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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 OVA1 test), and 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.

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, evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- Preoperative evaluation of adnexal masses to triage for malignancy, or
- Screening for ovarian cancer, or
- Selecting individuals for surgery for an adnexal mass, or
- Evaluation of individuals with clinical or radiologic evidence of malignancy, or
- Evaluation of individuals 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

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 19,880 women in the U.S. were expected to be diagnosed in 2021 with ovarian cancer, and approximately 12,810 were expected to 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 multimer 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 multimer 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 2A) that all patients with suspected ovarian cancer should be evaluated 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. 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.

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, April 2023
Provider Update, April 2022
Provider Update, March 2021
Provider Update, April 2020
Provider Update, April 2019

REFERENCES

1. Surveillance Epidemiology and End Results (SEER) Program. SEER Stat Fact Sheets: Ovarian Cancer. n.d.; <https://seer.cancer.gov/statfacts/html/ovary.html>. Accessed November 4, 2022.
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. Matthews BJ, Qureshi MM, Fiascone SJ, et al. Racial disparities in non-recommendation of adjuvant chemotherapy in stage II-III ovarian cancer. *Gynecol Oncol*. Jan 2022; 164(1): 27-33. PMID 34785030
4. Zhang C, Zhang C, Wang Q, et al. Differences in Stage of Cancer at Diagnosis, Treatment, and Survival by Race and Ethnicity Among Leading Cancer Types. *JAMA Netw Open*. Apr 01 2020; 3(4): e202950. PMID 32267515
5. Joslin CE, Brewer KC, Davis FG, et al. The effect of neighborhood-level socioeconomic status on racial differences in ovarian cancer treatment in a population-based analysis in Chicago. *Gynecol Oncol*. Nov 2014; 135(2): 285-91. PMID 25173584
6. Mattei LH, Robb L, Banning K, et al. Enrollment of Individuals From Racial and Ethnic Minority Groups in Gynecologic Cancer Precision Oncology Trials. *Obstet Gynecol*. Oct 01 2022; 140(4): 654-661. PMID 36075065
7. Zhong P, Yang B, Pan F, et al. Temporal trends in Black-White disparities in cancer surgery and cancer-specific survival in the United States between 2007 and 2015. *Cancer Med*. Aug 15 2022. PMID 35968573
8. Ellis L, Canchola AJ, Spiegel D, et al. Racial and Ethnic Disparities in Cancer Survival: The Contribution of Tumor, Sociodemographic, Institutional, and Neighborhood Characteristics. *J Clin Oncol*. Jan 01 2018; 36(1): 25-33. PMID 29035642
9. Albright BB, Nasioudis D, Craig S, et al. Impact of Medicaid expansion on women with gynecologic cancer: a difference-in-difference analysis. *Am J Obstet Gynecol*. Feb 2021; 224(2): 195.e1-195.e17. PMID 32777264
10. Bodurtha Smith AJ, Applebaum J, Fader AN. Association of the Affordable Care Act's Medicaid Expansion With 1-Year Survival Among Patients With Ovarian Cancer. *Obstet Gynecol*. Jun 01 2022; 139(6): 1123-1129. PMID 35675609
11. Smick AH, Holbert M, Neff R. Association of Physician Densities and Gynecologic Cancer Outcomes in the United States. *Obstet Gynecol*. Nov 01 2022; 140(5): 751-757. PMID 36201771
12. 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

13. 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
14. 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
15. Yanaranop M, Tiyaon J, Siricharonthai 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. PMID26996662
16. 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 November 4, 2022.
17. 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
18. U.S. Food and Drug Administration (FDA). 510(k) Substantial Equivalence Determination Decision Summary: OVA1™ Test(K081754) n.d.; https://www.accessdata.fda.gov/cdrh_docs/reviews/K081754.pdf. Accessed November 5, 2022.
19. 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
20. 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
21. Moore RG, Brown AK, Miller MC, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma inpatients with a pelvic mass. *Gynecol Oncol.* Feb 2008; 108(2): 402-8. PMID 18061248
22. 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): 280-288. PMID 21775843
23. Suri A, Perumal V, Ammalli P, et al. Diagnostic measures comparison for ovarian malignancy risk in Epithelial ovarian cancer patients: a meta-analysis. *Sci Rep.* Aug 27 2021; 11(1): 17308. PMID 34453074
24. Dayyani F, Uhlig S, Colson B, et al. Diagnostic Performance of Risk of Ovarian Malignancy Algorithm Against CA125 and HE4in Connection With Ovarian Cancer: A Meta-analysis. *Int J Gynecol Cancer.* Nov 2016; 26(9): 1586-1593. PMID 27540691
25. 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
26. 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
27. 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
28. 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
29. 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
30. 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

31. 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
32. 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
33. Carreras-Dieguez N, Glickman A, Munmany M, et al. Comparison of HE4, CA125, ROMA and CPH-I for Preoperative Assessment of Adnexal Tumors. *Diagnostics (Basel)*. Jan 17 2022; 12(1). PMID 35054393
34. 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. PMID31311023
35. Davenport C, Rai N, Sharma P, et al. Menopausal status, ultrasound and biomarker tests in combination for the diagnosis of ovarian cancer in symptomatic women. *Cochrane Database Syst Rev*. Jul 26 2022; 7: CD011964. PMID 35879201
36. 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
37. 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
38. National Center for Clinical Excellence (NICE). Ovarian cancer: recognition and initial management [CG122]. 2011; <https://www.nice.org.uk/guidance/cg122>. Accessed November 8, 2022.
39. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tub Cancer and Primary Peritoneal Cancer. Version 5.2022. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed November 8, 2022.
40. 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

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