

Corporate Medical Policy

Proteomics-based Testing Related to Ovarian Cancer

File Name: proteomics_based_testing_related_to_ovarian_cancer
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Last CAP Review: 3/2018
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Description of Procedure or Service

A variety of gene-based 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 (FDA). The intended use of OVA1 and Overa is 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 as an aid, in conjunction with clinical assessment, to assess whether a pre- or post-menopausal woman presenting with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery.

The term epithelial ovarian cancer collectively includes high-grade serous epithelial ovarian, fallopian tubal, and peritoneal carcinomas due to their shared pathogenesis, clinical presentation, and treatment. We use epithelial ovarian cancer to refer to this group of malignancies in the discussion that follows. There is currently no serum biomarker that can distinguish between these types of carcinoma. An estimated 22,440 women in the United States are expected to be diagnosed in 2017 with ovarian cancer, and approximately 14,080 will die of the disease. The mortality rate depends on 3 variables: (1) patient characteristics; (2) tumor biology (grade, stage, type); and (3) treatment quality (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.

OVA1 is a qualitative serum test that combines immunoassay results for 5 analytes (cancer antigen 125 [CA 125], prealbumin, apolipoprotein AI [apo AI], β 2-microglobulin, transferrin) into a single numeric score.

Overa is a qualitative serum test that combines immunoassay results for 5 analytes (CA 125, apo AI, transferrin, follicular stimulating hormone, human epididymis protein 4 [HE4]) into a single numeric score.

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 numeric score.

Black Box Warning: On December 10, 2011, the FDA amended its regulation for classifying ovarian adnexal mass assessment score test systems. The change required that off-label risks be highlighted using a black box warning. The warning is intended to mitigate the risk to health associated with off-label use as a screening test, standalone diagnostic test, or as a test to determine whether to proceed with surgery. Considering the history and currently unmet medical needs for ovarian cancer testing, the FDA concluded that there is a risk of off-label use of this device. To address this risk, the FDA requires that manufacturers provide notice concerning the

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risks of off-label uses in the labeling, advertising, and promotional material of ovarian adnexal mass assessment score test systems. Manufacturers must address the following risks:

- Women without adnexal pelvic masses (ie, for cancer “screening”) are not part of the intended use population for the ovarian adnexal mass assessment score test systems. Public health risks associated with false-positive results for ovarian cancer screening tests are well described in the medical literature and include morbidity or mortality associated with unneeded testing and surgery. The risk from false-negative screening results also includes morbidity and mortality due to failure to detect and treat ovarian malignancy.
- Analogous risks, adjusted for prevalence and types of disease, arise if test results are used to determine the need for surgery in patients who are known to have ovarian adnexal masses.
- If used outside the “OR” rule that is described in this special control guidance, results from ovarian adnexal mass assessment score test systems pose a risk for morbidity and mortality due to nonreferral for oncologic evaluation and treatment.

Related Policy:

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
- 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 (eg, OVA1 test [Overa test], ROMA

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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.

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.

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. 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.

National Comprehensive Cancer Network (NCCN) guidelines on ovarian cancer (v.4.2017) include the following statement:

“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 has approved the use of HE4 and CA-125 for estimating the risk of ovarian cancer in women with a 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

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documenting an increased survival, NCCN Guidelines Panel Members recommend that all patient should undergo surgery by an experienced gynecologic oncologist (category 1).”

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.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 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.

Scientific Background and Reference Sources

U.S. Food and Drug Administration. 510(k) substantial Equivalence Determination Decision summary. OVA1™ Test (K081754). Retrieved 7/14/10 from: http://www.accessdata.fda.gov/cdrh_doc/reviews/K081754.pdf

Goff BA, Matthews BJ, Larson EH, et al. Predictors of comprehensive surgical treatment in patients with ovarian cancer. *Cancer* 2007; 109(10):2031-42

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.62, 4/08/2010

Senior Medical Director review 7/22/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.62, 4/14/2011

Specialty Matched Consultant Advisory Panel – 3/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.62, 11/08/12

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.62, 11/14/13

Specialty Matched Consultant Advisory Panel – 3/2014

U.S. Preventive Services Task Force. Screening for Ovarian Cancer. 2012;

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<http://www.uspreventiveservicestaskforce.org/uspstf12/ovarian/ovarcancerrr.htm>. Accessed January 16, 2015.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.62, 11/13/14

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.62, 11/12/15
Specialty Matched Consultant Advisory Panel – 3/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.62, 12/8/2016

American College of O, Gynecologists' Committee on Practice B-G. Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. *Obstet Gynecol.* Nov 2016;128(5):e210-e226. PMID 27776072

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tub Cancer and Primary Peritoneal Cancer. Version 4.2017. http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.62, 12/14/2017

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)
- 1/18/2011 Specialty Matched Consultant Advisory Panel review 12/16/2010. Policy accepted as written. (adn)
- 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)
- 2/11/14 Specialty Matched Consultant Advisory Panel review 12/16/2010. Policy accepted as written. (adn) Specialty Matched Consultant Advisory Panel review 3/20/13. Related policy deleted. Related guideline added. Policy title changed from Proteomics-based Testing for the Evaluation of Ovarian (Adnexal) Masses to Proteomics-based Testing Related to Ovarian Cancer. Policy description extensively revised. Policy Guidelines updated. No change to Policy statement. Senior Medical Director review. (sk)

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- 4/29/14 Specialty Matched Consultant Advisory Panel review 12/16/2010. Policy accepted as written. (adn) Specialty Matched Consultant Advisory Panel review. No change to Policy statement. (sk)
- 1/27/15 References added. No change to Policy statement. (sk)
- 9/1/15 Specialty Matched Consultant Advisory Panel review 3/25/2015. (sk)
- 1/26/16 Specialty Matched Consultant Advisory Panel review 3/20/16. Policy statement unchanged. (an)
- 4/29/16 Specialty Matched Consultant Advisory Panel review 12/16/2010. Policy accepted as written. (adn)
- 12/30/16 Minor changes to description section. No change to policy statement. (an)
- 1/27/17 Added code 0003U. (an)
- 4/28/17 Updated Description section and Policy Guidelines. Reference added. Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (an)
- 4/27/18 Revised Description section and Policy Guidelines. References added. Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. (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.