Test Specific Guidelines

OVA1

MOL.TS.260.A
v1.0.2023

Procedure Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure covered by this guideline	Procedure code
OVA1	81503

What Is Ovarian Cancer?

Definition

According to the National Cancer Institute, " Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies, with almost 50% of all cases occurring in women older than 65 years."[1]

Incidence

There are an estimated 19,880 new cases of ovarian cancer per year.[1] Ovarian cancer incidence increases with age, peaking in the 6th and 7th decades of life.[2]

Symptoms

Signs and symptoms of ovarian cancer include the following:[1]

"Pain, swelling, or a feeling of pressure in the abdomen or pelvis.

Urinary urgency or frequency.

Difficulty eating or feeling full.

A lump in the pelvic area.

Gastrointestinal problems such as gas, bloating, or constipation."

Diagnosis

Current screening methods include gynecological assessment, vaginal ultrasound, and cancer antigen 125 (CA -125) assay.[1] However, these screening

methods have low predictive value in women with average risk, and the cancer is often widespread by the time it is detected.[1]

One finding that may raise concern for ovarian cancer is a pelvic mass. Approximately 20% of women will have a pelvic mass during their lifetime; however, not all pelvic masses are cancerous.[3]

As a result of the low specificity and sensitivity of current diagnostic evaluations, there is greater interest in the discovery of better screening methods in order to identify ovarian cancer at early stages.

Survival

In 2022, there are expected to be 12,810 deaths from ovarian cancer making it the 5th most common cancer in terms of mortality.[1,2] Survival and prognosis depends on multiple factors. The following are the most favorable prognostic factors:[1]

"Younger age

Good performance status

Cell type other than mucinous or clear cell

Well-differentiated tumor

Early-stage disease

Absence of ascites

Lower disease volume before surgical debulking

Smaller residual tumor after primary cytoreductive surgery

BRCA1 or BRCA2 mutation carrier"

Test Information

Introduction

OVA1®, OVERA®, and OVA1®plus are multivariate index assays used in women with adnexal masses of undetermined clinical significance.

OVA1

The OVA1 test is indicated for the pre-surgical evaluation of women with an ovarian tumor or mass or women suspected of having an ovarian neoplasm, when the clinical and radiological evaluations do not suggest the presence of malignancy.[3]

This test examines the following 5 serum protein markers to assess risk:[2]

Transthyretin, Apolipoprotein A1, Transferrin, Beta-2 microglobulin, CA-125

OVA1 test scores range from 0-10.

Low risk: postmenopausal: <4.4; premenopausal: <5.0

Intermediate risk: postmenopausal: 4.4-6.0; premenopausal: 5.0-7.0

Elevated risk: any menopausal status: ≥5.0

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Markedly elevated risk: postmenopausal: >6.0; premenopausal: >7.0

OVERA

The OVERA test is indicated for women who receive an intermediate risk score from OVA1 testing. The second-generation OVERA assay assesses a woman's malignancy risk using combined results from the following 5 immunoassays:[3]

Apolipoprotein A1, Human Epididymis Protein 4 [HE4], CA-125 II, Follicle Stimulating Hormone [FSH], and Transferrin

OVA1plus

OVA1plus (also reported as OVA1+) is not an independent test, but is a term used to describe a "reflex process" that is designed to help stratify the risk of malignancy in adult women diagnosed with an adnexal (pelvic) mass. The reflex process involves initially performing OVA1. If OVA1 results indicate intermediate risk, then OVERA is performed. The combined results of OVA1 and OVERA are intended to aid in the risk assessment of malignancy in adult women diagnosed with a pelvic mass who are planning to undergo surgery.[3]

Guidelines and Evidence

Introduction

This section includes guidelines and evidence pertaining to OVA1, OVERA, and OVA1plus testing.

American College of Obstetrics and Gynecologists

The American College of Obstetrics and Gynecologists (ACOG, 2016) stated the following regarding OVA1:[4]

"Serum biomarker panels may be used as an alternative to CA 125 level alone in determining the need for referral to or consultation with a gynecologic oncologist when an adnexal mass requires surgery. These biomarker panels are not recommended for use in the initial evaluation of an adnexal mass, but may be helpful in assessing which women would benefit from referral to a gynecologic oncologist."

