% confidence interval 81.2% to 87.0%). The Risk of Malignancy Index had sensitivity 57.2% (95% confidence interval 50.3% to 63.8%) and specificity 92.5% (95% confidence interval 90.3% to 94.2%). The Assessment of Different Neoplasias in the adnexa model had higher sensitivity at 95.5% (95% confidence interval 91.0% to 97.8%) and lower specificity at 77.8% (95% confidence interval 67.4% to 85.5%) (Davenport, 2022).

For postmenopausal participants, the Risk of Ovarian Malignancy Algorithm had sensitivity 90.3% (95% confidence interval 87.5% to 92.6%) and specificity 81.5% (95% confidence interval 76.5% to 85.5%). The Risk of Malignancy Index had sensitivity 78.4% (95% confidence interval 74.6% to 81.7%) and specificity 85.4% (95% confidence interval 82.0% to 88.2%). The Assessment of Different Neoplasias in the adnexa model had sensitivity 97.6% (95% confidence interval 95.6% to 98.7%) and specificity 55.0% (95% confidence interval 42.8% to 66.6%) (Davenport, 2022).

A meta-analysis limited to head-to-head studies of the Risk of Ovarian Malignancy Algorithm and the Risk of Malignancy Index version I included 8 papers and 2,662 participants. In postmenopausal participants, the 2 methods had similar diagnostic performance. In premenopausal participants, the Risk of Malignancy Index version I had higher specificity than the Risk of Ovarian Malignancy Algorithm, 89% compared with 78% (P value = 0.022), with similar sensitivity, 73% compared with 80% (P value = 0.27). Most included studies had high risk of bias for participant selection and substantial heterogeneity (Chacón, 2019).

Additional meta-analyses of the Risk of Ovarian Malignancy Algorithm reported high pooled diagnostic estimates but provided less direct comparative evidence. One meta-analysis of 23 studies and 5,954 cases reported pooled sensitivity 90% (95% confidence interval 88% to 93%), specificity 91% (95% confidence interval 89% to 94%), positive predictive value 90% (95% confidence interval 88% to 95%), negative predictive value 93% (95% confidence interval 91% to 95%), and area under the receiver operating characteristic curve 0.96 (Cui, 2019). A

2025 postmenopausal meta-analysis included 34 studies and reported overall sensitivity 89%, specificity 89%, and diagnostic performance that varied by continent, study design, and threshold (Fathi, 2025).

Risk stratification performance

Serum biomarker panels generally emphasize sensitivity and negative predictive value. This profile may reduce false-negative classifications, but it may also increase false-positive classifications when specificity is low. The OVA1 multivariate index assay has been reported in payer evidence reviews to classify more early-stage malignancies as abnormal than CA-125 alone, but with relatively low specificity (approximately 42% for OVA1 and approximately 65% for Overa in the populations studied) and a corresponding number of false-positive classifications in prospective evaluations (American College of Obstetricians and Gynecologists Practice Bulletin No. 174, 2016; Salvador et al., Society of Obstetricians and Gynaecologists of Canada Guideline No. 403, 2020; payer evidence review for multimarker serum testing related to ovarian cancer, 2025).

The Risk of Ovarian Malignancy Algorithm also stratifies individuals into high-risk and low-risk categories based on biomarker levels and menopausal status. Across reviews, it appears more sensitive than the Risk of Malignancy Index in some postmenopausal populations, but the degree of benefit depends on threshold, comparator, population, and clinical setting. In premenopausal populations, improved sensitivity may be offset by lower specificity (Chacón, 2019; Davenport, 2022).

Clinical utility and referral outcomes

The strongest available evidence addresses diagnostic classification rather than clinical utility. Across Davenport 2022, Chacón 2019, Cui 2019, Fathi 2025, and Barreñada 2024, no identified trial or prospective comparative study establishes that ovarian cancer serum biomarker risk assessment testing—whether OVA1, ROMA, Overa, or OvaWatch—improves referral appropriateness to gynecologic oncology, selection of surgical setting, completeness of surgical staging or debulking, perioperative morbidity, overall survival, quality of life, or downstream resource use when compared with standard clinical, imaging, and laboratory evaluation. The Cochrane review further notes that included populations were highly selected, with ovarian cancer prevalence higher than expected in community or initial referral settings, which limits transferability to the population in whom referral decisions are commonly made (Davenport, 2022; payer evidence review for multimarker serum testing related to ovarian cancer, 2025).

