



# Louisiana

## Multimarker Serum Testing Related to Ovarian Cancer

**Policy #** 00281

**Original Effective Date:** 12/15/2010

**Current Effective Date:** 05/01/2018

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers all uses of the OVA1<sup>®‡</sup>, Overa<sup>™‡</sup>, and ROMA<sup>™‡</sup> tests to be **investigational\***, including but not limited to:

- Preoperative evaluation of adnexal masses to triage for malignancy, or
- Screening for ovarian cancer, or
- Selecting patients for surgery for an adnexal mass, or
- Evaluation of patients with clinical or radiologic evidence of malignancy, or
- Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy, or
- Post-operative 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 CPT calls multianalyte assays with algorithmic analyses [MAAAs]).

### **Background/Overview**

#### **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 22,440 women in the United States are expected to be diagnosed in 2017 with ovarian cancer, and approximately 14,080 will 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.

In 1997, the Society of Surgical Oncology recommended ovarian cancer surgery and follow-up treatment be performed by physicians with ovarian cancer disease expertise. Numerous articles have been published on the application of this recommendation examining long- and short-term outcomes as well as process measures (e.g., types of treatment such as complete staging or tumor debulking). At least 2 meta-analyses have concluded that outcomes are improved when patients with ovarian cancer are treated by gynecologic oncologists. The available data are most convincing for patients with advanced-stage disease.

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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 2005, the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists jointly released referral guidelines that addressed criteria for referring women with pelvic masses suspicious for ovarian cancer to gynecologic oncologists. Separate criteria were developed for premenopausal and postmenopausal women. In premenopausal women, referral criteria included at least one of the following: elevated cancer antigen 125 (CA 125; >200 U/mL), ascites, evidence of abdominal or distant metastasis, or a positive family history. The referral criteria for postmenopausal women were similar, except that a lower threshold for an elevated CA 125 test was used (35 U/mL); moreover, a nodular or fixed pelvic mass was an added criterion.

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). 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. 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-Approved Multimarker Serum-Based Tests Specific to Ovarian Cancer**

Variables	OVA1	Overa	ROMA
Approved	2009	2016	2011
Manufacturer	Quest Diagnostics	Vermillion	Roche Diagnostics
<b>Biomarkers used</b>			
CA 125 II	X	X	X
β <sub>2</sub> -microglobulin	X		
Transferrin	X	X	
Transthyretin	X		
Apolipoprotein AI	X	X	
HE4		X	X
FSH		X	

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Score range	0-10	0-10	0-10
<b>Risk categorization</b>			
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: Food and Drug Administration; FSH: follicle stimulating hormone; HEA: human epididymis secretory protein 4.

### **FDA or Other Governmental Regulatory Approval**

#### **U.S. Food and Drug Administration (FDA)**

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.

#### **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 (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.

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- 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.

### **Centers for Medicare and Medicaid Services (CMS)**

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.

### **Rationale/Source**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. The following is a summary of the key findings to date.

## **MULTIMARKER SERUM TESTING RELATED TO OVARIAN CANCER**

### **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.

The questions addressed in this evidence review are: (1) Is there evidence that multimarker serum testing of individuals described above has clinical validity?; and (2) Does multimarker serum testing of such individuals change patient management in a way that improves outcomes as a result of testing?

The following PICOTS were used to select literature to inform this review.

### ***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.

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### **Interventions**

The relevant interventions are 3 commercially multimarker serum genetic tests (e.g., OVA1, Overa, ROMA).

### **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.

### **Timing**

Multimarker serum testing for related to ovarian cancer may be performed at any point when an individual presents with an ovarian adnexal mass for which surgery is planned, but physician's independent clinical and radiologic evaluation does not indicate malignancy and referral to an oncologist is being considered.

### **Setting**

Most patients are likely to be tested in an outpatient setting.