"The multivariate index assay has demonstrated higher sensitivity and negative predictive value for ovarian malignancy when compared with clinical impression and CA 125 alone."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) stated the following regarding OVA1:[2]

"[T]he OVA1 test is a multivariate index assay (MIA) that uses five markers (including transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125) in preoperative serum to assess the likelihood of malignancy in patients with an adnexal mass for which surgery is planned, with the aim of helping community practitioners determine which patients to refer to a gynecologic oncologist for evaluation and surgery."

"[T]he second generation MIA (MIAG2, branded name OVERA) [is] based on CA-125, transferrin, apolipoprotein A1, follicle-stimulating hormone [FSH], and HE4."

"The Society of Gynecologic Oncology (SGO) and the FDA have stated that the OVA1 test should not be used as a screening tool to detect ovarian cancer in patients without any sign of cancer, or as a stand-alone diagnostic tool."

"Moreover, based on data documenting an increased survival, NCCN Guidelines Panel recommend that all patients with suspected ovarian malignancies (especially those with an adnexal mass) should undergo evaluation by an experienced gynecologic oncologist prior to surgery."

"Although the American Congress of Obstetricians and Gynecologists (ACOG) has suggested that ROMA and OVA1 may be useful for deciding which patient to refer to a gynecologic oncologist, other professional organizations have been non-committal."

"Currently the NCCN Panel does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass."

Selected Relevant Publications

Several clinical studies in the peer-reviewed publication literature have evaluated the use of OVA1 and OVERA.[5-22]

OVA1 has the potential to improve some aspects of diagnostic accuracy, particularly sensitivity and negative predictive value, beyond the current disease management strategies for ovarian tumors. When used alongside a clinician's assessment, some studies have shown that OVA1 has the ability to increase accurate detection of ovarian malignancies, although specificity and positive predictive values suffer. Compared with clinical assessment alone or ACOG guidelines, OVA1 improves diagnostic assessment, and OVA1 appears to demonstrate improvement over its predecessor test for CA-125.

The overall body of evidence for OVERA is low quality due to serious risk of bias, indirectness, and inconsistency across the individual studies. Results generally showed reasonable sensitivity and negative predictive values, but specificity was generally low. Accurate estimates of false negative results were not consistently reported, and thus, it is difficult to infer the downstream consequences of missed malignancies associated with OVERA. No clinical utility studies were found for

OVERA to evaluate the benefit of test use on overall survival, progression-free survival, or quality of life.

No peer-reviewed studies were found that evaluated the OVA1plus "reflex process" in which patients with indeterminate results on first-generation OVA1 also undergo subsequent testing with second-generation OVERA to guide surgical planning. No conclusions can be drawn regarding the clinical validity or clinical utility of OVA1plus to assess risk of malignancy, improve the surgical planning process, potentially shorten the time to surgery, and/or guide low risk women to safely avoid surgery. A meaningful clinical utility study of OVA1plus would examine the net benefits of the use of the step-wise testing process and combined results on patient health outcomes.

Criteria

Coverage for OVA1 is considered medically necessary when the following criteria are met:

The member has surgery planned for an ovarian adnexal mass that is neither clearly benign nor clearly malignant based on clinical or ultrasound evaluation, AND

No previous successful OVA1 testing for the current ovarian adnexal mass, AND

The member is over 18 years of age, AND

The member has not yet been referred to a gynecologic oncologist, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Billing and Reimbursement Considerations

If OVA1plus (OVA1 + OVERA) is requested and billed as separate CPT codes to reflect the independent testing elements that make up the OVA1plus reflex process (81503 and 0003U), only the OVA1 component (81503) of the process will be reimbursable when medical necessity criteria are met.

If a single procedure code (such as 81479, 84999, 81599, or others) is billed to represent the combined OVA1plus test, it will be considered investigational and experimental given that there is no evidence base supporting the use of the combined test.

References

Ovarian epithelial, fallopian tube, and primary peritoneal cancer treatment. National Cancer Institute website. Available at: https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq#link/_416_toc

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National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. V1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

Aspira Women's Health. OVA1 Products. Available at: https://aspirawh.com/ova-products/

The American College of Obstetrics and Gynecologists Practice Bulletin No. 174: evaluation and management of adnexal masses. *Obstet Gynecol.* 2016;128(5):e210-e226.

Bristow RE, Hodeib M, Smith A, et al. Impact of a multivariate index assay on referral patterns for surgical management of an adnexal mass. *Am J Obstet Gynecol.* 2013;209(6):581.e1-8.

