Corporate Medical Policy

Proteomics-based Testing Related to Ovarian Cancer

Description of Procedure or Service

There are a variety of gene-based biomarkers that 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 and ROMA™ test) have now been cleared by the U.S. Food and Drug Administration (FDA) for use in individuals with adnexal masses undergoing surgery as an aid to further assess the likelihood that malignancy is present.

More than 22,000 individuals in the U.S. are diagnosed each year with ovarian cancer and more than 14,000 die of this disease. The mortality rate depends on three variables: 1) characteristics of the patient; 2) the biology of the tumor (grade, stage and type); and 3) the 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 first recommended ovarian cancer surgery and follow-up treatment be performed by physicians with ovarian cancer disease expertise. To date dozens of articles have been published relevant to this recommendation looking at long-term outcomes, short-term outcomes, and process measures (eg, 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. Data have been most convincing for patients with advanced stage disease.

Adults 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 those with masses that have a high likelihood of malignancy should undergo surgical staging by gynecologic oncologists. However, those 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 (ACOG) and the Society of Gynecologic Oncologists (SGO) jointly released referral guidelines that address criteria for referring individuals with pelvic masses that are suspicious for ovarian cancer to gynecologic oncologists. Separate criteria were developed for premenopausal and postmenopausal individuals. In premenopausal individuals, referral criteria included at least one of the following: elevated CA 125 (greater than 200 U/mL), ascites, evidence of abdominal or distant metastasis, or a positive family history. The referral criteria in postmenopausal individuals 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 FDA with the intended use to triage patients with adnexal masses. The proposed use of the tests is to identify individuals 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
Proteomics-based Testing Related to Ovarian Cancer

in patients with adnexal masses who are going on to have 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 are intended to be used 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.

Black Box Warning: 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.

Related Guideline
Serum Biomarker Human Epididymis Protein 4 (HE4)

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
Proteomics-based Testing Related to Ovarian Cancer is considered investigational. BCBSNC does not provide coverage for investigational services.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When proteomics-based testing related to ovarian cancer is covered
Not applicable.

When proteomics-based testing related to ovarian cancer is not covered
All uses of the Ova1™ test and ROMA™ test are investigational, including but not limited to:

- Preoperative evaluation of adnexal masses to triage for malignancy, or
Proteomics-based Testing Related to Ovarian Cancer

- 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
- post-operative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

Policy Guidelines

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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

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]).

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

81500 is specific to the ROMA test.

81503 is specific to OVA1.

0003U is specific to Overa, a new version of OVA1.

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

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.
Proteomics-based Testing Related to Ovarian Cancer

Scientific Background and Reference Sources


Senior Medical Director review 7/22/2010


Policy Implementation/Update Information

8/17/10 New policy issued. The proteomics-based OVA1™ test may be considered medically necessary as an aid to further assess the likelihood that malignancy is present when the physician’s (other than gynecologic oncologist) independent clinical and radiological preoperative evaluations do not indicate malignancy in a patient with an ovarian (adnexal) mass. All other uses of the OVA1™ test are investigational including but not limited to: 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 post-operative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment. Notification given 8/17/10 for policy effective date of 11/23/10. (adn)
Proteomics-based Testing Related to Ovarian Cancer


4/17/12 Related policies added. Reworded when covered section. No change to policy intent. Specialty Matched Consultant Advisory Panel review 3/21/12. (sk)

1/1/13 Description section and Policy Guidelines section updated. Policy statement changed to investigational for all indications. New coding information added to Billing/Coding section. Reviewed by Senior Medical Director 12/19/12. Notification given 01/01/13. Policy effective 4/1/13. (sk)


4/29/14 Specialty Matched Consultant Advisory Panel review. No change to Policy statement. (sk)

1/27/15 References added. No change to Policy statement. (sk)


1/26/16 Reference added. Policy Guidelines updated. (sk)


12/30/16 Minor changes to description section. No change to policy statement. (an)

1/27/17 Added code 0003U. (an)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.