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MEDICAL POLICY – 2.04.62

Multimarker Serum Testing Related to Ovarian Cancer

BCBSA Ref. Policy:	2.04.62	
Effective Date:	Mar. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Feb. 10, 2025	2.04.125 Proteomic Testing for Systemic Therapy in Non-Small Cell Lung Cancer
Replaces:	N/A	

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Introduction

When a mass of tissue is found next to the uterus (adnexal mass) it usually isn't cancer. The OVA1, ROMA, and Overa tests are a combination of several lab tests that some doctors order to try to see how likely it is that a mass is cancer. Other reasons doctors may order these tests are to try to decide if an individual should be referred to a gynecological oncologist (a doctor who specializes in women's cancers), to try to screen for ovarian cancer, to try to determine if previous surgery was successful in removing ovarian cancer, or to try to find out if ovarian cancer has come back.

The OVA1, ROMA, and Overa tests are still being studied. There is little evidence in published medical studies to show how these tests will lead to improved diagnoses or individual care. There are no studies that show how information from these tests will impact health outcomes. These tests are investigational (unproven) for all uses.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Test Name	Investigational
OVA1 **Overa** **ROMA**	**All uses of the OVA1, Overa, 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

Coding

Code	Description
CPT	
0003U	Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score – is specific to the Overa test
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score – is specific to the ROMA test

Code	Description
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apoliproprotein A1, beta-2 microglobulin, transferrin and pre-albumin), utilizing serum, algorithm reported as a risk score – is specific to OVA1 test

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

OVA1, Overa, and ROMA tests are combinations of several separate lab tests and involve proprietary algorithms for determining risk (i.e., what CPT codes call 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 and evidence review will be considered if it is cleared.

Evidence Review

Description

A variety of serum biomarkers have been studied for their association with ovarian cancer. Of particular interest have been tests that integrate results from multiple analytes into a risk score to predict the presence of disease. Three tests based on this principle, OVA1, Overa (the second-generation OVA1 test), and Risk of Ovarian Malignancy Algorithm (ROMA) have been cleared by the US Food and Drug Administration. The intended use of OVA1 and Overa as an aid to further assess whether malignancy is present in an individual with an ovarian adnexal mass who has not yet been referred to an oncologist, even when the physician's independent clinical and radiologic evaluation does not indicate malignancy. The intended use of ROMA is as an aid, in conjunction with clinical assessment, to assess whether a premenopausal or a postmenopausal woman who presents with an ovarian adnexal mass and has not yet been referred to an oncologist, is at high likelihood or low likelihood of finding malignancy on surgery.

Background

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 carcinoma. An estimated 19,710 women in the US were estimated to be diagnosed in 2023 with ovarian cancer, and approximately 13,270 were expected to die of the disease.[1] The mortality rate depends on three variables:

1. Individual characteristics
2. Tumor biology (grade, stage, type)
3. Treatment quality (nature of staging, surgery, and chemotherapy used)[2]

In particular, comprehensive staging and completeness of tumor resection appear to have a positive impact on individual outcomes. Racial, ethnic, and socioeconomic disparities in management and outcomes are prominent in individuals with ovarian cancer. Compared to non-Hispanic White and Asian individuals, Hispanic and non-Hispanic Black individuals are more likely to be diagnosed with advanced disease, and are less likely to undergo optimal primary surgery and adjuvant chemotherapy.[3,4,5] Individuals with ovarian cancer from racial and ethnic minorities are also less likely to be enrolled in clinical trials.[6] These are among the contributing factors to worsened overall survival among these racial and ethnic groups.[7,4,8] Individuals 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.[9,10,11,5]

Adult women presenting with an adnexal mass have an estimated 68% likelihood of having a benign lesion.[12] 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.[13] 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 was 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 US Food and Drug Administration (FDA) with the intended use of triaging individuals with adnexal masses (see **Regulatory Status**). They are summarized in **Table 1**. 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. Individuals with positive results may be considered candidates for referral to a gynecologic oncologist for treatment. The tests have been developed and evaluated only in individuals with adnexal masses and planned surgeries. Other potential uses, such as selecting individuals to have surgery, screening asymptomatic individuals, 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.[14,15]

