Multimarker Serum Testing Related to Ovarian Cancer

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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. OVA1, Overa (the second generation OVA1 test), and ROMA (Risk of Ovarian Malignancy Algorithm) have been cleared by the U.S. Food and Drug Administration (FDA). The intended use of OVA1 and Overa is to use them as an aid to further assess whether malignancy is present, even when the physician's independent clinical and radiologic evaluation does not indicate malignancy. The intended use of ROMA is to use it as an aid, in conjunction with clinical assessment, to assess whether a premenopausal or a postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. Currently, there are several assessment methods possible for differentiating between a benign and malignant adnexal mass. Multiple analyte testing to predict the presence of disease have been developed to supplement current methods for evaluation.

Ovarian neoplasms consist of several histopathologic entities and treatment depends on the specific tumor type. Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 90%), other less common subtypes may occur such as malignant germ cell and sex cord-stromal cell tumors. Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women. In 2022, it is estimated that 19,880 new cases will be diagnosed and an estimated 12, 810 deaths from ovarian cancer will occur in the United States. Five-year survival is about 49%, although survival is longer for select patients with certain rarer subtypes. This cancer mainly develops in older women. About half of the women who are diagnosed with ovarian cancer are 63 years or older. It is more common in white women than African American women. The rate at which women are diagnosed with ovarian cancer has been slowly falling over the past 20 years. 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.

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 a 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. 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 U.S. Food and Drug Administration (FDA) with the intended use of triaging patients with adnexal masses, they are summarized in the below table. 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.

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	0-10	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

Clinical Context and Test Purpose

The purpose of multimarker serum testing of individuals over age 18 with an ovarian adnexal mass for which surgery is planned and not yet referred to an oncologist is to use the test as an aid to further assess the probability that malignancy is present, even when the physician's independent clinical and radiologic evaluation does not indicate malignancy.

Patients
The relevant population of interest is individuals who:

- Are over age 18
- Have ovarian adnexal mass for which surgery is planned
- Have not yet been referred to an oncologist
- A physician's independent clinical and radiologic evaluation does not indicate malignancy

Interventions
The relevant interventions are three U.S. FDA cleared multimarker serum genetic tests (e.g., OVA1, Overa, Risk of Ovarian Malignancy Algorithm [ROMA]). Multimarker serum testing related to ovarian cancer may be performed at any point when an individual presents with an ovarian adnexal mass for which surgery is planned, in conjunction with physician's independent clinical and radiologic evaluation to assess the probability that malignancy is present and aid in the decision of whether a referral to an oncologist is indicated.

Comparators
The comparator of interest is standard clinical assessment

Outcomes
The potential beneficial outcomes of primary interest in the case of a true negative would be the avoidance of unnecessary surgery and its associated consequences (e.g., morbidity, mortality, resource utilization, patient anxiety). The potential harms from a false-positive could be inappropriate assessment and improper management of patients with ovarian malignancies, which could result in the following: inappropriate surgical decisions, high frequency of unnecessary further testing, and unnecessary patient anxiety. The potential harms from a false negative could be a determination that the patient does not have ovarian malignancy, which would lead to a delay in surgery and tumor diagnosis.

Off-label use of the test (e.g., in patients who have not already been identified as needing surgery for pelvic mass, or patients without reference to an independent clinical and radiologic evaluation), might lead to a high frequency of unnecessary testing and surgery due to false-positive results, or to a delay in tumor diagnosis due to false-negative results.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Ova1 Test
Descriptions of the developmental process for the OVA1 test have been published in the FDA documents and in a perspective by Fung (2010). Candidate biomarkers were selected based on initial studies using mass spectroscopy but were converted to standard immunoassays to improve analytic performance. Seven final markers were evaluated, none of which individually appears to be highly specific for malignant ovarian disease.

