Medical Coverage Policy | Multimarker Serum Testing Related to Ovarian Cancer

EFFECTIVE DATE: 10|01|2015
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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 OVA1test), and ROMA have been cleared by the U.S. Food and Drug Administration. 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 premenopausal or a postmenopausal woman who presents with an ovarian adnexal mass is at a high or low likelihood of finding malignancy on surgery.

This policy is applicable to Commercial Products only. For Medicare Advantage Plans, 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 Medicare Advantage Plans, see related policy section for the Medicare Advantage Plans 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 21,750 women in the U.S. are expected to be diagnosed in 2020 with ovarian cancer, and approximately 13940 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 outcomes.

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 2016, the American College of Obstetricians and Gynecologists updated a practice bulletin that addressed criteria for referring women with adnexal masses to gynecologic oncologists. Separate criteria were developed for premenopausal and postmenopausal women because the specificity and positive predictive value of cancer antigen 125 (CA 125) are higher in postmenopausal women. Prior guidance, which was based on expert opinion, recommended a CA 125 >200 U/mL for referring premenopausal women with an adnexal mass to a gynecologic oncologist. The current guidance advises using very elevated CA 125 levels with other clinical factors such as ultrasound findings, ascites, a nodular or fixed pelvic mass, or evidence of abdominal or distant metastasis for referral. The referral criteria for postmenopausal women are similar, except that a lower threshold for an elevated CA 125 test is used (35 U/mL). The practice bulletin states that serum biomarker panels are alternatives to CA 125 levels when deciding about a gynecologic oncologist referral.

Three 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 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 multimarker 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, stand-alone 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, the National Comprehensive Cancer Network guidelines recommend (category 1) that all patients undergoing surgery should undergo surgery by an experienced gynecologic oncologist. Given the National Comprehensive Cancer Network recommendation, direct evidence will be required to demonstrate that the use of FDA-cleared multimarker serum testing to inform decisions regarding referral to a gynecologic oncology specialist for surgery has clinical usefulness. Direct evidence of clinical usefulness is provided by studies that have compared health outcomes for patients managed with and without the FDA-cleared multimarker serum testing. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No trials were identified that have evaluated whether referral based on FDA-cleared multimarker serum testing improves health outcomes.

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

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

PUBLISHED

Provider Update, March 2021
Provider Update, April 2020
Provider Update, April 2019
Provider Update, June 2018
Provider Update, May 2017
Provider Update, January 2017
Provider Update, August 2015

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