FEP Medical Policy Manual

FEP 2.04.62 Multimarker Serum Testing Related to Ovarian Cancer

Effective Policy Date: April 1, 2021

Original Policy Date: December 2011

Related Policies:

None

Multimarker Serum Testing Related to Ovarian Cancer

Description

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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 the Risk of Ovarian Malignancy Algorithm (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.

OBJECTIVE

The objective of this evidence review is to evaluate whether multimarker serum testing related to ovarian cancer improves the net health outcome in patients undergoing surgery for ovarian cancer.

POLICY STATEMENT

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

1. preoperative evaluation of adnexal masses to triage for malignancy, OR
2. screening for ovarian cancer, OR
3. selecting patients for surgery for an adnexal mass, OR
4. evaluation of patients with clinical or radiologic evidence of malignancy, OR
5. evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy, OR
6. 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 (ie, what CPT calls multianalyte assays with algorithmic analyses [MAAAs]).

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

section). These tests 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.[5,6,]

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

Variables	OVA1	Overa	ROMA
Cleared	2009	2016	2011
Manufacturer	Quest Diagnostics	Vermillion	Roche Diagnostics
Biomarkers used			
CA 125 II	X	X	X
b_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: U.S. Food and Drug Administration; FSH: follicle-stimulating hormone; HE4: human epididymis secretory protein 4 ;ROMA: Risk of Ovarian Malignancy Algorithm.

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 a 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.[7] 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.

RATIONALE

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, 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 U.S. Food and Drug Administration (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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists

In 2017, with reaffirmation in 2019, the American College of Obstetricians and Gynecologists (ACOG) opinion on the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer addressed using multimarker serum testing.[26.] The opinion states that multimarker panels lack strong evidence for use in asymptomatic women without adnexal masses and do not improve early detection and survival rates in average-risk women. The Society for Gynecologic Oncology endorsed this ACOG opinion.

In 2016, an ACOG Practice Bulletin address ing the evaluation and management of adnexal masses made a level B recommendation (based on limited or inconsistent scientific evidence) that consultation with or referral to a gynecologic oncologist is recommended for premenopausal or postmenopausal with an elevated score on a formal risk assessment test such as the multivariate index assay, risk of malignancy index, or the Risk of Ovarian Malignancy Algorithm, or 1 of the ultrasound-based scoring systems from the International Ovarian Tumor Analysis group.[4.] A level C recommendation (based on consensus and expert opinion) was given to using serum biomarker panels as an alternative to cancer antigen 125 (CA 125) level to decide about the referral to a gynecologic oncologist for an adnexal mass requiring surgery.

National Institute for Health and Care Excellence

In 2011, the National Institute for Health and Care Excellence issued guidance on the identification and management of ovarian cancer.[27.] The guideline does not provide any recommendations regarding additional serum marker testing besides testing for serum CA 125 levels in women with symptoms suggestive of ovarian cancer.

National Comprehensive Cancer Network

In 2020, the NCCN guideline on ovarian cancer (v.1.2020) includes the following statement[28.]:

"It has been suggested that specific biomarkers (serum HE4 and CA 125) along with an algorithm (Risk of Ovarian Malignancy Algorithm [ROMA]) may be useful for determining whether a pelvic mass is malignant or benign. The FDA has approved the use of HE4 and CA-125 for estimating the risk of ovarian cancer in women with a pelvic mass. Currently, the NCCN Panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass."

Regarding the OVA1 test, the NCCN guideline states:

"The OVA1 test uses 5 markers (including transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA 125) to assess who should undergo surgery by an experienced gynecologic oncologist and who can have surgery in the community.... Based on data documenting an increased survival, NCCN Guidelines Panel Members recommend that all patients should undergo surgery by an experienced gynecologic oncologist (category 1)."

U.S. Preventive Services Task Force Recommendations

In 2018, the U.S. Preventive Services Task Force recommended against screening asymptomatic women for ovarian cancer (D recommendation). [29.] The Task Force has not addressed multimarker serum testing related to ovarian cancer.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Surveillance Epidemology and End Results (SEER) Program. SEER Stat Fact Sheets: Ovarian Cancer. n.d.; https://seer.cancer.gov/statfacts/html/ovary.html. Accessed October 29, 2020.
2. du Bois A, Rochon J, Pfisterer J, et al. Variations in institutional infrastructure, physician specialization and experience, and outcome in ovarian cancer: a systematic review. Gynecol Oncol. Feb 2009; 112(2): 422-36. PMID 18990435
3. 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): 81-7. PMID 20217895
4. Eskander R, Berman M, Keder L. Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. Obstet Gynecol. Nov 2016; 128(5): e210-e226. PMID 27776072
5. 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): 1070-7. PMID 27206285
6. Yanaranop M, Tiyayon J, Siricharoenthai 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
7. Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Ovarian Adnexal Mass Assessment Score Test System. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/class-ii-special-controls-guidance-document-ovarian-adnexal-mass-assessment-score-test-system. Updated February 27, 2018. Accessed October 29, 2020.
8. U.S. Food and Drug Administration (FDA). 510(k) Substantial Equivalence Determination Decision Summary: OVA1TM Test (K081754) n.d.; https://www.accessdata.fda.gov/cdrh_docs/reviews/K081754.pdf. Accessed October 31, 2020.
9. Fung ET. A recipe for proteomics diagnostic test development: the OVA1 test, from biomarker discovery to FDA clearance. Clin Chem. Feb 2010; 56(2): 327-9. PMID 20110452
10. 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 01 2015; 438: 358-63. PMID 25283731
11. U.S. Food and Drug Administration (FDA). 510(k) Substantial Equivalence Determination Decision Summary: OVA1TM Next Generation Test (K150588). n.d.; https://www.accessdata.fda.gov/cdrh_docs/reviews/K150588.pdf. Accessed October 30, 2020.
12. Bristow RE, Smith A, Zhang Z, et al. Ovarian malignancy risk stratification of the adnexal mass using a multivariate index assay. Gynecol Oncol. Feb 2013; 128(2): 252-9. PMID 23178277
13. Moore RG, Brown AK, Miller MC, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. Gynecol Oncol. Feb 2008; 108(2): 402-8. PMID 18061248