However, the choice of five of these (CA-125, transthyretin [prealbumin], apolipoprotein AI [apo AI], B_2- microglobulin, and transferrin) produced a composite profile that did not appear to have discriminatory ability. The test, as cleared by the FDA, is performed on a blood sample, which is sent to a reference laboratory for testing using the 5 immunoassays previously described. Results of the 5 determinations are entered manually into an Excel spreadsheet used by the OvaCalc software. This software contains an algorithm that combines the 5 discrete values into a single unit-less numeric score from 0.0 to 10.0.

Details of the algorithm appear proprietary, but the development is described as an empirical process; it is a process based on several different factors; the use of banked samples from academic partners; a small prospective study of samples from Europe; and a designated subset of samples from the clinical study used to support the submission to the FDA. It appears that, at an undisclosed point in the developmental process as a result of interaction with the FDA, separate cut-points were developed for premenopausal and postmenopausal women.

The clinical validity was evaluated in a prospective, double-blind, clinical study using 27 enrollment sties. The study was supported by the commercial sponsor of the test. Patients underwent a complete clinical evaluation before surgical intervention, and only patients with adnexal masses who had a planned surgical intervention, and only patients with adnexal masses who had a planned surgical intervention were included. The study enrolled 743 patients, with 146 subjects used in the training set and 516 in the testing set. Seventy-four patients were excluded because of missing information or samples. The final prevalence of cancer in the population was 27%.

Using pathologic diagnosis is the criterion standard, OVA1 test performance, when combined with a clinical assessment by non-gynecological oncologists, was as follows (see table below). The method used for combing clinical assessment and OVA1 result was to consider the test positive if either clinical assessment or OVA1 test was positive. Thus, in practice, OVA1 testing would not be necessary if clinical assessment alone indicated cancer. Using OVA1 testing in this manner guarantees that OVA1 testing will be more sensitive and less specific than clinical assessment alone, even if it has no better than chance capability of detecting ovarian cancer. Sensitivity improved from 72% to 92%, and specificity decreased from 83% to 42%.

Clinical Validity of the OVA1 Test Among 269 Patients Evaluated by Non-gynecologic Oncologists

Diagnostic Characteristics	Clinical Assessment Alone, %	Clinical Assessment with OVA1 Test, %
Sensitivity	72	92
Specificity	83	42
Positive Predictive Value	61	37
Negative Predictive Value	89	93

Note: Confidence intervals not provided

(2015) Grenache et al. evaluated the diagnostic performance of the OVA1 test. However, it did not evaluate diagnostic performance in conjunction with clinical assessment, as the test was intended to be used. By itself, OVA1 was 97% sensitive and 55% specific. This means that with clinical assessment (as intended to be used), the test would be no worse than 97% sensitive and no better than 55% specific, but these characteristics cannot be determined from the study.

(2021) Dunton et al. noted that ovarian cancer is the deadliest gynecologic cancer, with no recommended screening test to aid in early detection. Cancer antigen 125 (CA125) is a serum biomarker commonly used by clinicians to evaluate pre-operative cancer risk, but it under-performs in pre-menopausal women, early-stage malignancies, and several histologic subtypes. OVA1 is a multi-variate index assay that combines CA125 and 4 other serum proteins to evaluate the malignant risk of an adnexal mass. These researchers examined the performance of OVA1 in a cohort of patients with low-risk serum CA125 values. They analyzed patient data from previous collections (n = 2,305, prevalence = 4.5 %) where CA125 levels were at or below 67 units/milliliter (U/ml) for pre-menopausal women and 35 U/ml for post-menopausal women. These investigators compared the performance of OVA1 to CA125 in classifying the risk of malignancy in this cohort, including sensitivity, specificity, PPV and NPV. The overall sensitivity of OVA1 in patients with a low-risk serum CA125 was 59 % with a false-positive rate of 30 %. OVA1 detected over 50 % of ovarian malignancies in pre-menopausal women despite a low-risk serum CA125. OVA1 also correctly identified 63 % of early-stage cancers missed by CA125. The most common epithelial ovarian cancer subtypes in the study population were mucinous (25 %) and serous (23 %) carcinomas. Despite a low-risk CA125, OVA1 successfully detected 83 % of serous, 58 % of mucinous, and 50 % of clear cell ovarian cancers. The authors concluded that as a standalone test, CA125 missed a significant number of ovarian malignancies that could be detected by OVA1. This was particularly important for pre-menopausal women and early-stage cancers, which have a much better long-term survival than late-stage malignancies. These investigators stated that using OVA1 in the setting of a normal serum CA125 could aid in identifying at-risk ovarian tumors for referral to a gynecologic oncologist, potentially improving OS. The authors stated that a drawback of this study was the retrospective nature of the data analysis, which was carried out after merging several study databases. Furthermore, the percentage of early-stage ovarian cancer in this study (70 %) was twice that expected in the general population, suggesting a possible sampling bias. However, this shift toward early-stage cancers allowed for a more robust evaluation of test performance in this cohort.

