

MEDICAL POLICY

POLICY TITLE	MULTIMARKER SERUM TESTING RELATED TO OVARIAN CANCER
POLICY NUMBER	MP 2.270

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

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I. POLICY

All uses of the OVA1[®], Overa[®], OvaWatchSM, and ROMA[™] tests are **investigational**, including but not limited to:

- Preoperative evaluation of adnexal masses to triage for malignancy; or
- Screening for ovarian cancer; or
- Selecting individuals for surgery for an adnexal mass; or
- Evaluation of individuals with clinical or radiologic evidence of malignancy; or
- Evaluation of individuals with nonspecific signs or symptoms suggesting possible malignancy; or
- Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

Policy Guidelines

OVA1[®], Overa[®], and ROMA[™] tests are combinations of several separate lab tests and involve a proprietary algorithm for determining risk (i.e., what CPT calls multianalyte assays with algorithmic analyses [MAAAs]). Ova1Plus is a proprietary reflex process combining two FDA-cleared tests, Ova1, leveraging high sensitivity, and Overa. No separate evidence was identified for Ova1Plus and as both of the individual tests are included within the policy no additional evidence review provided at this time. OvaWatch is a multivariate index assay that provides a single risk assessment score; currently, an FDA submission is in process.

Cross-Reference:

MP 2.269 Serum Biomarkers for Human Epididymis Protein 4 (HE4)

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II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

III. DESCRIPTION/BACKGROUND

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Epithelial Ovarian Cancer

The term *epithelial ovarian cancer* collectively includes high-grade serous epithelial ovarian, fallopian tubal, and peritoneal carcinomas due to their shared pathogenesis, clinical presentation, and treatment. We use epithelial ovarian cancer to refer to this group of malignancies in the discussion that follows. There is currently no serum biomarker that can distinguish between these types of carcinomas. An estimated 19,710 women in the United States were estimated to be diagnosed with ovarian cancer in 2023, and approximately 13,270 were expected to die of the disease. The mortality rate depends on 3 variables: (1) patient characteristics; (2) tumor biology (grade, stage, type); and (3) treatment quality (nature of staging, surgery, and chemotherapy used). In particular, comprehensive staging and completeness of tumor resection appear to have a positive impact on patient outcome. Racial, ethnic, and socioeconomic disparities in management and outcomes are prominent in patients with ovarian cancer. Compared to non-Hispanic White and Asian patients, Hispanic and non-Hispanic Black patients are more likely to be diagnosed with advanced disease and are less likely to undergo optimal primary surgery and adjuvant chemotherapy. Patients with ovarian cancer from racial and ethnic minorities are also less likely to be enrolled in clinical trials. These are among the contributing factors to worsened overall survival among these racial and ethnic groups. Patients with impediments to access healthcare (e.g., those living in underserved areas, with low household income, and/or who are underinsured or uninsured), which frequently intersect with racial and ethnic determinants, also experience longer time to diagnosis, suboptimal treatment, and worse outcomes.

Adult women presenting with an adnexal mass have an estimated 68% likelihood of having a benign lesion. About 6% of women with masses have borderline tumors; 22% possess invasive malignant lesions, and 3% have metastatic disease. Surgery is the only way to diagnose ovarian cancer; this is because biopsy of an ovary with suspected ovarian cancer is usually not performed due to the risk of spreading cancer cells. Most clinicians agree that women with masses that have a high likelihood of malignancy should undergo surgical staging by a gynecologic oncologist. However, women with clearly benign masses do *not* require a referral to see a specialist. Therefore, criteria and tests that help differentiate benign from malignant pelvic masses are desirable.

In 2016, the American College of Obstetricians and Gynecologists updated a practice bulletin that addressed criteria for referring women with adnexal masses to gynecologic oncologists.

