MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Proteomics-Based Testing for the Evaluation of Ovarian (Adnexal) Masses**
Policy Number	**2.02.43**
Category	**Technology Assessment**
Original Effective Date	**10/20/11**
Committee Approval Date	**08/16/12, 10/17/13, 08/21/14, 07/16/15, 07/21/16, 07/20/17, 10/18/18, 07/18/19, 07/16/20**
Current Effective Date	**08/17/23**
Archived Date	**07/16/20**
Archive Review Date	**07/15/21, 07/21/22, 08/17/23**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

Based upon our criteria and assessment of the peer-reviewed literature, the OVA1, Overa, and Risk of Ovarian Malignancy Algorithm (ROMA) tests have not been medically proven to be effective and, therefore, are considered **not medically necessary** including, but not limited to, the following indications:

I. Screening for ovarian cancer;

II. Selecting patients for surgery for an adnexal mass;

III. Evaluation of patients with clinical or radiologic evidence of malignancy;

IV. Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy; or

V. Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

DESCRIPTION

The OVA1, Overa, and ROMA tests are intended to be used in women with adnexal masses who are planning to have surgery by a non-gynecologic oncologist for disease considered benign using routine clinical and radiologic evaluation. In this patient subset, the test serves as an aid to further assess the likelihood that malignancy is present.

The OVA1 test (Vermillion, Inc., Fremont, CA) is a qualitative serum test that combines immunoassay results for five analytes (CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, and transferrin) into a single numerical score. Overa is a second-generation version of this test, combining CA 125, apolipoprotein A-1, beta2 microglobulin, follicle stimulating hormone, and transferrin. It is suggested as a reflex process, that if the result of the OVA1 test indicates an

intermediate range level of risk, the Overa test should be completed. Vermillion refers to the completion of these two tests as OVA1+.The ROMA (Roche Diagnostics) test is also a qualitative serum test; it combines two analytes (HE4 and the Architect CA 125), along with menopausal status into a numerical score.

RATIONALE

OVA1, Overa, and OVA1+ are intended for use in patients for whom clinical assessment does not clearly 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%.

Direct evidence on the clinical utility of the proteomic tests is lacking. For patients who are considering treatment by a non-gynecologic oncologist, use of proteomic tests will decrease the likelihood that an adnexal mass is categorized as benign when it is actually malignant. This might impact referral patterns to a gynecologic oncologist and decrease the likelihood that a patient will require a second follow-up procedure for comprehensive staging, lymphadenectomy, and/or tumor debulking, but empirical evidence of this is lacking. Because of the unknown effect on referral patterns, the effect on health outcomes is uncertain.

On December 10, 2011, the U.S. Food and Drug Administration (FDA) published an amendment to the regulation for classifying ovarian adnexal mass assessment score test systems to restrict these devices by requiring that a prescribed warning statement that addresses off-label risks be highlighted by 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 test to determine whether or not to proceed with surgery.

On March 21, 2016, the FDA approved the next generation of Vermillion's OVA1 test, Overa, which is used for determining ovarian cancer risk in conjunction with independent clinical and imaging assessment prior to planned surgery for women with a pelvic mass. The approval contained a precaution stating that OVA1 Next Generation test should not be used without an independent clinical and imaging evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of the OVA1 Next Generation test carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

The National Comprehensive Cancer Network (NCCN) Guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer V2.2023 recommend, based on data documenting an increased survival, that all patients with ovarian malignancies (especially those with an adnexal mass) should undergo evaluation by an experienced gynecologic oncologist prior to surgery. The NCCN panel has stated, in agreement with the Society of Gynecologic Oncology (SGO) and FDA, that the OVA1 screening test should not be used to detect ovarian cancer in patients without any other signs of cancer, be utilized as a stand-alone diagnostic tool, or for determining the status of an undiagnosed adnexal/pelvic mass.

Given the NCCN 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81500 (**NMN)**	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score (ROMA)
81503 **(NMN)**	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 (OVA1)
0003U **(NMN)**	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 (Overa (OVA1 Next Generation), Aspira Labs, Inc, Vermillion, Inc)

HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
D27.0-D27.9	Benign neoplasm of ovary (code range)
D39.10-D39.12	Neoplasm of uncertain behavior of ovary (code range)

REFERENCES

Al-Musalhi K, 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 2016 Sep;31(5):336-44.

Aslan K, et al. Comparison of HE 4, CA 125, ROMA Score and Ultrasound Score in the Differential Diagnosis of Ovarian Masses. J Gynecol Obstet Hum Reprod 2020 May;49(5):101713.