(2016) Eskander et al. conducted a retrospective chart review of patients who received the OVA1. Twenty-two obstetricians/gynecologists were recruited from a variety of practices and hospitals throughout the United States. A total of 136 patients with elevated-risk assay results were assessed, of whom 122 underwent surgery to remove an adnexal mass. Prior to surgery, 98 (80%) of the patients were referred to a gynecologic oncologist with an additional 11 (9%) having a gynecologic oncologist available if required by intra-operative findings. Primary ovarian cancer was found in 65 (53%)

patients, and gynecologic oncologists performed 61 (94%) of the initial surgeries these patients. Similar results were found in premenopausal and postmenopausal patients. (2016) Stewart et al. reported on a survey of primary care physicians on how often they refer patients diagnosed with ovarian cancer to gynecological oncologists, finding that a total of 84% of primary care physicians (87% of family/general practitioners, 81% of internists and obstetrician/gynecologists) said they always referred patients to gynecologic oncologists for treatment. Common reasons for not always referring were patient preference or lack of gynecologic oncologists in the practice area. A total of 23% of primary care physicians had heard of the OVA1 test, which helps to determine whether gynecologic oncologist referral is needed. The authors noted that, although referral rates reported here are high, it is not clear whether ovarian cancer patients are actually seeing gynecologic oncologists for care.

OVA1plus

OVA1plus (also reported as OVA1 is designed to help stratify the risk of malignancy in adult women diagnosed with an adnexal (pelvic) mass. The reflex process involves initially performing OVA1. If OVA1 results indicate intermediate risk, then OVERA is performed. The combined results of OVA1 and OVERA are intended to aid in the risk assessment of malignancy in adult women diagnosed with a pelvic mass who are planning to undergo surgery.

Overa Test

Descriptions of the developmental process for the Overa test have been published in FDA documents. The FDA documents do not provide details on how biomarkers were selected. The test, as cleared by the FDA, is performed on a blood sample, which is to be sent to a reference laboratory for testing using the 5 immunoassays previously described. Results of the 5 determinations are entered into a proprietary algorithm, called OvaCalc software (v4.0), which combines the 5 discrete values into a single unit-less numeric score from 0.0 to 10.0.

Clinical validity was evaluated in a non-concurrent prospective study of 493 preoperatively collected serum specimens from premenopausal and postmenopausal women presenting with an adnexal mass requiring surgical intervention. Overa test scores were determined based on the analysis of archived serum specimens from a previous study, and the patient was stratified into a low or high-risk group for finding malignancy on surgery. The analysis examined whether patient referral to a gynecologic oncologist was supported when dual assessment was determined to be positive (either Overa or clinical assessment was positive, or both were positive) A dual assessment was considered negative when both Overa and clinical assessment were negative.

Using pathologic diagnosis as the criterion standard, Overa test performance, when combined with clinical assessment by non-gynecologic oncologists, was as follows (see below table). The method used for combining clinical assessment and Overa test result was to consider the test positive if either clinical assessment or Overa test was positive. Thus, in practice, Overa testing would not be necessary if clinical assessment alone

indicated cancer. Using Overa testing in this manner guarantees that Overa testing will be more sensitive and less specific than clinical assessment alone, even if it has no better than chance capability of detecting ovarian cancer. Sensitivity improved from 74% to 94% and specificity decreased from 93% to 65%.

