BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.62 Multimarker Serum Testing Related to Ovarian Cancer

Annual Effective Policy Date: April 1, 2026

Original Policy Date: December 2011

Related Policies:

2.04.66 - Serum Biomarker Human Epididymis Protein 4

Multimarker Serum Testing Related to Ovarian Cancer

Description

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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 the Risk of Ovarian Malignancy Algorithm (ROMA) have been cleared by the U.S. Food and Drug Administration. The intended use of OVA1 and Overa is 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 a high or low likelihood of finding malignancy on surgery.

OBJECTIVE

The objective of this evidence review is to evaluate whether multimarker serum testing related to ovarian cancer improves the net health outcome in individuals undergoing surgery for ovarian cancer.

POLICY STATEMENT

All uses of the OVA1, Overa, and ROMA tests are **investigational**, including but not limited to:

1. preoperative evaluation of adnexal masses to triage for malignancy, OR
2. screening for ovarian cancer, OR
3. selecting individuals for surgery for an adnexal mass, OR
4. evaluation of individuals with clinical or radiologic evidence of malignancy, OR
5. evaluation of individuals with nonspecific signs or symptoms suggesting possible malignancy, OR
6. postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

POLICY GUIDELINES

OVA1, Overa, and ROMA tests are combinations of several separate lab tests and involve proprietary algorithms for determining risk (ie, what current procedural terminology [CPT] calls multianalyte assays with algorithmic analyses [MAAAs]). Ova1Plus is a proprietary reflex process combining 2 U.S. Food and Drug Administration (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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Three multimarker serum-based tests specific to ovarian cancer have been cleared by the U.S. Food and Drug Administration (FDA) with the intended use of triaging patients with adnexal masses (see Regulatory Status section). These tests 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. 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.[14,15,]

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			
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 a high or low likelihood of finding malignancy on 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 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 (ie, 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 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.

RATIONALE

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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" 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.[38,] 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 (reaffirmed in 2023) made 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 (ROMA), or 1 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 Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guideline on ovarian cancer (v.3.2025) includes the following statement[39,]:

"The FDA [U.S. Food and Drug Administration] 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 patients 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 (ie, sensitivity, specificity, positive predictive value, negative predictive value) for prediction of malignancy compared with other methods (eg, 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 patients with suspected ovarian malignancies (especially those with an adnexal mass) should undergo evaluation by an experienced gynecologic oncologist prior to surgery."

National Institute for Health and Care Excellence

In 2011, NICE issued guidance (most recently updated in 2023) on the identification and management of ovarian cancer.[40,] 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.

U.S. Preventive Services Task Force Recommendations

In 2018, the U.S. Preventive Services Task Force recommended against screening asymptomatic women for ovarian cancer (D recommendation). [41,] The Task Force has not addressed multimarker serum testing related to ovarian cancer.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
March 2013	Replace policy	Policy update with literature search, results of TEC assessment. References 7, 13, and 17-28 added, Policy statement changed to not medically necessary for preoperative evaluation.
March 2014	Replace policy	Policy updated with literature search. 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.
March 2015	Replace policy	Policy updated with literature review through September 25, 2014. References 1, 14, 18 and 24 added. Policy statement unchanged.
March 2018	Replace policy	Policy update with literature through October 16, 2017; references 1, 8-10, 12, 14, 16-21, and 27 were added. Policy statement changed with addition of the Overa test. Title changed to "Multimarker Serum Testing Related to Ovarian Cancer,
March 2019	Replace policy	Policy updated with literature review through October 30, 2018; reference 25 updated. Policy statement is unchanged.
March 2020	Replace policy	Policy updated with literature review through October 19,2019; references added. Policy statement unchanged.
March 2021	Replace policy	Policy updated with literature review through October 30, 2020; references added. Policy statement unchanged.
March 2022	Replace policy	Policy updated with literature review through October 27, 2021; references added. Policy statement unchanged.
March 2023	Replace policy	Policy updated with literature review through November 4, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
March 2024	Replace policy	Policy updated with literature review through October 31, 2023; no references added. Policy statement unchanged.
March 2025	Replace policy	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.
March 2026	Replace policy	Policy updated with literature review through October 29, 2025; no references added. Policy statement unchanged.