Medical Policy
Multimarker Serum Testing Related to Ovarian Cancer

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Policy Number: 249
BCBSA Reference Number: 2.04.62
NCD/LCD: Local Coverage Determination (LCD): Non-covered Services (L33629)

Related Policies
Serum Biomarker Human Epididymis Protein 4-HE4, #290

Policy
Commercial Members: Managed Care (HMO and POS), and Indemnity

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.

Medicare HMO Blue^{SM} and Medicare PPO Blue^{SM} Members

This is not a covered service.

Medical necessity criteria and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the link(s) below.

[Local Coverage Determinations (LCDs) for National Government Services, Inc.](#)

Local Coverage Determination (LCD): Non-covered Services (L33629)

Note: To review the specific LCD, please remember to click "accept" on the CMS licensing agreement at the bottom of the CMS webpage.

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website at https://www.cms.gov for information regarding your specific jurisdiction.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for situations where prior authorization might be required if the procedure is performed outpatient.

	Outpatient
Commercial Managed Care (HMO and POS)	This is **not** a covered service.
Commercial PPO and Indemnity	This is **not** a covered service.
Medicare HMO BlueSM	This is **not** a covered service.
Medicare PPO BlueSM	This is **not** a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for <u>Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue</u>:

CPT Codes

CPT Codes	Description
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score – is specific to the ROMA test.
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apoliproprotein A1, beta-2 microglobulin, transferrin and pre-albumin), utilizing serum, algorithm reported as a risk score – is specific to OVA1.
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores
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

Description

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 3 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 (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.[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
Beta$_2$-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; HEA: human epididymis secretory protein 4.

Summary

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.

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.

Policy History

Date	Action
2/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
5/2018	BCBSA National medical policy. Policy statement revised to add the Overa test. Prior Authorization Information reformatted. Effective 5/1/2018.
2/2017	BCBSA National medical policy review. Title changed. Clarified coding information. New references added.
1/2016	New references added from BCBSA National medical policy.
12/2015	Added coding language.
1/2015	BCBSA National medical policy review. Title changed to "Proteomics-Based Testing Related to Ovarian Cancer."
12/2014	New references added from BCBSA National medical policy.
2/2014	New references added from BCBSA National medical policy.
1/2014	Updated to add new CPT code 81504.
6/2013	BCBSA National medical policy review. Policy statement changed to investigational for all indications. Effective 6/1/2013.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
9/2011	Reviewed - Medical Policy Group - Urology, Obstetrics and Gynecology. No changes to policy statements.

| 7/2011 | Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements. |
| 12/1/2010 | Medical policy 249 effective 12/1/2010. |

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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