Clinical Validity of the Overa Test Among 493 Patients Evaluated by Non-gynecologic Oncologists

Diagnostic Characteristics	Clinical Assessment Alone, %	Dual Assessment with Overa Test, %
Sensitivity (95% CI)	74 (64 to 82)	94 (87 to 97)
Specificity (95% CI)	93 (90 to 95)	65 (60 to 70)
Positive predictive value (95% CI)	70 (62 to 77)	38 (35 to 41)
Negative predictive value	94 (92 to 96)	98 (95 to 99)

Note: CI: confidence interval

ROMA Test

The FDA labelling for ROMA, unlike that for OVA1, does not indicate how ROMA is to be used in conjunction with clinical assessment. All previously cited literature assessed ROMA as a stand-alone test for ovarian cancer and did not provide a comparison with clinical assessment alone. The study by Moore et. al. (2014) evaluated ROMA in conjunction with clinical assessment, using either a positive clinical assessment or a positive ROMA as a positive test (similar to the recommended usage for OVA1). Using this method of combining tests guarantees a higher sensitivity and lower specificity for the combined test than for either test alone. Used in this way, ROMA would only need to be given to patients with a negative clinical assessment. In this study, 461 women were enrolled, of whom 86 (19%) had a malignancy. Combined assessment improved sensitivity from 77.9% to 89.7%, but specificity worsened from 84.3% to 67.2%.

(2014) Wang et al. published a meta-analysis of studies evaluating the clinical validity of the ROMA test algorithm and comparing it with the performance of single biomarkers HE4 and CA 125. To be included in the meta-analysis, studies had to investigate both HE4 and CA 125 or calculate ROMA, enroll women with ovarian cancer and benign gynecologic disease, use pathology diagnosis as the reference standard, and collect blood samples before treatment was initiated. Thirty-two studies met these inclusion criteria; six were conducted in the United States. Findings of the overall pooled analysis of diagnostic accuracy are in the below table.

Meta-Analytic Findings for Diagnostic Performance of the ROMA Test vs HE4 and CA-125

Test	Number of Studies	Sensitivity (95% CI), %	Specificity (95% CI), %
ROMA Test	14	85.3 (81.2 to 88.6)	82.4 (77.4 to 86.5)
Human epididymis secretory protein 4	28	76.3 (72.0 to 80.1)	93.6 (90.0 to 95.9)

Cancer antigen 125	28	79.2 (74.0 to 83.6)	82.1 (76.6 to 86.5)

Note: CI: confidence interval

Findings were similar when diagnostic performance in premenopausal women and postmenopausal women were evaluated separately. ROMA had similar or higher sensitivity than HE4 and CA125, and HE4 had the highest specificity.

(2021) Suri et al. found ROMA had better diagnostic accuracy in postmenopausal women (sensitivity 88%, specificity 83%) than premenopausal women (sensitivity 80%, specificity 80%), and better discrimination (AUROC 0.94 [SE 0.01) and 0.88 [SE 0.01], respectively). The review found no evidence of publication bias, nor did it find differential results when analyses were limited to blinded studies.

(2016) Dayyani et al. conducted a meta-analysis comparing ROMA with HE4 and CA 125 in patients with suspected ovarian cancer. Six studies met the inclusion criteria, four of which were included in the 2014 Wang meta-analysis. Two studies were published in 2014 or later. Based on area under the curve analysis, ROMA had higher values than either HE4 (0.921; 95% CI, 0.855 to 0.960) or CA 125 alone (0.899; 95% CI, 0.835 to 0.943) and HE4 plus CA 125 (0.883; 95% CI, 0.771 to 0.950).

The point estimates for sensitivity and specificity were lower in pre- and postmenopausal women, with wider confidence intervals.

