Medical Policy
Multimarker Serum Testing Related to Ovarian Cancer

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Policy Number: 249
BCBSA Reference Number: 2.04.62
NCD/LCD: Local Coverage Determination (LCD): Non-covered Services (L33629)

Related Policies
- Serum Biomarker Human Epididymis Protein 4-HE4, #290

Policy
Commercial Members: Managed Care (HMO and POS), and Indemnity

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.

Medicare HMO Blue™ and Medicare PPO Blue™ Members
Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Non-covered Services (L33629)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>This is not a covered service.</th>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
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<td>Medicare HMO Blue℠</td>
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<td>Medicare PPO Blue℠</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<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 – is specific to the ROMA test.</td>
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<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 – is specific to OVA1.</td>
</tr>
<tr>
<td>81504</td>
<td>Oncology (tissue of origin), microarray gene expression profiling of &gt; 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores</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</td>
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Description
More than 22,000 women in the United States are diagnosed each annually with ovarian cancer, and approximately 14,000 die of the disease. 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). 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 (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. 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.

Summary
A variety of serum biomarkers have been studied for their association with ovarian cancer. Of particular interest have been tests that integrate results from multiple analytes into a risk score to predict the presence of disease. Two tests based on this principle (OVA1 test [now Overa], 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.

For individuals who have adnexal mass(es) undergoing surgery for possible ovarian cancer who receive multimarker serum testing related to ovarian cancer (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.

This evidence review focuses on the Food and Drug Administration-approved uses of the OVA1 [Overa] and ROMA tests. There are few data supporting the use of serum-based makers with algorithmic analyses for other clinical situations involving detection of ovarian cancer (eg, screening, selection for surgery, posttreatment cancer monitoring). For these indications, the evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

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<th>Date</th>
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<tr>
<td>2/2017</td>
<td>BCBSA National medical policy review. Title changed. Clarified coding information. New references added.  2/1/2017</td>
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<tr>
<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>12/2015</td>
<td>Added coding language.</td>
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<tr>
<td>1/2015</td>
<td>BCBSA National medical policy review. Title changed to “Proteomics-Based Testing Related to Ovarian Cancer.”</td>
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<td>12/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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<td>2/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>1/2015</td>
<td>Updated to add new CPT code 81504.</td>
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### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### 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