Multimarker Serum Testing Related to Ovarian Cancer

Number: 2.04.62
Effective Date: March 1, 2017
Revision Date(s): 02/14/17; 8/9/16; 12/08/15; 12/17/14; 12/09/13; 12/11/12
Replaces: N/A

Policy

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

- Preoperative evaluation of adnexal masses to triage for malignancy, OR
- Screening for ovarian cancer, OR
- Selecting 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
- Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment

Related Policies

2.04.125 Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer

Policy Guidelines

OVA1 and ROMA tests are combinations of several separate lab tests and involve a proprietary algorithm for determining risk (i.e., Multianalyte Assays with Algorithmic Analyses [MAAAs]).

Overa, also known as OVA2, is a second-generation OVA1 multivariate index assay for malignancy risk of adnexal masses. The test received FDA 510(k) clearance on March 21, 2016. (See Regulatory Status)

Coding

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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<tbody>
<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 – is specific to the Overa test</td>
</tr>
<tr>
<td>81500</td>
<td>Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with</td>
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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. The U.S. Food and Drug Administration (FDA) has cleared two tests based on this principle (Ova1™ test [now Overa], ROMA™ test) for use in women with adnexal masses undergoing surgery as an aid to further assess the likelihood that malignancy is present.

This policy focuses on the OVA1/Overa and ROMA tests to assess the analytic and clinical validity and clinical utility of serum markers for ovarian cancer. There are few data supporting the use of serum-based makers with algorithmic analyses for other clinical situations involving detection of ovarian cancer (e.g., screening, selection for surgery, posttreatment cancer monitoring). For these indications, 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 year with ovarian cancer and approximately 14,000 die of the disease.(1) The mortality rate depends on three 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) To date, dozens of articles have been published on the application of this recommendation looking at long-term outcomes, short-term outcomes, and process measures (e.g. types of treatment such as complete staging or tumor debulking). At least two meta-analyses have concluded that outcomes are better in patients with ovarian cancer when they are treated by gynecologic oncologists.(4, 5) Data have been 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.(6) 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 address criteria for referring women with pelvic masses that are suspicious for ovarian cancer to gynecologic oncologists.(7) Separate criteria were developed for pre-menopausal and post-menopausal women. In premenopausal women, referral criteria included at least one of the following: elevated CA125 (>200 U/mL), ascites, evidence of abdominal or distant metastasis, or a positive family history. The referral criteria in postmenopausal women were similar, except that a lower threshold for an elevated CA125 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.(8,9)

**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 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 10, 2011, FDA published an amendment to the regulation for classifying ovarian adnexal mass assessment score test systems to restrict these devices so that a prescribed warning statement that addresses off-label risks be highlighted by 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 or not to proceed with surgery.

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**Scope**

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

**Benefit Application**

N/A

**Rationale**

This policy was originally created in 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 three issues related to evaluation of diagnostic tests.
Assessment of a diagnostic technology typically focuses on 3 parameters:

1. Technical performance;
2. Diagnostic performance (sensitivity, specificity, and positive and negative predictive values) in appropriate populations of patients;
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 in comparison with the criterion standard. The sensitivity of a test is the ability to detect a disease when the condition is present (true positive), while specificity indicates the 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], β2-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 (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 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).(11-13) 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, β2-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

<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>

*Confidence intervals not provided.

One additional study was identified that evaluated the diagnostic performance of the OVA1 test, by Grenache et al.(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 cannot be determined from the study.

Overa Test

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 (17)

<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 (18)

<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>
<tr>
<td>CA 125</td>
<td>6</td>
<td>79.6% (66.3 to 88.5)</td>
<td>82.5% (82.5 to 91.9)</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 (22)

<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>
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</table>
Clinical Utility
The ideal study design to evaluate clinical utility of proteomics-based testing 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 both OVA1 and ROMA when used in conjunction with clinical assessment improve the sensitivity for detection of malignancy, specificity also declines. For the OVA1 test, specificity declines so much that most patients test positive. In the one 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). Since 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 show 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 when 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.

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 policy.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input 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 (NICE) 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 recommended against screening women for ovarian cancer (D recommendation).(27) The task force has not addressed proteomics-based 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.