Since the Wang and Dayyani meta-analyses, multiple studies have described the use of the ROMA test in populations of women in whom decisions to pursue surgery had been made, including Al Musalhi et al. (2016; n=213 cases), Cho et al. (2015; n=90 cases), and Terlikowska et al. (2016; n=224 cases).

(2019) Han et al. identified the power of tumor markers to predicting ovarian cancer according to menopausal status. The medical records of 876 women with ovarian cysts were retrospectively reviewed. Cancer antigen 125 (CA 125), human epididymis protein 4 (HE4), and Risk of Ovarian Malignancy Algorithm (ROMA) were analyzed. Sensitivity, specificity, and the receiver operating characteristic (ROC) curve analyses of these tumor markers were evaluated. The sensitivity of ROMA was 66.7% and the specificity was 86.8% to detect ovarian malignancy. The patients were divided into 2 groups according to menopausal status: premenopause (n=532, 60.7%) and postmenopause (n=344, 39.3%). For diagnostic accuracy, ROMA was lower than HE4 in premenopausal women (82.7% vs. 91.4%) and lower than CA 125 in postmenopausal women (86.9% vs. 88.7%). The ROC curve analysis revealed that the power of ROMA was not significantly better than that of HE4 in premenopausal women (area under the curve [AUC], 0.731 vs. 0.732, p=0.832), and it was also not significantly better than that of CA 125 in postmenopausal women (AUC, 0.871 vs. 0.888, p=0.440). The authors concluded, the discrimination power of tumor markers for ovarian cancer was different according to menopausal status. In predicting ovarian malignancy, ROMA was neither

superior to HE4 in premenopausal women nor superior to CA 125 in postmenopausal women.

ROMA Compared with Risk Malignancy Index-I
(2019) Chacon et al. performed and systematic review and meta-analysis of studies comparing the diagnostic accuracy of Risk of Ovarian Malignancy Algorithm (ROMA) and risk of malignancy index (RMI) for detecting ovarian cancer. Sixty-six citations were identified. After exclusions, 8 papers comprising 2,662 women (1,319 premenopausal and 1,343 postmenopausal) were ultimately included. The mean prevalence of ovarian malignancy was 29.0% in premenopausal women and 51.0% in postmenopausal women. High risk of bias for patient selection was observed for most studies. ROMA and RMI-I had a similar diagnostic performance in postmenopausal women (pooled sensitivity [87 vs. 77%] and specificity [75 vs. 85%], respectively. p = 0.29). In premenopausal women, RMI-I showed better specificity than ROMA (89 vs. 78%, p = 0.022) with similar sensitivity (73 vs. 80%, p= 0.27). Significant heterogeneity was found for sensitivity and specificity in comparisons of both groups. The authors concluded, ROMA and RMI-I have similar diagnostic performance for detecting ovarian cancer in women presenting with an adnexal mass. However, RMI-I showed a higher specificity than ROMA in premenopausal women. Notwithstanding, as the risk of bias is high in most studies, our results should be interpreted with caution.

Section Summary
Evidence for the clinical validity for the OVA1 and Overa tests include prospective, double-blind studies that have evaluated the clinical validity of these tests in predicting the likelihood of malignancy in women who are planning to have surgery for an adnexal mass. They have not been studied for ovarian cancer screening. The prospective studies showed that, in patients with adnexal mass who had a planned surgical intervention, use of OVA1 and Overa in conjunction with a clinical assessment by non-gynecologic oncologists increased the sensitivity but decreased the specificity compared with clinical assessment alone. When used with clinical assessment in this manner, the sensitivity to ovarian malignancy was 92%, and the specificity was 42%. ROMA is intended for use in conjunction 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 a specificity of 67%. Two meta-analyses reported less than 90% sensitivity and specificity with ROMA testing.

Clinically Useful
The test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary testing.

