FEP 2.04.62 Multimarker Serum Testing Related to Ovarian Cancer

Effective Date: April 1, 2019

Related Policies:
2.04.66 Serum Biomarker Human Epididymis Protein 4

Multimarker Serum Testing Related to Ovarian Cancer

Description
A variety of serum biomarkers have been studied for their association with ovarian cancer. Of particular interest have been tests that integrate results from multiple analytes into a risk score to predict the presence of disease. Three tests based on this principle, OVA1, Overa (the second-generation OVA1 test), and ROMA have been cleared by the U.S. Food and Drug Administration. The intended use of OVA1 and Overa is to use them as an aid to further assess whether malignancy is present even when the physician’s independent clinical and radiologic evaluation does not indicate malignancy. The intended use of ROMA is to use it as an aid, in conjunction with clinical assessment, to assess whether a premenopausal or a postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery.

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.8,9

Table 1. Summary of FDA-Approved Multimarker Serum-Based Tests Specific to Ovarian Cancer

<table>
<thead>
<tr>
<th>Variables</th>
<th>OVA1</th>
<th>Overa</th>
<th>ROMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>2009</td>
<td>2016</td>
<td>2011</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Quest Diagnostics</td>
<td>Vermillion</td>
<td>Roche Diagnostics</td>
</tr>
<tr>
<td>Biomarkers used</td>
<td>CA 125 II</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>β2-microglobulin</td>
<td>X</td>
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<table>
<thead>
<tr>
<th>Transferrin</th>
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<th>X</th>
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<tbody>
<tr>
<td>Transthyretin</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
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<td>X</td>
</tr>
<tr>
<td>HE4</td>
<td></td>
<td>X</td>
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<tr>
<td>FSH</td>
<td>X</td>
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</tr>
<tr>
<td><strong>Score range</strong></td>
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<tr>
<td><strong>Risk categorization</strong></td>
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</tr>
<tr>
<td>Premenopausal</td>
<td>&lt;5.0: low</td>
<td>&lt;5.0: low</td>
</tr>
<tr>
<td></td>
<td>≥5.0: high</td>
<td>≥5.0: high</td>
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<tr>
<td>Postmenopausal</td>
<td>&lt;4.4: low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥4.4: high</td>
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</table>


**OBJECTIVE**

The objective of this evidence review is to evaluate whether multimarker serum testing related to ovarian cancer improves the net health outcome in patients undergoing surgery for ovarian cancer.

**POLICY STATEMENT**

All uses of the OVA1, Overa, 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. postoperative 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]).

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).
FDA REGULATORY STATUS

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 [Sequn, 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.

RATIONALE

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.

SUPPLEMENTAL INFORMATION

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, and these guidelines were confirmed in 2017. In 2013, the Society for Gynecologic Oncology endorsed these ACOG guidelines. 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.”

Further, in 2016, an ACOG Practice Bulletin addressed the evaluation and management of adnexal masses makes a level B recommendation (based on limited or inconsistent scientific evidence) that
consultation with or referral to a gynecologic oncologist is recommended for premenopausal or postmenopausal with an elevated score on a formal risk assessment test such as the multivariate index assay, risk of malignancy index, or the Risk of Ovarian Malignancy Algorithm, or one of the ultrasound-based scoring systems from the International Ovarian Tumor Analysis group.\(^{27}\)

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence issued guidance in 2011 on the identification and management of ovarian cancer.\(^{28}\) This guidance is currently being updated and is under review.

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network (NCCN) guidelines on ovarian cancer (v.2.2018) include the following statement.\(^{29}\)

“It has been suggested that specific biomarkers (serum HE4 [human epididymis secretory protein 4] and CA-125 [cancer antigen 125]) 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 CA-125 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**

Not applicable.

**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**


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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25. American College of Obstetricians Gynecologists Committee on Gynecologic Practice.
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Detection-of-Epithelial-Ovarian-Cancer-in (2017)" cross-number="26" cross-reference="reference" name="reference-26">


POLICY HISTORY

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<th>Date</th>
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<th>Description</th>
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<tr>
<td>March 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search. 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.</td>
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<tr>
<td>March 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature through October 16, 2017: references 1, 8-10, 12, 14, 16-21, and 27 were added. Policy statement changed with addition of the Overa test. Title changed to “Multimarker Serum Testing Related to Ovarian Cancer”</td>
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<td>March 2019</td>
<td>Update Policy</td>
<td>Policy updated with literature review through October 30, 2018; reference 25 updated. Policy statement is unchanged.</td>
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