References
4. Vernooij F, Heintz P, Witteveen E, et al. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. Gynecol Oncol.
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


Appendix
N/A

History

<table>
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<tr>
<td>06/13/11</td>
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</tr>
<tr>
<td>12/19/12</td>
<td>Replace policy. Policy updated to change the use of the OVA1™ and ROMA tests from medically necessary to investigational for all indications. Rationale updated based on a literature review through September 2012, results of TEC Assessment, and results of clinical vetting. References 7, 13, 17-28 added; others renumbered or removed. New CPT codes added. Policy statement changed as noted.</td>
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<td>03/15/13</td>
<td>Update Related Policies. Add 2.03.501.</td>
</tr>
<tr>
<td>10/16/13</td>
<td>Update Related Policies. Add 12.04.66 and remove policy 2.04.34 as it was archived.</td>
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<tr>
<td>12/27/13</td>
<td>Replace policy. Policy updated with literature search through September 30, 2013. References 14, 15 and 20 added; other references renumbered or removed. No change to policy statement. Title changed to Proteomic-based Testing Related to Ovarian Cancer. Clarification note added that this policy is only to be used when HE4 is included in the ROMA combination test. When HE4 is billed as an individual test, 12.04.66 – Serum Biomarker Human Epididymis Protein 4 (HE4) should be used.</td>
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<td>12/17/14</td>
<td>Annual review. Policy updated with literature review through September 25, 2014. References 1, 14, 18 and 23 added. Policy statement unchanged. Policy title changed to “Proteomics-Based Testing Related to Ovarian Cancer”. ICD-9 and ICD-10 diagnosis and procedure codes removed; these are not utilized in adjudication of the policy.</td>
</tr>
<tr>
<td>12/08/15</td>
<td>Annual Review. Policy updated with literature review through October 25, 2015; references 14 and 18 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>02/14/17</td>
<td>Annual review. Title changed to “Multimarker Serum Testing Related to Ovarian Cancer”. Policy updated with literature review through October 24, 2016; references added. New code for Overa test was added. Policy statement unchanged, this testing is considered investigational for all indications.</td>
</tr>
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</table>

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This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
بيحوي هذا الإشعار معلومات هامة. قد يحتوي هذا الإشعار معلومات مهمة بخصوص طلبك أو المادة المتعلقة التي تفيد الحصول عليها من خلال هذه المعلومات. يُطلب منك أن تكون لديك ترجمة للخطوة المطلوبة من خلال هذه المعلومات والمساعدة بذلك تعقيدها. 전화 800-722-1471 (TTY: 800-842-5357) للمزيد من المعلومات.

中文 (Chinese):
本通知有重要的讯息。本通知可能有关您透过 Premera Blue Cross 提交的申请或保险的重要讯息。本通知内可能有重要日期。您可能需要在截止日期之前采取行动，以保留您的健康保险或费用补助。您有权利免费以您的母语得到本讯息和帮助。请拨电话 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avis sila a gen Enfòmasyon Enpòtan ladan. Avis sila a kapab genyen enfòmasyon enpòtan konsènlik aplikasyon w lan oswa konsewn kouvètis arias lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avis sila a. Ou ka gen pou pou kòm aksyon avan sèten dat limit pou ka kette kouvètis ariasante w lan oswa pou yo ka ede w avèk depans yo. Se dwa w pou resëwva enfòmasyon sa a ak assistans nan lang ou pale a, san ou pa gen pou peyey pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaa ket naglaon iti Napateg nga Impormacion. Daytoy a pakdaa mabalain nga adda ket naglaon iti napateg nga impormanasion maipanggep iti aplikasyonony weno coverage babaen ti Iti Premera Blue Cross. Daytoy ket mabalain dagiti importante a pelta iti daytoy a pakdaa. Mabalain nga adda rumbeng nga aramideng nga adda sakkay dagiti partikular a na tauling nga adda alaw tanpop napagatalinadayo ti coverage ti salun-atyo weno tulog kadagiti gastos. Adda karbenganyo a manga ti daytoy nga impormanasion ken tulog ti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Premera Blue Cross provides important information about your health or assistance rights in this notice. This notice contains information about your health coverage or assistance rights. The notice includes important information about how to maintain your health care coverage or assistance rights. You should read and understand this notice to make informed decisions about your health care coverage or assistance rights.

If you have questions about the information in this notice, you can call Premera Blue Cross at 1-800-722-1471 (TTY: 1-800-842-5357) for assistance.

Română (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Українська (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує ймовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

日本語 (Japanese):
この通時には重要な情報が含まれています。この通時には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれています。この通時には、記録されている情報を重要なもの日をご確認ください。健康保険や資料サポートを維持するには、特定の期日までに行動を取られなければなりません。ご自分の言語による情報とサポートが無償で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관련하여 그리고 Premera Blue Cross를 통해 커버리지에 관한 정보를 포함하고 있습니다. 본 통지서에는 책임이 되는 날짜가 있을 수 있습니다. 귀하의 건강 커버리지의 전산 유지가 필요할 수 있기 때문에 정확한 맥락까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보를 귀하의 언어에 따라 받을 것 없을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)으로 전화해보십시오.

한국어 (Korean):
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