Multimarker Serum Testing Related to Ovarian Cancer

**Policy Number:** 2.04.62  
**Origination:** 9/2010  
**Last Review:** 9/2017  
**Next Review:** 9/2018

**Policy**

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for proteomics-based testing for the evaluation of ovarian masses. This is considered investigational.

**When Policy Topic is covered**

N/A

**When Policy Topic is not covered**

All uses of the OVA1 and ROMA tests are *investigational* including but not limited to
a. preoperative evaluation of adnexal masses to triage for malignancy, or
b. screening for ovarian cancer, or
c. selecting patients for surgery for an adnexal mass, or
d. evaluation of patients with clinical or radiologic evidence of malignancy, or
e. evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy, or
f. post-operative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

**Considerations**

OVA1 and ROMA tests are combinations of several separate lab tests and involve a proprietary algorithm for determining risk (i.e., they are what the American Medical Association’s CPT calls “Multianalyte Assays with Algorithmic Analyses” [MAAAs]).

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
</table>
| Individuals:  
- With adnexal mass(es) undergoing surgery for possible ovarian cancer | Interventions of interest are:  
- Multimarker serum testing related to ovarian cancer (eg, OVA1 test [Ovare test], ROMA test) in conjunction with clinical assessment |  
- Clinical assessment |  
- Overall survival  
- Test accuracy |
A variety of gene-based biomarkers have been studied in 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. Two tests based on this principle (OVA1™ test, ROMA™ test) have been cleared by the U.S. Food and Drug Administration for use in women with adnexal masses undergoing surgery as an aid to further assess the likelihood that malignancy is present.

The evidence for use of proteomics-based testing (OVA1 test or ROMA test) in conjunction with clinical assessment in patients who have adnexal masses undergoing surgery includes studies assessing the technical performance and diagnostic accuracy of the tests. Relevant outcomes are overall survival and test accuracy. OVA1 is intended to be used in patients for whom clinical assessment does not indicate cancer. When used with clinical assessment in this manner, sensitivity for ovarian malignancy was 92% and specificity was 42%. ROMA is intended to be used 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 specificity of 67%. It is uncertain whether these test characteristics result in meaningful benefit to patients. The chain of evidence supporting improved outcomes resulting from improved diagnostic test performance is weak. There is no direct evidence in terms of assessing patient outcomes based on the use of such testing prior to undergoing surgery. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for use of proteomics-based testing (OVA1 test or ROMA test) in patients who have other clinical situations involving ovarian cancer (eg, screening, selection for surgery, posttreatment cancer monitoring) is lacking. Relevant outcomes are overall survival and test accuracy. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

More than 22,000 women in the United States are diagnosed each annually with ovarian cancer, and approximately 14,000 die of the disease.(1) The mortality rate depends on 3 variables: (1) characteristics of the patient; (2) biology of the tumor (grade, stage, type); and (3) quality of treatment (nature of staging, surgery and chemotherapy used).(2) 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.(3) Numerous articles have been published on the application of this recommendation examining long- and short-term outcomes as well as process measures (eg, 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.(4,5) The available data are most convincing for patients with advanced-stage disease.
Adult women presenting with an adnexal mass have an estimated 68% likelihood of having a benign lesion. About 6% have borderline tumors; 22%, invasive malignant lesions, and 3%, metastatic disease. Clinicians generally agree that women with masses that have a high likelihood of malignancy should undergo surgical staging by gynecologic oncologists. However, women with clearly benign masses do not require referral to a specialist. Criteria and tests that help differentiate benign from malignant pelvic masses are thus 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) and nodular or fixed pelvic mass was an additional criterion.

Two multimarker serum-based tests specific to ovarian cancer have been cleared by the Food and Drug Administration (FDA) with the intended use of triaging patients with adnexal masses (see Regulatory Status section). The proposed use of the tests is to identify women with a substantial likelihood of malignant disease who may benefit from referral to a gynecologic oncology specialist. Patients with positive results may be considered candidates for referral to a gynecologic oncologist for treatment. The tests have been developed and evaluated only in patients with adnexal masses and planned surgical removal. 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, but are not yet commercially available.

