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OVERVIEW

This policy documents the coverage determination for Multimarker Serum Testing Related to Ovarian Cancer. A variety of gene-based 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. Two tests based on this principle (OVA1 test [now Overa], ROMA test) have been cleared by the U.S. Food and Drug Administration (FDA) for use in women with adnexal masses as an aid to further assess the likelihood that malignancy is present.

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

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Commercial Products

All uses of the OVA1 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

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

More than 22,000 women in the United States are diagnosed each year with ovarian cancer and approximately 14,000 die of the disease. The mortality rate depends on 3 variables: (1) characteristics of the patient; (2) biology of the tumor (grade, stage, type); and (3) 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 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 (e.g., types of treatment such as complete staging or tumor debulking). At least 2 metaanalyses 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% have borderline tumors, 22% have invasive malignant lesions, and 3% have metastatic disease. Clinicians generally agree that women with masses that have a high likelihood of malignancy should undergo surgical staging by gynecologic oncologists. However, women 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 and the Society of Gynecologic Oncologists jointly released referral guidelines that address criteria for referring women with pelvic masses that are 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 (CA125 >200 U/mL), ascites, evidence of abdominal or distant metastasis, or a positive family history. The referral criteria in postmenopausal women were similar, except that a lower threshold for an elevated CA125 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 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 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 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.

In 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

In December 2011, FDA amended its regulation for classifying ovarian adnexal mass assessment score test systems. The change required 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, stand-alone diagnostic test, or as a test to determine whether to proceed with surgery.

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 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. 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 (New Code Effective 2/1/2017)

RELATED POLICIES

BlueCHIP for Medicare National and Local Coverage Determinations Policy
Genetic Testing Services

PUBLISHED

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: Ovary Cancer. <http://seer.cancer.gov/statfacts/html/ovary.html>. Accessed October 7, 2014.
2. Vernooij F, Heintz P, Witteveen E, et al. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. *Gynecol Oncol*. Jun 2007;105(3):801- 812. PMID 17433422
3. 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
4. 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
5. 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

6. Medical Devices: Ovarian adnexal mass assessment score test system; Labeling; Black box restrictions. 21 CFR Part 866, Federal Register 2011;76(251):82128-82123. PMID
7. 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
8. U.S. Food and Drug Administration (FDA). 510(k) substantial equivalence determination decision summary: ROMA™ test – K103358. http://www.accessdata.fda.gov/cdrh_docs/reviews/K103358.pdf. Accessed August 21, 2014.
9. 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
10. 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
11. 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
12. Yanaranop M, Tiyayon J, Siricharoenchai 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
13. 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
14. 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
15. 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
16. 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

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