Bristow RE, Smith A, Zhang Z, Chan DW, Crutcher G, Fung ET, Munroe DG. Ovarian malignancy risk stratification of the adnexal mass using a multivariate index assay. *Gynecol Oncol.* 2013;128(2):252-259.

Cramer DW, Bast RC Jr, Berg CD, et al. Ovarian cancer biomarker performance in prostate, lung, colorectal, and ovarian cancer screening trial specimens. *Cancer Prev Res (Phila).* 2011;4(3):365-374.

Eskander RN, Carpenter BA, Wu HG, Wolf JK. The clinical utility of an elevated-risk multivariate index assay score in ovarian cancer patients. *Curr Med Res Opin.* 2016;32(6):1161-1165.

Goodrich ST, Bristow RE, Santoso JT, et al. The effect of ovarian imaging on the clinical interpretation of a multivariate index assay. *Am J Obstet Gynecol.* 2014;211(1):65.e1-65.e11.

Grenache DG, Heichman KA, Werner TL, Vucetic Z. Clinical performance of two multi-marker blood tests for predicting malignancy in women with an adnexal mass. *Clin Chim Acta.* 2015;438:358-363.

Longoria TC, Ueland FR, Zhang Z, et al. Clinical performance of a multivariate index assay for detecting early-stage ovarian cancer. *Am J Obstet Gynecol.* 2014;210(1):78.e1-9.

Moore LE, Pfeiffer RM, Zhang Z, et al. Proteomic biomarkers in combination with CA 125 for detection of epithelial ovarian cancer using prediagnostic serum samples from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *Cancer.* 2012;118(1):91-100.

Ueland FR, Desimone CP, Seamon LG, et al. Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumors. *Obstet Gynecol.* 2011;117(6):1289-1297.

Ware Miller R, Smith A, DeSimone CP, et al. Performance of the American College of Obstetricians and Gynecologists' ovarian tumor referral guidelines with a multivariate index assay. *Obstet Gynecol.* 2011;117(6):1298-1306.

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

Moore RG, RG, Blackman A, Miller MC, et al. Multiple biomarker algorithms to predict epithelial ovarian cancer in women with a pelvic mass: Can additional makers improve performance? *Gynecol Oncol*. 2019;154(1):150-155. doi: https://doi.org/10.1016/j.ygyno.2019.04.006

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;11:1-4. doi: 10.1177/1179299x19853785

Dunton C, Bullock RG, Fritsche H. Ethnic disparity in clinical performance between multivariate index assay and CA125 in detection of ovarian malignancy. *Future Oncol*. 2019;15(26):3047-3051. doi: 10.2217/fon-2019-0310

Terzic M, Aimagambetova G, Norton M, et al. Scoring systems for the evaluation of adnexal masses nature: current knowledge and clinical applications. *J Obstet Gynaecol*. 2020:1-8. doi: 10.1080/01443615.2020.1732892

Dunton CJ, Eskander RN, Bullock RG, et al. Low-risk multivariate index assay scores, physician referral and surgical choices in women with adnexal masses. *Curr Med Res Opin*. 2020;36(12):2079-2083. doi: 10.1080/03007995.2020.1842726

Zhang Z, Bullock RG, Fritsche H. Adnexal mass risk assessment: a multivariate index assay for malignancy risk stratification. *Future Oncol*. 2019;15(33):3783-3795. doi: 10.2217/fon-2019-0479

Shulman LP, Francis M, Bullock R, et al. Clinical performance comparison of two in-vitro diagnostic multivariate index assays (IVDMIAs) for presurgical assessment for ovarian cancer risk. *Adv Ther*. 2019;36(9):2402-2413. doi: 10.1007/s12325-019-01010-8 Beksac AT, Ratnani P, Dovey Z, et al. Unified model involving genomics, magnetic resonance imaging and prostate-specific antigen density outperforms individual co-variables at predicting biopsy upgrading in patients on active surveillance for low risk prostate cancer. *Cancer Reports*. 2021. doi: 10.1002/cnr2.1492Oki E, Watanabe J, Sato T, et al. Impact of the 12-gene recurrence score assay on deciding adjuvant chemotherapy for stage II and IIIA/B colon cancer: the SUNRISE-DI study. *ESMO Open*. 2021;6(3):100146. doi: 10.1016/j.esmoop.2021.100146

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