**REGULATORY STATUS**

On July 2009, the OVA1® test (Aspira Labs) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The intended use of OVA1® is as an aid to further assess the likelihood that malignancy is present when the physician’s independent clinical and radiological evaluation does not indicate malignancy. In March 2016, a second-generation test called Overa™, 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 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.

On September 2011, the Risk of Ovarian Malignancy Algorithm (ROMA™ test; Fujirebio Diagnostics) was cleared for marketing by 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.

FDA product code: ONX.

**Black Box Warning**
On December 2011, FDA amended its regulation for classifying ovarian adnexal mass assessment score test systems. The change required off-label risks be highlighted using a black box warning.(10) 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.

**Rationale**
This evidence review was originally created in April 2010 and has been updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through October 24, 2016. The literature review focuses on the following 3 issues related to evaluation of diagnostic tests.

Assessment of a diagnostic technology typically focuses on 3 domains: (1) technical performance; (2) diagnostic performance (sensitivity, specificity, likelihood ratios, and positive and negative predictive values) in appropriate populations of patients; and (3) demonstration that the diagnostic information can be used to improve patient outcomes (clinical utility).

Technical performance is typically assessed with 2 types of studies: those that compare test measurements with a criterion standard and those that compare results taken with the same device on different occasions (test-retest).

Diagnostic performance is evaluated by the ability of a test to accurately diagnose a clinical condition compared with the criterion standard. The sensitivity of a test is its ability to detect a disease when the condition is present (true positive), while specificity indicates its ability to detect patients who are suspected of disease but who do not have the condition (true negative). Evaluation of diagnostic performance, therefore, requires independent assessment by the test under consideration and the criterion standard in a population of patients who are suspected of disease.

Clinical utility involves assessing the data linking use of a test to improvement in patient management and/or health outcomes. The clinical utility of tests can often be evaluated adequately using technical and diagnostic performance when there is a strong chain of evidence linking improved diagnostic performance to improved health outcomes. However, when the chain of evidence is weak, or when a test identifies a new or different group of patients with a disease, clinical trials are desired to demonstrate impact of the test on the net health outcome.
TECHNICAL PERFORMANCE

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], 2-microglobulin, transferrin) into a single numerical score. Analytic performance for 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 (eg, 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 numerical score. Analytical 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.

DIAGNOSTIC PERFORMANCE

OVA1 Test

Development
Descriptions of the developmental process for the OVA1 test have been published in U.S. Food and Drug Administration (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 5 of these (CA 125, prealbumin, apo AI, 2-microglobulin, transferrin) produced a composite profile that did appear to have discriminatory ability. The test, as cleared by 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 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 empiric process, based on use of banked samples from academic partners, on a small prospective study of samples from Europe and using a designated subset of
samples from the clinical study used to support submission to FDA. It appears at an undisclosed point in the developmental process as a result of interaction with FDA; separate cutpoints were developed for premenopausal and postmenopausal women.

Validation
The diagnostic performance of the OVA1 test was evaluated in a prospective, double-blind, clinical study using 27 enrollment sites.(13) 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 clinical assessment by nongynecologic oncologists, was as follows (see Table 1). 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 1. Diagnostic Performance of OVA1 Test

<table>
<thead>
<tr>
<th>Diagnostic Characteristics</th>
<th>Clinical Assessment Alone</th>
<th>Clinical Assessment With OVA1 Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>72%</td>
<td>92%</td>
</tr>
<tr>
<td>Specificity</td>
<td>83%</td>
<td>42%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>61%</td>
<td>37%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>89%</td>
<td>93%</td>
</tr>
</tbody>
</table>

a Confidence intervals not provided.

One additional 2015 study (by Grenache et al) was identified; it evaluated the diagnostic performance of the OVA1 test.(14) 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.

No studies were identified that addressed the diagnostic performance of the Overa test.
ROMA Test

Development
Moore et al (2008) described the development of the ROMA test.(15) The authors studied 9 biomarkers and chose human epididymis protein 4 (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.(16) Again, separate cutoffs were used for premenopausal and postmenopausal women.

Validation

Meta-Analyses
In 2014, Wang et al published a meta-analysis of studies evaluating the diagnostic accuracy of the ROMA test algorithm and comparing it to the performance of single biomarkers HE4 and CA 125.(17) 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; 6 of these were conducted in the United States. Findings of the overall pooled analysis of diagnostic accuracy are presented in Table 2.

