

EFFECTIVE DATE: 10|01|2015

POLICY LAST UPDATED: 04|17|2018

OVERVIEW

This policy documents the coverage determination for Multimarker Serum Testing Related to Ovarian Cancer. A variety of serum biomarkers 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. 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.

This policy is applicable to Commercial Products only. For BlueCHiP for Medicare, see Related Policy section.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Commercial Products

All uses of the OVA1, Overa and ROMA tests are not medically necessary, including but not limited to the following, because there is insufficient peer-reviewed literature that demonstrates that the service is effective:

- 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

For BlueCHiP for Medicare, see related policy section for the BlueCHiP for Medicare National and Local Coverage Determinations policy.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

BACKGROUND

EPITHELIAL OVARIAN CANCER

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.

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% of women with masses have borderline tumors; 22% possess invasive malignant lesions, and 3% have metastatic disease. Surgery is the only way to diagnose ovarian cancer; this is because biopsy of an ovary with suspected ovarian cancer is usually not performed due to the risk of spreading cancer cells. Most clinicians agree that women with masses that have a high likelihood of malignancy should undergo surgical staging by a gynecologic oncologist. However, women with clearly benign masses do *not* require a referral to see a specialist. Therefore, criteria and tests that help differentiate benign from malignant pelvic masses are 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); moreover, a nodular or fixed pelvic mass was an added criterion.

Three multimer 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 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 multimer panels and longitudinal screening algorithms are under development; however, these are not yet commercially available.

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 [Sequin, 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.

Black Box Warning

In December 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 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.

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. Therefore, these services are considered not medically necessary for Commercial products.

CODING

Commercial Products

The following services are considered not medically necessary:

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

RELATED POLICIES

BlueCHiP for Medicare National and Local Coverage Determinations Policy
Genetic Testing Services
Proprietary Laboratory Analyses (PLA) Codes

PUBLISHED

Provider Update, June 2018
Provider Update, May 2017
Provider Update, January 2017
Provider Update, August 2015
Provider Update, December 2013

REFERENCES

1. Surveillance Epidemiology and End Results (SEER) Program. SEER Stat Fact Sheets: Ovarian Cancer. n.d.; <https://seer.cancer.gov/statfacts/html/ovary.html>. Accessed October 17, 2017
2. Giede KC, Kieser K, Dodge J, et al. Who should operate on patients with ovarian cancer? An evidence-based review. *Gynecol Oncol*. Nov 2005;99(2):447-461. PMID 16126262
3. Van Holsbeke C, Van Belle V, Leone FP, et al. Prospective external validation of the 'ovarian crescent sign' as a single ultrasound parameter to distinguish between benign and malignant adnexal pathology. *Ultrasound Obstet Gynecol*. Jul 2010;36(1):81-87. PMID 20217895
4. Im SS, Gordon AN, Buttin BM, et al. Validation of referral guidelines for women with pelvic masses. *Obstet Gynecol*. Jan 2005;105(1):35-41. PMID 15625139
5. Fung ET. A recipe for proteomics diagnostic test development: the OVA1 test, from biomarker discovery to FDA clearance. *Clin Chem*. Feb 2010;56(2):327-329. PMID 20110452
6. U.S. Food and Drug Administration (FDA). 510(k) substantial equivalence determination decision summary: ROMA™ test – K103358. n.d.; http://www.accessdata.fda.gov/cdrh_docs/reviews/K103358.pdf. Accessed November 13, 2017
7. Grenache DG, Heichman KA, Werner TL, et al. Clinical performance of two multi-marker blood tests for predicting malignancy in women with an adnexal mass. *Clin Chim Acta*. Jan 1 2015;438:358-363. PMID 25283731
8. Moore RG, Hawkins DM, Miller MC, et al. Combining clinical assessment and the Risk of Ovarian Malignancy Algorithm for the prediction of ovarian cancer. *Gynecol Oncol*. Dec 2014;135(3):547-551. PMID 25449569
9. Simmons AR, Clarke CH, Badgwell DB, et al. Validation of a biomarker panel and longitudinal biomarker performance for early detection of ovarian cancer. *Int J Gynecol Cancer*. Jul 2016;26(6):1070-1077. PMID 27206285
10. Yanaranop M, Tiyayon J, Siricharonthai S, et al. Rajavithi-ovarian cancer predictive score (R-OPS): A new scoring system for predicting ovarian malignancy in women presenting with a pelvic mass. *Gynecol Oncol*. Jun 2016;141(3):479-484. PMID 26996662
11. Wang J, Gao J, Yao H, et al. Diagnostic accuracy of serum HE4, CA125 and ROMA in patients with ovarian cancer: a meta-analysis. *Tumour Biol*. Jun 2014;35(6):6127-6138. PMID 24627132

12. Al Musalhi K, Al Kindi M, Al Aisary F, et al. Evaluation of HE4, CA-125, Risk of Ovarian Malignancy Algorithm (ROMA) and Risk of Malignancy Index (RMI) in the preoperative assessment of patients with adnexal mass. *Oman Med J*. Sep 2016;31(5):336-344. PMID 27602187
13. Cho HY, Park SH, Park YH, et al. Comparison of HE4, CA125, and risk of ovarian malignancy algorithm in the prediction of ovarian cancer in Korean women. *J Korean Med Sci*. Dec 2015;30(12):1777-1783. PMID 26713052
14. Terlikowska KM, Dobrzycka B, Witkowska AM, et al. Preoperative HE4, CA125 and ROMA in the differential diagnosis of benign and malignant adnexal masses. *J Ovarian Res*. Jul 19 2016;9(1):43. PMID 27436085
15. Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Ovarian Adnexal Mass Assessment Score Test System.
<https://www.fda.gov/RegulatoryInformation/Guidances/ucm237299.htm>.
Accessed October 17, 2017.
16. U.S. Food and Drug Administration (FDA). 510(k) Substantial Equivalence Determination Decision Summary: OVA1™ Next Generation Test (K150588). n.d.;
https://www.accessdata.fda.gov/cdrh_docs/reviews/K150588.pdf. Accessed October 19, 2017.
17. American College of Obstetricians and 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

[CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS](#)

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.