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

Variables	OVA1	Overa	ROMA
Cleared	2009	2016	2011
Manufacturer	Quest Diagnostics	Vermillion	Roche Diagnostics
Biomarkers used			

Variables	OVA1	Overa	ROMA
CA 125 II	X	X	X
β_2-microglobulin	X		
Transferrin	X	X	
Transthyretin	X		
Apolipoprotein AI	X	X	
HE4		X	X
FSH		X	
Score range	0-10	0-10	0-10
Risk categorization			
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: US Food and Drug Administration; FSH: follicle-stimulating hormone; HE4: human epididymis secretory protein 4; ROMA: Risk of Ovarian Malignancy Algorithm.

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 the technical performance and diagnostic accuracy. The relevant outcomes are overall survival and test accuracy. OVA1 and Overa are intended for use in individuals for whom clinical assessment does not 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 individuals undergoing surgery should undergo surgery by an experienced gynecologic oncologist. Given the National Comprehensive Cancer Network recommendation, direct evidence will be required to demonstrate that the use of 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 individuals 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 2**.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03837327	Clinical Validation of the InterVenn Ovarian CAncer Liquid Biopsy (VOCAL)	1025	Jan 2024

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received while this policy was under review in 2012. Input was mixed in support of these tests as a tool for triaging individuals 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 individuals with an adnexal mass, there was a lack of support for use of these tests.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists

In 2017, with reaffirmation in 2024, the American College of Obstetricians and Gynecologists (ACOG) opinion on the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer addressed using multimarker serum testing.[37] The opinion states that multimarker panels lack strong evidence for use in asymptomatic women without adnexal masses and do not improve early detection and survival rates in average-risk women. The Society for Gynecologic Oncology endorsed this ACOG opinion.

In 2016, an ACOG Practice Bulletin addressing the evaluation and management of adnexal masses makes a level B recommendation (based on limited or inconsistent scientific evidence) that consultation with or referral to a gynecologic oncologist is recommended for premenopausal or postmenopausal with an elevated score on a formal risk assessment test such as the multivariate index assay, risk of malignancy index, or the Risk of Ovarian Malignancy Algorithm, or one of the ultrasound-based scoring systems from the International Ovarian Tumor Analysis group.[13] A level C recommendation (based on consensus and expert opinion) was given to using serum biomarker panels as an alternative to cancer antigen 125 (CA 125) level to decide about the referral to a gynecologic oncologist for an adnexal mass requiring surgery.

National Institute for Health and Care Excellence

In 2011, the National Institute for Health and Care Excellence issued guidance on the identification and management of ovarian cancer.[38] The guideline does not provide any

recommendations regarding additional serum marker testing besides testing for serum CA 125 levels in women with symptoms suggestive of ovarian cancer.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guideline on ovarian cancer (v.3.2024) includes the following statement:[39]

The FDA has approved the use of ROMA, OVA1, and OVERA for estimating the risk for ovarian cancer in women with an adnexal mass for which surgery is planned and have not been referred to an oncologist. Although the American Congress of Obstetricians and Gynecologists (ACOG) has suggested that ROMA and OVA1 may be useful for deciding which individuals to refer to a gynecologic oncologist, other professional organizations have been non-committal. Not all studies have found that multi-biomarker assays improve all metrics (i.e. sensitivity, specificity, positive predictive value, negative predictive value) for prediction of malignancy compared with other methods (e.g., imaging, single-biomarker tests, symptom index/clinical assessment). Currently, the NCCN Panel does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass.

In addition, the guideline states "based on data documenting increased survival, the NCCN Guidelines Panel recommends that all individuals with suspected malignancies (especially those with an adnexal mass) should undergo evaluation by an experienced gynecologic oncologist prior to surgery."