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Separate criteria were developed for premenopausal and postmenopausal women because the specificity and positive predictive value of cancer antigen 125 (CA 125) are higher in postmenopausal women. Prior guidance, which was based on expert opinion, recommended a CA 125 >200 U/mL for referring premenopausal women with an adnexal mass to a gynecologic oncologist. The current guidance advises using very elevated CA 125 levels with other clinical factors such as ultrasound findings, ascites, a nodular or fixed pelvic mass, or evidence of abdominal or distant metastasis for referral. The referral criteria for postmenopausal women are similar, except that a lower threshold for an elevated CA 125 test is used (35 U/mL). The practice bulletin states that serum biomarker panels are alternatives to CA 125 levels when deciding about a gynecologic oncologist referral.

Three multimarker serum-based tests specific to ovarian cancer have been cleared by the Food and Drug Administration (FDA) with the intended use of triaging patients with adnexal masses (see Regulatory Status section). The proposed use of the tests is to identify women with a substantial likelihood of malignant disease who may benefit from referral to a gynecologic oncology specialist. Patients with positive results may be considered candidates for referral to a gynecologic oncologist for treatment. The tests have been developed and evaluated only in patients with adnexal masses and planned surgeries. Other potential uses, such as selecting patients to have surgery, screening asymptomatic patients, and monitoring treatment, have not been investigated. Furthermore, the tests are not intended to be used as stand-alone tests, but in conjunction with clinical assessment.

Other multimarker panels and longitudinal screening algorithms are under development; however, these are not yet commercially available.

Table 1. Summary of FDA-Cleared Multimarker Serum-Based Tests Specific to Ovarian Cancer

Variables	OVA1	Overa	ROMA
Cleared	2009	2016	2011
Manufacturer	Quest Diagnostics	Vermillion	Roche Diagnostics
Biomarkers used			
CA 125 II	X	X	X
b ₂ -microglobulin	X		
Transferrin	X	X	
Transthyretin	X		
Apolipoprotein AI	X	X	
HE4		X	X
FSH		X	
Score range	0 to 10	0 to 10	0 to 10
Risk categorization			

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Premenopausal	<5.0: low ≥5.0: high	<5.0: low ≥5.0: high	≥1.3: high
Postmenopausal	<4.4: low ≥4.4: high		≥2.77: high

CA 125: cancer antigen 125; FDA: U.S. Food and Drug Administration; FSH: follicle-stimulating hormone; HE4: human epididymis secretory protein 4; ROMA: Risk of Ovarian Malignancy Algorithm.

Regulatory Status

In July 2009, the OVA1® test (Aspira Labs [Austin, TX]) was cleared for marketing by the FDA through the 510(k) process. OVA1® was designed as a tool to further assess the likelihood that malignancy is present when the physician's independent clinical and radiologic evaluation does not indicate malignancy.

In September 2011, the Risk of Ovarian Malignancy Algorithm (ROMA™ test; Fujirebio Diagnostics [Sequin, TX]) was cleared for marketing by the FDA through the 510(k) process. The intended use of ROMA™ is as an aid, in conjunction with clinical assessment, in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery.

In March 2016, a second-generation test called Overa™ (also referred as next-generation OVA1®), in which 2 of the 5 biomarkers in OVA1® are replaced with human epididymis secretory protein 4 and follicle stimulating hormone, was cleared for marketing by the FDA through the 510(k) process. Similar to OVA1®, Overa™ generates a low or high risk of malignancy on a scale from 0 to 10.

In December 2022, Aspira Women's Health introduced OvaWatchSM. This test is intended for use in assessing the risk of ovarian cancer for women with adnexal masses that have been considered indeterminate or benign in initial clinical assessment. The OvaWatchSM test has not been FDA approved.