Table 2. Meta-Analytic Findings for Diagnostic Performance of ROMA Test vs HE4 and CA 125 (Wang et al, 2014)

<table>
<thead>
<tr>
<th>Test</th>
<th>No. Studies</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, %, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROMA test</td>
<td>14</td>
<td>85.3% (81.2 to 88.6)</td>
<td>82.4% (77.4 to 86.5)</td>
</tr>
<tr>
<td>HE4</td>
<td>28</td>
<td>76.3% (72.0 to 80.1)</td>
<td>93.6% (90.0 to 95.9)</td>
</tr>
<tr>
<td>CA125</td>
<td>28</td>
<td>79.2% (74.0 to 83.6)</td>
<td>82.1% (76.6 to 86.5)</td>
</tr>
</tbody>
</table>


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.(18) Six studies met the inclusion criteria, 4 of which were included in the 2014 Wang et al meta-analysis. Two studies were published in 2014 or later. Based on area under the curve (AUC), 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). Findings of the pooled analysis of diagnostic accuracy are shown in Table 3.

Table 3. Meta-Analytic Findings for Diagnostic Performance of ROMA Test vs HE4 and CA 125 (Dayyani et al, 2016)

<table>
<thead>
<tr>
<th>Test</th>
<th>No. Studies</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROMA test</td>
<td>6</td>
<td>87.3% (75.2 to 94.0)</td>
<td>85.5% (71.9 to 93.2)</td>
</tr>
<tr>
<td>HE4</td>
<td>6</td>
<td>68.2% (69.3 to 90.1)</td>
<td>85.1% (71.6 to 92.8)</td>
</tr>
</tbody>
</table>
The point estimates for sensitivity and specificity were lower in pre- and postmenopausal women, with wider confidence intervals.

**Individual Studies**
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 (2016; n=213 cases),(19) Cho et al (2015; n=90 cases),(20) and Terlikowska et al (2016; n=224 cases).(21)

FDA labelling for ROMA, unlike that for OVA1, does not indicate how ROMA is to be used in conjunction with clinical assessment. All the previously cited literature assesses ROMA as a stand-alone test for ovarian cancer, and does not provide a comparison to clinical assessment alone. One study by Moore et al evaluates ROMA in conjunction with clinical assessment, using either positive clinical assessment or positive ROMA as a positive test (similar to the recommended usage for OVA1).(22) 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 evaluated in 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 worsened specificity from 84.3% to 67.2% (see Table 4).

**Table 4. Diagnostic Performance of ROMA for All Malignancy (Moore et al, 2014)**

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

CI: confidence interval.

**CLINICAL UTILITY**
The ideal study design to evaluate the clinical utility of multimarker serum-based test would be a randomized controlled trial comparing health outcomes (eg, 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 both OVA1 and ROMA, when used in conjunction with clinical assessment, improve the sensitivity for detection of malignancy, but specificity also declines. For the OVA1 test, specificity declines so much that most patients test positive. In the 1 study using either positive ROMA or clinical assessment as a positive test, although sensitivity improved, it was still less than 90%. It is
uncertain that there is meaningful clinical benefit from using a test that either does not avoid very many referrals or is not highly sensitive (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 actually result in improved patient outcomes. Although prior studies have shown improved 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.

**SUMMARY OF EVIDENCE**

For individuals who have adnexal mass(es) undergoing surgery for possible ovarian cancer who receive multimarker serum testing related to ovarian cancer (e.g., OVA1 test [Overa test], ROMA test) in conjunction with clinical assessment, the evidence includes studies assessing the technical performance and diagnostic accuracy. Relevant outcomes are overall survival and test accuracy. OVA1 is intended for use in patients for whom clinical assessment does not indicate cancer. When used with clinical assessment in this manner, sensitivity for ovarian malignancy was 92% and 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 specificity of 67%. 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 and so offer meaningful benefit to patients. The chain of evidence supporting improved outcomes is therefore incomplete. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS**

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

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

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**American Congress of Obstetricians and Gynecologists**
The American Congress of Obstetricians and Gynecologists (ACOG) addressed the use of the OVA1 test in its 2011 guidelines on the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer.\(^{(23)}\) In May 2013, the Society for Gynecologic Oncology endorsed these ACOG guidelines.\(^{(24)}\) This ACOG document included the following comments, which were not specific guidelines about the use of the test:

- The OVA1 test “appears to improve the predictability of ovarian cancer in women with pelvic masses.”
- “This is not a screening test, but it may be useful for evaluating women with a pelvic mass.”
- “Clinical utility is not yet established.”