US Preventive Services Task Force Recommendations

In 2018, the US Preventive Services Task Force recommended against screening asymptomatic women for ovarian cancer (D recommendation).[40] The Task Force has not addressed multimarker serum testing related to ovarian cancer.

Medicare National Coverage

There is no national coverage determination.

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 radiological 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 risk of having malignancy at surgery.

In March 2016, a second-generation test called Overa (also referred to 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.

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 or not 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.[16] 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 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 individuals 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.

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History

Date	Comments
06/13/11	Add to Pathology/Laboratory Section - Reviewed by OAP on May 12, 2011. New medical policy.
12/19/12	Replace policy. Policy updated to change the use of the OVA1 and ROMA tests from medically necessary to investigational for all indications. Rationale updated based on a literature review through September 2012, results of TEC Assessment, and results of

Date	Comments
	clinical vetting. References 7, 13, 17-28 added; others renumbered or removed. New CPT codes added. Policy statement changed as noted.
03/15/13	Update Related Policies. Add 2.03.501.
10/16/13	Update Related Policies. Add 12.04.66 and remove policy 2.04.34 as it was archived.
12/27/13	Replace policy. Policy updated with literature search through September 30, 2013. References 14, 15 and 20 added; other references renumbered or removed. No change to policy statement. Title changed to Proteomic-based Testing Related to Ovarian Cancer. Clarification note added that this policy is only to be used when HE4 is included in the ROMA combination test. When HE4 is billed as an individual test, 12.04.66 – Serum Biomarker Human Epididymis Protein 4 (HE4) should be used.
12/17/14	Annual Review. Policy updated with literature review through September 25, 2014. References 1, 14, 18 and 23 added. Policy statement unchanged. Policy title changed to "Proteomics-Based Testing Related to Ovarian Cancer". ICD-9 and ICD-10 diagnosis and procedure codes removed; these are not utilized in adjudication of the policy.
01/23/15	Update Related Policies. Add 2.04.125.
12/08/15	Annual Review. Policy updated with literature review through October 25, 2015; references 14 and 18 added. Policy statement unchanged.
09/01/16	Annual Review, approved August 9, 2016. Policy statement unchanged. No new references added.
03/01/17	Annual Review, approved February 14, 2017. Title changed to "Multimarker Serum Testing Related to Ovarian Cancer". Policy updated with literature review through October 24, 2016; references added. New code for Overa test was added. Policy statement unchanged, this testing is considered investigational for all indications.
11/10/17	Policy moved into new format; no change to policy statements.
02/01/18	Annual Review, approved January 30, 2018. Policy update with literature through October 2017; references 1, 10, 12, 16, and 27 were added. The Overa test was added to policy statement, the intent is unchanged.
03/01/19	Annual Review, approved February 5, 2019. Policy updated with literature review through October 2018; reference 25 updated. Policy statement is unchanged.
03/01/20	Annual Review, approved February 4, 2020. Policy updated with literature review through October 2019; references added. Policy statement unchanged.
03/01/21	Annual Review, approved February 2, 2021. Policy updated with literature review through October 30, 2020; references added. Policy statement unchanged.
03/01/22	Annual Review, approved February 7, 2022. Policy updated with literature review through October 27, 2021; references added. Policy statement unchanged.

Date	Comments
02/01/23	Annual Review, approved January 23, 2023. Policy updated with literature review through November 4, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
03/01/24	Annual Review, approved February 12, 2024. Policy updated with literature review through October 31, 2023; no references added. Policy statement unchanged.
03/01/25	Annual Review, approved February 10, 2025. Policy updated with literature review through October 30, 2024; no references added. OvaWatch does not have its own 510K # or FDA approval paperwork yet, but FDA 510(k) submission is planned and in process according to Aspira. Recommend adding when it is cleared. Policy statement unchanged.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.