

(20462)

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Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With adnexal mass(es) undergoing surgery for possible ovarian cancer	Interventions of interest are: • Multimarker serum testing with clinical assessment preoperatively to assess ovarian cancer risk	Comparators of interest are: • Clinical assessment	Relevant outcomes include: • Overall survival

DESCRIPTION

A variety of serum 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. 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. The intended use of ROMA is to use it 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 high or low likelihood of finding malignancy on surgery.

SUMMARY OF EVIDENCE

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 evi-

dence supporting improved outcomes is incomplete. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

All uses of the OVA1, Overa, and ROMA tests are **investigational**, including but not limited to:

- a. preoperative evaluation of adnexal masses to triage for malignancy, or
- b. screening for ovarian cancer, or
- c. selecting patients for surgery for an adnexal mass, or
- d. evaluation of patients with clinical or radiologic evidence of malignancy, or
- e. evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy, or
- f. postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

POLICY GUIDELINES

OVA1, Overa, and ROMA tests are combinations of several separate lab tests and involve proprietary algorithms for determining risk.

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.¹ The mortality rate depends on three variables: (1) patient characteristics; (2) tumor biology (grade, stage, type); and (3) treatment quality (nature of staging, surgery, and chemotherapy used).² 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.³ 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 two meta-analyses have concluded that outcomes are improved when patients with ovarian cancer are treated by gynecologic oncologists.^{4,5} 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.⁶ 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.⁷ 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 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). They are summarized in Table 1. 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.^{8,9}

Table 1. Summary of FDA-Approved Multimarker Serum-Based Tests Specific to Ovarian Cancer

Variables	OVA1	Overa	ROMA
Approved	2009	2016	2011
Manufacturer	Quest Diagnostics	Vermillion	Roche Diagnostics
Biomarkers used			
CA 125 II	X	X	X
β_2 -microglobulin	X		
Transferrin	X	X	
Transthyretin	X		
Apolipoprotein AI	X	X	
HE4		X	X
FSH		X	
Score range	0-10	0-10	0-10
Risk categorization			
Premenopausal	<5.0: low ≥5.0: high	<5.0: low ≥5.0: high	≥1.3: high
Postmenopausal	<4.4: low ≥4.4: high		≥2.77: high

CA 125: cancer antigen 125; FDA: Food and Drug Administration; FSH: follicle stimulating hormone; HE4: human epididymis secretory protein 4.

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 two of the five 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 zero 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.¹⁰ 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 (i.e., 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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