14. Moore RG, Miller MC, Disilvestro P, et al. Evaluation of the diagnostic accuracy of the risk of ovarian malignancy algorithm in women with a pelvic mass. Obstet Gynecol. Aug 2011; 118(2 Pt 1): 280-8. PMID 21775843
15. 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): 6127-38. PMID 24627132
16. Dayyani F, Uhlig S, Colson B, et al. Diagnostic Performance of Risk of Ovarian Malignancy Algorithm Against CA125 and HE4 in Connection With Ovarian Cancer: A Meta-analysis. Int J Gynecol Cancer. Nov 2016; 26(9): 1586-1593. PMID 27540691
17. 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): 336-44. PMID 27602187
18. 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): 1777-83. PMID 26713052
19. 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
20. Shen Y, Zhao L, Lu S. Diagnostic performance of HE4 and ROMA among Chinese women. Clin Chim Acta. Jan 2020; 500: 42-46. PMID 31626761
21. Shin KH, Kim HH, Kwon BS, et al. Clinical Usefulness of Cancer Antigen (CA) 125, Human Epididymis 4, and CA72-4 Levels and Risk of Ovarian Malignancy Algorithm Values for Diagnosing Ovarian Tumors in Korean Patients With and Without Endometriosis. Ann Lab Med. Jan 2020; 40(1): 40-47. PMID 31432638
22. Dunton C, Bullock RG, Fritsche H. Multivariate Index Assay Is Superior to CA125 and HE4 Testing in Detection of Ovarian Malignancy in African-American Women. Biomark Cancer. 2019; 11: 1179299X19853785. PMID 31236012
23. Han KH, Park NH, Kim JJ, et al. The power of the Risk of Ovarian Malignancy Algorithm considering menopausal status: a comparison with CA 125 and HE4. J Gynecol Oncol. Nov 2019; 30(6): e83. PMID 31576682
24. Chacon E, Dasi J, Caballero C, et al. Risk of Ovarian Malignancy Algorithm versus Risk Malignancy Index-I for Preoperative Assessment of Adnexal Masses: A Systematic Review and Meta-Analysis. Gynecol Obstet Invest. 2019; 84(6): 591-598. PMID 31311023
25. 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): 547-51. PMID 25449569
26. Matteson KA, Gunderson C, Richardson DL. Committee Opinion No. 716: The Role of the Obstetrician-Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk. Obstet Gynecol. Sep 2017; 130(3): e146-e149. PMID 28832487
27. National Center for Clinical Excellence (NICE). Ovarian cancer: recognition and initial management [CG122]. 2011; https://www.nice.org.uk/guidance/cg122. Accessed October 28, 2020.
28. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tub Cancer and Primary Peritoneal Cancer. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf Accessed October 29, 2020.
29. Grossman DC, Curry SJ, Owens DK, et al. Screening for Ovarian Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. Feb 13 2018; 319(6): 588-594. PMID 29450531

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
March 2013	Replace policy	Policy update with literature search, results of TEC assessment. References 7, 13, and 17-28 added, Policy statement changed to not medically necessary for preoperative evaluation.

Date	Action	Description
March 2014	Replace policy	Policy updated with literature search. References 14, 15 and 20 added; other references renumbered or removed. No change to policy statement. Title changed to Proteomic based Testing Related to Ovarian Cancer.
March 2015	Replace policy	Policy updated with literature review through September 25, 2014. References 1, 14, 18 and 24 added. Policy statement unchanged.
March 2018	Replace policy	Policy update with literature through October 16, 2017; references 1, 8-10, 12, 14, 16-21, and 27 were added. Policy statement changed with addition of the Overa test. Title changed to "Multimarker Serum Testing Related to Ovarian Cancer"
March 2019	Replace policy	Policy updated with literature review through October 30, 2018; reference 25 updated. Policy statement is unchanged.
March 2020	Replace policy	Policy updated with literature review through October 19,2019; references added. Policy statement unchanged.
March 2021	Replace policy	Policy updated with literature review through October 30, 2020; references added. Policy statement unchanged.