Dochez V, et al. Efficacy of HE4,CA125, Risk of Malignancy Index and Risk of Ovarian Malignancy Index to Detect Ovarian Cancer in Women with Presumed Benign Ovarian Tumours: A Prospective, Multicentre Trial. J Clin Med 2019 Oct 25;8(11):1784.

*Fung ET. A recipe for proteomics diagnostic test development: the OVA1 test, from biomarker discovery to FDA clearance. Clin Chem 2010;56(2):327-9.

*Giede KC, et al. Who should operate on patients with ovarian cancer? An evidenced-based review. Gynecol Oncol 2005;99(2):447-61.

Granato T, et al. HE4 in the different diagnosis of ovarian masses. Clin Chim Acta 2015 Jun 15;446:147-55.

Grenache DG, et al. Clinical performance of two multi-marker blood tests for predicting malignancy in women with an adnexal mass. Clin Chim Acta 2015 Jan 1;438:358-63.

Hoskins W, et al. Ovarian cancer surgical practice guidelines. Society of Surgical Oncology practice guidelines. [https://www.cancernetwork.com/view/practice-guidelines-ovarian-cancer] accessed 07/06/23.

*Kaijser J, et al. A comparison between an ultrasound based prediction model (LR2) and the risk of ovarian malignancy algorithm (ROMA) to assess the risk of malignancy in women with an adnexal mass. Gynecol Oncol 2013May;129(2):377-83.

*Kobayashi E, et al Biomarkers for screening, diagnosis, and monitoring of ovarian cancer. Cancer Epidemiol Biomarkers Prev 2012 Nov;21(11):1902-12.

Kotowicz B, et al. Clinical value of human epididymis protein 4 and the Risk of Ovarian Malignancy Algorithm in differentiating borderline pelvic tumors from epithelial ovarian cancer in early stages. Eur J Obstet Gynecol Reprod Biol 2015 Nov;194:141-6.

Liujia Q, et al. Mass spectrometry-based proteomics of epithelial ovarian cancers: a clinical perspective. Mol Cell Proteomics 2023; 22(7):1-21.

Lokich E, et al. Assessing the risk of ovarian malignancy algorithm for the conservative management of women with a pelvic mass. Gynecol Oncol 2015 Nov;139(2):248-52.

Lycke M, er al. A multicenter clinical trial validating the performance of HE4, CA125, risk of ovarian malignancy algorithm and risk of malignancy index. Gynecol Oncol 2018 Oct;151(1):159-165.

*Medical Devices: Ovarian adnexal mass assessment score test system; Labeling; Black box restrictions. 21 CFR Part 866, Federal Register 2011;76(251):82128-33.

Moro F, et al. Role of CA125/CEA ratio and ultrasound parameters in identifying metastases to the ovaries in patients with multilocular and multilocular-solid ovarian masses. Ultrasound Obstet Gynecol 2019 Jan;53(1):116-123.

*Muller CY. Doctor, should I get this new ovarian cancer test-OVA1? Obstet Gynecol 2010;116(2 Pt 1):246-7.

National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer V.2.2023[https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf] accessed 07/06/23.

Terlikowska KM, et al. Preoperative HE4, CA125 and ROMA in the differential diagnosis of benign and malignant adnexal masses. J Ovarian Res 2016 Jul 19;9(1):43.

Ueland FR, et al. A perspective on ovarian cancer biomarkers: past, present and yet-to-come. Diagnostics (basel) 2017 Mar 8;7(1).E14.

*Ueland FR, et al. Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumors. Obstet Gynecol 2011;117:1289–97.

U.S. Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary: OVA1™ Test (K081754) [http://www.accessdata.fda.gov/cdrh_docs/reviews/K081754.pdf] accessed 07/06/23.

*Yip P, et al. Comprehensive serum profiling for the discovery of epithelial ovarian cancer biomarkers. PLoS One 2011;6(12):e29533.

Yoshida A, et al. Comparing the Copenhagen Index (CPH-I) and the Risk of Ovarian Malignancy Algorithm (ROMA); two equivalent ways to differentiate malignant form benign ovarian tumors before surgery? Gynecol Oncol 2016 Mar;140(3):481-5.

*Key Article

KEY WORDS

Ova1, Overa, ROMA score, proteomic-based testing

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) (L38371) for Multimarker Serum Tests Related to Ovarian Cancer Testing. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38371&ver=12&bc=0 accessed 07/06/23.

There is currently a Local Coverage Determination (LCD) (L35000) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ContrId=298&ver=133&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AAQAAAIAAAAA& accessed 07/06/23.

There is currently a Local Coverage Article (LCA) (A57020) for Multimarker Serum Tests Related to Ovarian Cancer Testing. Please refer to the following LCA website for Medicare Members: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=57020&ver=3 accessed 07/06/23.