The ideal study design to evaluate clinical utility of multimarker serum-based testing would be a randomized controlled trial (RCT) comparing health outcomes (e.g., mortality) in patients managed using the tests with those managed according to best current clinical practices. According to the chain of logic, greater numbers of persons

referred for initial surgical treatment with ovarian cancer should result in improved overall health outcomes. No randomized or nonrandomized studies with these comparisons were identified.

Although OVA1, Overa, and ROMA, when used in conjunction with clinical assessment, improve the sensitivity for detection of malignancy, the specificity declines. In studies using either positive ROMA or clinical assessment as a positive test, sensitivity improved, but it was still less than 90%. It is uncertain whether there is meaningful clinical benefit from using a test that avoids a high number of referrals and does not contain sensitive data (even though incrementally better). Because there is no established or recommended method for using ROMA in conjunction with clinical assessment, diagnostic performance characteristics are uncertain since it would vary depending on how it is used.

It is also uncertain whether the incremental yield of malignancy resulting from use of the tests would result in improved patient outcomes. Although prior studies revealed an improvement of outcomes when women with ovarian cancer are initially managed by gynecologic oncologists, it is uncertain whether improved outcomes would occur in the additional cases detected by use of these tests. These additional cancer cases may differ from other cases detected by clinical assessment alone. If they tend to be earlier stage cancers or biologically less aggressive cancers, initial treatment by a gynecologic oncologist may not provide incremental benefit.

Section Summary
As no trials were identified that have compared health outcomes for patients managed with and without the use of FDA-cleared multimarker serum-based tests, there is no direct evidence of clinical usefulness. It is uncertain whether discrimination is sufficient to alter decision-making based on clinical assessment alone, thus offering a meaningful benefit to patients. Therefore, the chain of evidence supporting improved outcomes is incomplete.

UptoDate
(Last Updated 2021; Literature current through 2022) The main biomarker that has been studied for use in the initial evaluation of an adnexal mass is cancer antigen 125 (CA 125), although this is not its U.S. Food and Drug Administration-approved indication. OVA1, Overa, and the Risk of Malignancy Algorithm (ROMA) have only been studied in patients for whom surgery has already been planned and thus likely have a higher prevalence of ovarian cancer than the general population of patients with an ovarian tumor. In the absence of data regarding the use of OVA1, Overa, and ROMA in the initial evaluation of an adnexal mass, we do not recommend use of these tests alone to decide whether to proceed with surgical exploration for an adnexal mass. (*Accessed March 2022)*

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. Based on review of the peer reviewed medical literature, 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 gynecologist oncologist, other professional organization 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 tests for determining the status of an undiagnosed adnexal/pelvic mass. The Society of Gynecologic (SGO) and the FDA have stated that the OVA1 test should not be used as a screening tool to detect ovarian cancer in patients without any other signs or cancer, or as a stand-alone diagnostic tool. Moreover, based on data documenting an 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. 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 the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists (ACOG)
(2016) An ACOG Practice Bulletin addressing the evaluation and management of adnexal masses with the following recommendations:

- 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 1 of the ultrasound-based scoring systems from the International Ovarian Tumor Analysis group.
- 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.

(*Accessed March 2022*)

Joint Guideline
(2017, with reaffirmation in 2021) The American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecology Oncology issued a joint committee opinion No. 716 (replaces number 477 March 2011) on the role of obstetrician

– gynecologists in the early detection of epithelial ovarian cancer in women at average risk which included the following:

