MEDICAL POLICY

Excellus

SUBJECT: PROTEOMICS-BASED TESTING FOR THE EVALUATION of OVARIAN (ADNEXAL) MASSES	EFFECTIVE DATE: 10/20/11 REVISED: 08/16/12, 10/17/13, 08/21/14, 07/16/15, 07/21/16, 07/20/17, 10/18/18
POLICY NUMBER: 2.02.43 CATEGORY: Laboratory	PAGE: 1 OF: 4

- ***If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.***
- ***If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.***
- ***If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.***

POLICY STATEMENT:

Based upon our criteria and review of the peer-reviewed literature, the OVA1™ and ROMA tests have not been medically proven to be effective and are considered **not medically necessary** including, but not limited to, the following indications:

I. Screening for ovarian cancer, or
II. Selecting patients for surgery for an adnexal mass, or
III. Evaluation of patients with clinical or radiologic evidence of malignancy, or
IV. Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy, or
V. Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

Refer to Corporate Medical Policy #2.02.10 regarding Serum Tumor Markers for Diagnosis and Management of Cancer.

POLICY GUIDELINES:

The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION:

The OVA1™ test (Vermillion, Inc., Fremont, CA) is a qualitative serum test that combines immunoassay results for 5 analytes (CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, and transferrin) into a single numerical score. The Roma test is also a qualitative serum test that combines 2 analytes (HE4 and the Architect CA 125) along with menopausal status into a numerical score. Both tests are intended to be used in women with adnexal masses who are planning to have surgery by a non-gynecologic oncologist for disease considered benign using routine clinical and radiologic evaluation. In this patient subset, the test serves as an aid to further assess the likelihood that malignancy is present.

RATIONALE:

A 2012 Blue Cross Blue Shield TEC Assessment of "Multi-analyte testing for the evaluation of adnexal masses" included evaluation of both the OVA1 and ROMA tests in regards to their impact on health outcomes. The following conclusions were made:

1. The evidence regarding the effect of OVA1 and ROMA and effects on health outcomes is indirect, and based on studies of diagnostic performance of the tests in patients undergoing surgery for adnexal masses. There are no prospective studies on the use of these tests in patients who present with an adnexal mass. There are no studies that report the impact of testing on referral patterns or the impact on health outcomes.
2. Although the studies show improvements in sensitivity and worsening of specificity with the use of the tests in conjunction with clinical assessment, there are problems in concluding that this results in improved health outcomes. The clinical assessment performed in the studies is not well characterized.
3. OVA1 appears to improve sensitivity for detection of malignancy, however specificity declines so much that most patients test positive.
4. ROMA does not appear to improve the sensitivity of testing to a great extent.

5. Underlying these issues is some uncertainty regarding the benefit of initial treatment by a gynecologic oncologist beyond the need for reoperation is some cases.

Assessment of a diagnostic technology typically focuses on 3 parameters: 1) technical performance; 2) diagnostic performance (sensitivity, specificity, and positive [PPV] and negative predictive value [NPV]) in appropriate populations of patients; and 3) demonstration that the diagnostic information can be used to improve patient outcomes. A summary of these 3 parameters follows.

Technical performance: Evidence on the technical performance of these tests has been evaluated by the U.S. Food and Drug Administration (FDA). The FDA information indicates acceptable technical performance for use in clinical care.

Diagnostic performance: The FDA decision summary describing the FDA's review of the OVA1 test data submitted to the agency as used to obtain market clearance. This clearance was based on a prospective, multicenter, double-blind clinical study of 747 patients from 27 demographically mixed sites. The ROMA test was also evaluated in a prospective, blinded clinical trial using 13 demographically mixed subject enrollment sites with company sponsorship. Patients all presented with an adnexal mass and were scheduled to undergo surgery. Both tests when added to pre-testing clinical assessment produced a fall in the PPV with a small increase in the NPV. The changes observed in the negative predictive value were of uncertain statistical and clinical significance. Thus use of the ROMA and OVA1 proteomic tests in combination with clinical assessment appears to produce very modest changes in diagnostic performance for identifying adnexal masses negative for ovarian cancer.

Improvement in clinical outcomes: No outcome studies have been performed using the OVA1 test or the ROMA test. It is not clear what impact use of either test would have on long-term healthcare outcomes. As is the case for false-positive cases identified and referred using existing clinical and radiologic diagnostic criteria, there is no evidence of harm to patients identified as false-positives.

The use of genomic testing to triage patients for malignancy may be only one of many factors in decision making about where treatment should be delivered. The clinical significance of the addition of these tests to currently used diagnostic modalities is unknown.

Direct evidence on the clinical utility of the proteomic tests is lacking. For patients who are considering treatment by a non-gynecologic oncologist, use of proteomic tests will decrease the likelihood that an adnexal mass is categorized as benign when it is actually malignant. This might impact referral patterns to a gynecologic oncologist and decrease the likelihood that a patient will require a second follow-up procedure for comprehensive staging, lymphadenectomy, and/or tumor debulking, but empirical evidence of this is lacking. Because of the unknown effect on referral patterns, the effect on health outcomes is uncertain.

On December 10, 2011, the 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. 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.

On March 21, 2016 the FDA approved the the next generation of Vermillion's OVA1 test, Overa® which is used for determining ovarian cancer risk in conjunction with independent clinical and imaging assessment prior to planned surgery for a women with a pelvic mass. The approval contained a precaution stating the OVA1 Next Generation test should not be used without an independent clinical and imaging evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of the OVA1 Next Generation test carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

Clinical practice guidelines and position statements by specialty societies do not support the use of the OVA1 or ROMA test as a replacement for a physician's clinical assessment or as a screening tool. While the tests suggest their usefulness as a tool to determine whether a pelvic mass is malignant or benign, their clinical utility is not yet established and their use for determining the status of an undiagnosed pelvic mass is not recommended.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

CPT:

81500	**(NMN)**	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score
81503	**(NMN)**	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
0003U	**(NMN)**	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

HCPCS: No specific code(s)

ICD10:

D27.0-D27.9	Benign neoplasm of ovary (code range)
D39.10-D39.12	Neoplasm of uncertain behavior of ovary (code range)

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KEY WORDS:

Ova1™, Overa, ROMA score, proteomic-based testing.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for Combined Ovarian Cancer Biomarker Tests.