### **Technically Reliable**

#### **OVA1 Test**

OVA1 is a qualitative serum test that combines immunoassay results for 5 analytes (cancer antigen 125 [CA 125], prealbumin, apolipoprotein AI [apo AI],  $\beta_2$ -microglobulin, transferrin) into a single numeric score. Analytic performance of the test demonstrated good test precision (coefficient of variation [CV] range, 1%-7.4%, depending on the sample levels studied) and good reproducibility (CV range, 2.8%-8.9%). The test appears linear, reagent and samples stable, and there was no observed interference evaluating common endogenous substances (e.g., hemoglobin, bilirubin).

#### **Overa Test**

Overa is a qualitative serum test that combines immunoassay results for 5 analytes (CA 125, apo AI, transferrin, follicular stimulating hormone, human epididymis protein 4 [HE4]) into a single numeric score. Analytic performance for the test demonstrated good test precision (CV range, 1.54%) and good

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reproducibility (overall percent CV, 1.63%). The test appears linear, reagent and samples stable, and there was no observed interference evaluating common endogenous substances (e.g., hemoglobin, bilirubin).

### **ROMA Test**

The ROMA test is also a qualitative serum test that combines 2 analytes (HE4 EIA and the ARCHITECT CA 125), along with menopausal status into a numeric score. Analytic performance for ROMA also exhibited good precision, with a total CV ranging from 0.49% to 7.72%, depending on both sample values and menopausal status. The reproducibility of the test was acceptable, with a CV that ranged from 0.98% to 25.9%, with highest values observed in patients with low scores, as expected. The reagents are variably stable, and users are instructed to follow package inserts for stability on each analyte used. The test was unaffected by interference with hemoglobin, bilirubin, lipids, or human antimouse antibodies. However, high levels of rheumatoid factor (>500 IU/mL) did appear to cause elevations in test values, and testing in patients with elevated rheumatoid factor is not recommended.

### **Section Summary: Technically Reliable**

Currently, 3 serum multimarker tests have been cleared by the U.S. FDA. Evidence for the analytic validity of these tests is provided in the FDA database. These data indicate that the analytic validity of the individual analytes that comprise these multimarker tests using commercial approved methods meets the acceptable criteria for high analytic validity.

### **Clinically Valid**

#### **OVA1 Test**

Descriptions of the developmental process for the OVA1 test have been published in 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 appeared to be highly specific for malignant ovarian disease. However, the choice of five of these (CA 125, prealbumin, apo AI,  $\beta_2$ -microglobulin, transferrin) produced a composite profile that did 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 unitless 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 cutpoints were developed for premenopausal and postmenopausal women.

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The clinical validity was evaluated in a prospective, double-blind, clinical study using 27 enrollment sites. 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 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 as the criterion standard, OVA1 test performance, when combined with a clinical assessment by nongynecologic oncologists, was as follows (see Table 2). The method used for combining 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%.

**Table 2. Clinical Validity of the OVA1 Test<sup>a</sup> Among 269 Patients Evaluated by Nongynecologic 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

<sup>a</sup> Confidence intervals not provided.

One additional 2015 study (by Grenache et al) was identified; it 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.

### 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 (v4.0.0), which combines the 5 discrete values into a single unitless numeric score from 0.0 to 10.0.

Clinical validity was evaluated in a nonconcurrent 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

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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 nongynecologic oncologists, was as follows (see Table 3). 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%.

**Table 3. Clinical Validity of the Overa Test Among 493 Patients Evaluated by Nongynecologic 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 (95% CI)	94 (92 to 96)	98 (95 to 99)
Prevalence	19 (92/493)	

CI: confidence interval.

### ROMA Test

Moore et al (2008) described the development of the ROMA test. The authors studied 9 biomarkers and chose HE4 and CA 125 because these markers in tandem produced the best performance. The algorithm developed was subsequently modified to include menopausal status and was independently validated. Again, separate cutoffs were used for premenopausal and postmenopausal women.

In 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 presented in Table 4.

**Table 4. Meta-Analytic Findings for Diagnostic Performance of the ROMA Test vs HE4 and CA 125**

Test	No. 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)

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Adapted from Wang et al (2014).  
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.

In 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% confidence interval [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). Findings of the pooled analysis of diagnostic accuracy are shown in Table 5.