- The U.S. Food and Drug Administration has approved laboratory panels of multiple tumor markers (including CA 125) to categorize women found to have adnexal masses on imaging as low risk or high risk of ovarian malignancy. However, these panels have not been rigorously evaluated among asymptomatic women without adnexal masses and have not been shown to improve early detection and survival rates for ovarian cancer in average risk women. Use of these markers for the management of adnexal masses is discussed in other publications.
- Direct-to-consumer marketing of ovarian cancer screening tests:
  - Ovarian cancer screening tests and early detection tests, such as those using the Risk of Ovarian Cancer Algorithm and laboratory panels of multiple tumor markers are being marketed directly to women. At this time, there is insufficient evidence to support the use of any of these tests or algorithms for the early detection of ovarian cancer in average-risk women. Women considering purchasing these tests which are approved nor cleared by the U.S. Food and Drug Administration for ovarian cancer screening are not financially covered by medical insurance, should be counseled on the risk of such tests.
- The American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecology Oncology offer the following recommendations and conclusions:
  - Currently, there is no strategy for early detection of ovarian cancer that reduces ovarian cancer mortality.
  - The use of transvaginal ultrasonography and tumor markers (such as CA-125), alone or in combination, for the early detection of ovarian cancer in average-risk women have not been proved to reduce mortality, and harms exist from invasive diagnostic testing (e.g., surgery) resulting from false-positive test results.
  - Epithelial ovarian cancer is most commonly detected in an advanced stage (65% of cases are stage III or stage IV) when the cure rate is only 18%.
  - Early stage (localized) ovarian cancer is associated with improved survival.
  - Taking a detailed personal and family history for breast, gynecologic, and colon cancer facilitates categorizing women based on their risk (average risk or high risk) of developing epithelial ovarian cancer.
  - The patient and her obstetrician-gynecologist should maintain an appropriate level of suspicion on potentially relevant signs and symptoms of ovarian cancer are present.

(*Accessed March 2022*)

National Institute for Health and Clinical Excellence (NICE)

(2017) The National Institute for Health and Clinical Excellence (NICE) issued a guideline regarding tests in secondary care to identify people at high risk of ovarian cancer which included the following recommendations:

- There is currently not enough evidence to recommend the routine adoption of the IOTA ADNEX model, Overa (MIA2G), RMI I (at thresholds other than 200 or 250), ROMA or IOTA Simple Rules in secondary care in the NHS to help decide whether to refer people with suspected ovarian cancer to a specialist multidisciplinary team (MDT).
- The NICE guideline on ovarian cancer recommends that people with an RMI I of 250 or more are referred to a specialist MDT. Evidence suggests that there is no substantial change in accuracy if the threshold for RMI I is lowered to 200.
- The IOTA ADNEX model, Overa (MIA2G), RMI I (at thresholds other than 250), ROMA and IOTA Simple Rules show promise. Further research is recommended on test accuracy and the impact of the test results on clinical decision making.

(*Accessed March 2022*)

National Comprehensive Cancer Network (NCCN)

- **Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer Version 1.2022**
  - **Screening with Other Biomarker Tests**
    - In addition to CA-125, there are a number of biomarker tests that have been explored as possible screening tools for early detection of ovarian cancer. Data for most of these proposed biomarkers is limited to retrospective analyses comparting biomarker levels in patients with known ovarian cancer versus healthy controls. Very few biomarkers have been tested prospectively to determine whether they can detect ovarian cancer or predict development of ovarian cancer in women who have no other signs or symptoms of cancer. Data show that several markers (including CA-125, HE4, mesothelin, B7-H4, decoy receptor 3 [DcR3], and spondin-2) do not increase early enough to be useful in detecting early-ovarian cancer.
    - There are a number of biomarker and prediction algorithms (based on a variety factor, such as symptoms, imaging results, biomarkers and patient characteristics) that have been developed for assessing the likelihood of malignancy among patients who have an adnexal mass (and have not yet had surgery). It is important to note that these tests are for preoperative assessment only, and none is suitable for ovarian cancer screening prior to detection of an adnexal mass; they are also not for use as stand-alone diagnostic tests. For example, the OVA1 tests is multivariate index assay (MIA) that uses five markers (including transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin and CA-125) in preoperative serum to assess the likelihood of malignancy in patients with adnexal mass for which surgery is planned, with the aim of helping community practitioners determine which patients to a gynecologic oncologist for evaluation and surgery.
    - The Society of Gynecologic (SGO) and the FDA have stated that the OVA1 test should not be used as a screening tool to detect ovarian cancer in patients without any other signs or cancer, or as a stand-alone

diagnostic tool. Moreover, based on data documenting an 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.