Black Box Warning

In December 2011, the FDA amended its regulation for classifying ovarian adnexal mass assessment score test systems. The change required that off-label risks be highlighted using a black box warning. The warning is intended to mitigate the risk to health associated with off-label use as a screening test, stand-alone diagnostic test, or as a test to determine whether to proceed with surgery. Considering the history and currently unmet medical needs for ovarian cancer testing, the FDA concluded that there is a risk of off-label use of this device. To address this risk, the FDA requires that manufacturers provide notice concerning the risks of off-label uses in the labeling, advertising, and promotional material of ovarian adnexal mass assessment score test systems. Manufacturers must address the following risks:

- Women without adnexal pelvic masses (i.e., for cancer "screening") are not part of the intended use population for the ovarian adnexal mass assessment score test systems. Public health risks associated with false-positive results for ovarian cancer screening

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tests are well described in the medical literature and include morbidity or mortality associated with unneeded testing and surgery. The risk from false-negative screening results also includes morbidity and mortality due to failure to detect and treat ovarian malignancy.

- Analogous risks, adjusted for prevalence and types of disease, arise if test results are used to determine the need for surgery in patients who are known to have ovarian adnexal masses.
- If used outside the “OR” rule that is described in this special control guidance, results from ovarian adnexal mass assessment score test systems pose a risk for morbidity and mortality due to nonreferral for oncologic evaluation and treatment.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who have adnexal mass(es) undergoing surgery for possible ovarian cancer who receive multimarker serum testing with clinical assessment preoperatively to assess ovarian cancer risk, the evidence includes studies assessing technical performance and diagnostic accuracy. Relevant outcomes are overall survival and test accuracy. OVA1 and Overa are intended for use in patients for whom clinical assessment does not clearly indicate cancer. When used in this manner, sensitivity for ovarian malignancy was 92% and specificity was 42% with OVA1; with Overa, sensitivity was 94% and specificity was 65%. ROMA is intended for use with clinical assessment, but no specific method has been defined. One study, which used clinical assessment and ROMA results, showed a sensitivity of 90% and specificity of 67%. However, the National Comprehensive Cancer Network guidelines recommend (category 2A) that all patients with suspected ovarian cancer should be evaluated by an experienced gynecologic oncologist. Given the National Comprehensive Cancer Network recommendation, direct evidence will be required to demonstrate that the use of U.S. Food and Drug Administration (FDA) cleared multimarker serum testing to inform decisions regarding referral to a gynecologic oncology specialist for surgery has clinical usefulness. Direct evidence of clinical usefulness is provided by studies that have compared health outcomes for patients managed with and without the FDA cleared multimarker serum testing. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No trials were identified that have evaluated whether referral based on FDA cleared multimarker serum testing improves health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

In response to requests, clinical input was received while this policy was under review in 2012. The input was mixed in support of these tests as a tool for triaging patients with an adnexal mass. Reviewers agreed that the evidence was insufficient to determine the impact of these tests on referral patterns. For indications other than triaging patients with an adnexal mass, there was a lack of support for the use of these tests.

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V. DEFINITIONS

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N/A

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes							
81500	81503						

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.270	11/03/2020 Consensus Review. No change to policy statement. Reference updated.
	05/11/2021 Consensus Review. Policy statement unchanged. Background, Rationale, and References updated.
	03/02/2022 Consensus Review. Added NCCN statement. Background, FEP, references updated.
	03/16/2023 Administrative Update. Added New code 0375U, effective 04/01/2023.
	04/10/2023 Minor Review. Added OvaWatch to statement. Updated background, coding table, and references.
	03/04/2024 Consensus Review. Updated FEP, background, and references. No changes to coding.
	09/18/2024 Administrative Update. New code 0507U added effective 10/01/2024.

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11/19/2024 Administrative Update.	Removed NCCN statement.
02/26/2025 Consensus Review.	Updated policy guidelines, background, rationale, and references. Moving 0507U to MP 2.277.
06/04/2025 Administrative Update.	Removing the Benefit Variations and updating the Disclaimer
08/13/2025 Administrative Update.	Removed procedure codes 0003U, 0375U
03/03/2026 Retirement Review.	Service to be managed by the vendor Evicore.

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