**National Institute for Health and Care Excellence**
The National Institute for Health and Care Excellence issued guidance in 2011 on the recognition and management of ovarian cancer.\(^{(25)}\) This guidance is currently being updated and is under review.

**National Comprehensive Cancer Network**
National Comprehensive Cancer Network (NCCN) guidelines on ovarian cancer (v.1.2016) include the following statement:\(^{(26)}\):

“It has been suggested that specific biomarkers (serum HE4 and CA125) along with an algorithm (Risk of Ovarian Malignancy Algorithm [ROMA]) may be useful for determining whether a pelvic mass is malignant or benign. The FDA [Food and Drug Administration] has approved the use of HE4 and CA125 for estimating the risk of ovarian cancer in women with a pelvic mass. Currently, the NCCN Panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass.”

Regarding the OVA1 test, NCCN guidelines state:

“The OVA1 test uses 5 markers (including transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125) to assess who should undergo surgery by an experienced gynecologic oncologist and who can have surgery in the community.... Based on data documenting an increased survival, NCCN Guidelines Panel Members recommend that all patients should undergo surgery by an experienced gynecologic oncologist (category 1).”
U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
In 2012, the U.S. Preventive Services Task Force (USPSTF) recommended against screening women for ovarian cancer (D recommendation). (27) USPSTF has not addressed multimarker serum testing related to ovarian cancer.

MEDICARE NATIONAL COVERAGE
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov in December 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

References:
10. Medical Devices: Ovarian adnexal mass assessment score test system; Labeling; Black box restrictions. 21 CFR Part 866, Federal Register 2011;76(251):82128-82123. PMID


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81500</td>
<td>Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score</td>
</tr>
<tr>
<td>81503</td>
<td>Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin and pre-albumin), utilizing serum, algorithm reported as a risk score</td>
</tr>
<tr>
<td>0003U</td>
<td>Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score (new code 02/01/17)</td>
</tr>
</tbody>
</table>

**ICD-10 Codes**
Benign neoplasm of ovary, code range D27.0-D27.9
Neoplasm of uncertain behavior, ovary, code range D39.10-D39.12
Neoplasm of unspecified nature, of other genitourinary organs (includes ovary) D49.5
Right upper quadrant abdominal swelling, mass and lump and left upper quadrant abdominal swelling, mass and lump codes R19.01, R19.02

Prior to 2013, these tests would most likely be reported using an unlisted CPT code such as 84999 unlisted chemistry procedure or 86849 unlisted immunology procedure.

There are specific CPT category I MAAA codes for these tests:

81500 Oncology (ovarian), biochemical assays of two proteins (CA125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score – is specific to the ROMA test.

81503 Oncology (ovarian), biochemical assays of five proteins (CA125, apolipoprotein A1, beta-2 microglobulin, transferrin and prealbumin), utilizing serum, algorithm reported as a risk score – is specific to OVA1.

CPT instructs that these codes cannot be reported with the component tests (ie, codes 86304 and 86305 cannot be reported with 81500, and codes 82172, 82232, 83695, 83700, 84134, 84466, and 86304 cannot be reported with 81503).

A new code effective February 1, 2017 is specific to Overa, the new version of OVA1 –

0003U - Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score.

Policy Implementation/Update Information

9/1/10 New policy; may be considered medically necessary.
9/1/11 No policy statement changes.
9/1/12 No policy statement changes.
9/1/13 ROMA™ testing was added to the policy; policy statement indicates both OVA1 and ROMA testing are investigational for all indications.
9/1/14 Title changed to Proteomic-Based Testing Related to Ovarian Cancer.
9/1/15 No policy statement changes.
9/1/16 No policy statement changes.
9/1/17 Title changed to “Multimarker Serum Testing Related to Ovarian Cancer”
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.