(*Accessed March 2022*)

- **Recommended Work-up**
  - **Laboratory Studies and Biomarker Tests**
    - A number of specific biomarkers and algorithms using multiple biomarker tests results have been proposed for preoperatively distinguishing benign from malignant tumors in patients who have an undiagnosed adnexal/pelvic mass. Biomarker tests developed and evaluated in prospective trials comparing preoperative serum levels to postoperative final diagnosis include serum HE4 and CA-125 either alone or combined using the Risk of Ovarian Malignancy Algorithm [ROMA], the MIA (brand name OVA1) based on serum levels of five markers transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin and CA-125, and the second-generation MIA (MIA2G, branded names OVERA) based on CA-125, transferrin, apolipoprotein A1, follicle-stimulating hormone [FSH], and HE4. The FDA has approved the use of ROMA, OVA1, or OVERA for estimating the risk in ovarian cancer in women with adnexal mass for which surgery is planned and have not yet 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 gynecologist oncologist, other professional organization 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 tests for determining the status of an undiagnosed adnexal/pelvic mass. (*Accessed March 2022)*

Regulatory Status

Test	Manufacturer	Clearance Date	Information
OVA1™	Vermillion Inc.	2009	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.

Overa™ (also referred as next-generation OVA1™)	Vermillion Inc.	2016	Overa™ is a second-generation test called in which 2 of the 5 biomarkers in OVA1™ are placed with human epididymis secretory protein 4 and follicle stimulating hormone, Similar to OVA1™, Overa™, generates a low or high risk of malignancy on a scale from 0 to 10.
Risk of Ovarian Malignancy Algorithm (ROMA™)	Fujirebio Diagnostics, Inc.	2011	The intended use of ROMA™ is 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.

Black Box Warning: In December 2011 (reaffirmed 2/27/2018), 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 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.

To address the risks of off-label use, labeling, advertising, and promotional materials for ovarian adnexal mass assessment score test systems should contain a precaution box with text using the following template or equivalent:

PRECAUTION: The [test name] should not be used without an independent clinical/radiological evaluation and is **not** intended to be a screening test or to determine

whether a patient should proceed to surgery. Incorrect use of the [test name] carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

PRIOR APPROVAL

Not applicable

POLICY

Multiserum marker testing panels including OVA1, Overa, and ROMA are considered **investigational** for all indications including but not limited to the following because the evidence is insufficient to determine the effects of the technology on net health outcomes:

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

Based on review of the peer reviewed medical literature, 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 gynecologist oncologist, other professional organization 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 tests for determining the status of an undiagnosed adnexal/pelvic mass. The Society of Gynecologic (SGO) and the FDA have stated that the OVA1 test should not be used as a screening tool to detect ovarian cancer in patients without any other signs or cancer, or as a stand-alone diagnostic tool. Moreover, based on data documenting an 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. 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 the effects of the technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81500 Oncology (ovarian), biochemical assays of two proteins (CA 125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score. (ROMA Test)
- 81503 Oncology (ovarian), biochemical assays of five proteins (CA 125, apolipoprotein A1, beta-2 microglobulin, transferring and pre-albumin), utilizing serum, algorithm reported as a risk score (OVA1 Test)
- 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 likelihood score. (Overa Test)

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POLICY HISTORY		
Date	**Reason**	**Action**
April 2022	Annual Review	Policy Renewal
April 2021	Annual Review	Policy Revised
April 2020	Annual Review	Policy Revised
April 2019	Annual Review	Policy Renewed
April 2018	Annual Review	Policy Revised
April 2017	Annual Review	Policy Renewed
April 2016	Annual Review	Policy Renewed
May 2015	Annual Review	Policy Renewed
June 2014	Annual Review	Policy Revised
August 2013	Annual Review	Policy Revised
April 2013	Interim Review	Policy Retired
September 2011	Evidence Review	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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