**Table 5. Meta-Analytic Findings for Diagnostic Performance of the ROMA Test vs HE4 and CA 125**

Test	No. Studies	Sensitivity (95% CI), %	Specificity (95% CI), %
ROMA test	6	87.3 (75.2 to 94.0)	85.5 (71.9 to 93.2)
Human epididymis secretory protein 4	6	68.2 (69.3 to 90.1)	85.1 (71.6 to 92.8)
Cancer antigen 125	6	79.6 (66.3 to 88.5)	82.5 (82.5 to 91.9)

Adapted from Dayyani et al (2016).  
CI: confidence interval.

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).

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% (see Table 6).

**Table 6. Diagnostic Performance of the ROMA Test for All Malignancy**

Diagnostic Characteristics	Clinical Assessment Alone (95% CI), %	Clinical Assessment With ROMA (95% CI), %
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Sensitivity	77.9 (66.2 to 87.1)	89.7 (79.9 to 95.8)
Specificity	84.3 (80.2 to 87.8)	67.2 (62.2 to 71.9)
Positive predictive value	47.3 (37.8 to 57.0)	33.2 (26.4 to 40.5)
Negative predictive value	95.5 (92.6 to 97.4)	97.3 (94.5 to 98.9)

Adapted from Moore et al (2014).

CI: confidence interval.

### **Section Summary: Clinically Valid**

Evidence for the clinical utility 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 nongynecologic 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-analysis reported less than 90% sensitivity and specificity with ROMA testing.

### **Clinically Useful**

The ideal study design to evaluate the clinical utility of multimarker serum-based test would be a randomized controlled trial 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 because it would vary depending on how it is used.

It is also uncertain whether the incremental yield of malignancy resulting from the use of the tests would result in improved patient outcomes. Although prior studies revealed an improvement of outcomes when women with ovarian cancer were 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.

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### **Section Summary: Clinically Useful**

There is no direct evidence in terms of assessing patient outcomes based on the use of such testing prior to undergoing surgery. 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.

### **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. Relevant outcomes are overall survival and test accuracy. OVA1 and Overa are intended for use in patients 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, there is no direct evidence in terms of assessing patient outcomes based on the use of such testing prior to undergoing surgery. Moreover, it is uncertain whether discrimination is sufficient to alter decision making based on clinical assessment alone and, therefore, it is uncertain whether patients will find the testing to be of meaningful benefit. Thus, the chain of evidence supporting improved outcomes is incomplete. The evidence is insufficient to determine the effects of the technology on health outcomes.

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# Louisiana

## Multimarker Serum Testing Related to Ovarian Cancer

Policy # 00281

Original Effective Date: 12/15/2010

Current Effective Date: 05/01/2018

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### Policy History

Original Effective Date: 12/15/2010

Current Effective Date: 05/01/2018

12/01/2010 Medical Policy Committee review

12/15/2010 Medical Policy Implementation Committee approval.

12/08/2011 Medical Policy Committee review

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Policy # 00281

Original Effective Date: 12/15/2010

Current Effective Date: 05/01/2018

12/21/2011 Medical Policy Implementation Committee approval. No change to coverage.  
 12/06/2012 Medical Policy Committee review  
 12/19/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
 01/23/2013 Coding updated  
 12/12/2013 Medical Policy Committee review  
 12/18/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
 12/04/2014 Medical Policy Committee review  
 12/17/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
 08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.  
 12/03/2015 Medical Policy Committee review  
 12/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
 12/01/2016 Medical Policy Committee review  
 12/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes  
 08/01/2017 Coding update  
 02/01/2018 Medical Policy Committee review  
 02/21/2018 Medical Policy Implementation Committee approval. Title changed from "Proteomics-Based Testing for the Evaluation of Ovarian (Adnexal) Masses" to "Multimarker Serum Testing Related to Ovarian Cancer". Eligible for coverage statement changed to investigational. Policy Guidelines section added.

Next Scheduled Review Date: 02/2019

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Code Type	Code
CPT	0003U, 81500, 81503
HCPCS	No codes

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ICD-10 Diagnosis	D27.0-D27.9, D39.10-D39.12, D49.5, R19.03-R19.04
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\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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