Guideline positions reflect this distinction. The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 174 (2016), which remains the most recent ACOG guidance specific to evaluation and management of adnexal masses available at the time of this review, states that serum biomarker panels may be used as an alternative to CA-125 alone to help determine the need for gynecologic oncology referral when an adnexal mass requires surgery, but that these panels are not recommended for the initial evaluation of an adnexal mass and that comparative research has not defined the best testing approach. Because Practice Bulletin No. 174 has not been updated since 2016, it is cited here as older specialty-society guidance rather than as current high-certainty evidence (ACOG Practice Bulletin No. 174, 2016).

The Society of Obstetricians and Gynaecologists of Canada Guideline No. 403 (Salvador et al., 2020) states that biomarker testing should not substitute for clinical judgment and decision-making in the initial investigation of adnexal masses. The same guideline states that International Ovarian Tumor Analysis (IOTA) methods have

shown greater diagnostic accuracy than the Risk of Malignancy Index or the Risk of Ovarian Malignancy Algorithm when compared in the same study populations (Salvador et al., Guideline No. 403, 2020).

The international consensus report describes the role of serum biomarkers, alone or within algorithms, as not clearly established. It emphasizes that indeterminate masses may be evaluated through several second-step approaches, including expert sonography, serial sonography, established risk prediction models, correlation with serum biomarkers, magnetic resonance imaging, or gynecologic oncology referral (Glanc, 2017).

The current National Comprehensive Cancer Network (NCCN) clinical practice guideline discussion for ovarian cancer emphasizes history and physical examination, imaging (primarily transvaginal ultrasonography with additional cross-sectional imaging when indicated), CA-125 or other tumor markers as clinically indicated, and evaluation by a gynecologic oncologist before surgery when malignancy is suspected. Based on payer evidence reviews that quote and summarize the current NCCN discussion, NCCN does not recommend ROMA, OVA1, Overa, or other proprietary serum biomarker algorithmic panels for determining the status of an undiagnosed adnexal or pelvic mass, and the NCCN discussion does not endorse these panels as a required or preferred element of the initial workup of a suspicious pelvic mass (National Comprehensive Cancer Network, Version 4.2026; payer evidence review for multimarker serum testing related to ovarian cancer, 2025).

Comparison with standard evaluation methods

Standard evaluation methods remain central because serum biomarker tests do not characterize mass morphology, disease extent, operative feasibility, or histologic subtype. Ultrasonography, particularly when performed by experienced examiners or interpreted through validated imaging rules, may outperform serum biomarker algorithms in selected settings. Magnetic resonance imaging may improve characterization of indeterminate lesions after ultrasonography and may increase specificity for benign diagnoses (Glanc, 2017; Salvador, 2020).

The Assessment of Different Neoplasias in the adnexa model, which incorporates clinical variables, ultrasonographic variables, and optionally cancer antigen 125, has been externally validated in 47 studies including 17,007 tumors. In participants who underwent surgery, the summary area under the receiver operating characteristic curve was 0.93 (95% confidence interval 0.92 to 0.94) when cancer antigen 125 was included and 0.93 (95% confidence interval 0.91 to 0.94) when cancer antigen 125 was not included. However, 91% of validations were at high risk of bias, and calibration was rarely assessed (Barreñada, 2024).

References

On 5/2026, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were:"ovarian cancer" . We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

Initial review date: 5/2026 and clinical policy effective date: 7/2026

6/2026: Policy created.

Related codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1561. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code description
CPT 81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score (Risk of Ovarian Malignancy Algorithm/ROMA–type testing).
CPT 81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A-1, beta-2 microglobulin, transferrin, and pre-albumin/transthyretin), utilizing serum, algorithm reported as a risk score (OVA1–type multivariate index assay).
CPT 0003U	Oncology (ovarian), biochemical assays of five proteins (apolipoprotein A-1, CA-125, follicle-stimulating hormone, human epididymis protein 4, and transferrin), utilizing serum, algorithm reported as a likelihood score (Overa or OVA1 Next Generation–type proprietary laboratory analysis [PLA] code).
CPT 0375U	OvaWatch–type proprietary assay: oncology (ovarian), biochemical assays of seven proteins (including CA-125, HE4, FSH, and additional analytes as specified by the manufacturer), utilizing serum, algorithm reported as an ovarian cancer risk score (OvaWatch/MIA3G–type PLA code).