OVA1, OVERA, and OVA1plus

Procedure Addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What Is Ovarian Cancer?

Definition

With an estimated 21,410 new cases a year, ovarian cancer is one of the most common gynecological cancers in women.\(^1\) In 2021, there are expected to be 13,770 deaths from ovarian cancer making it the 5\(^{\text{th}}\) most common cancer in terms of mortality.\(^{1,2}\)

- 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.”

- Current screening methods include gynecological assessment, vaginal ultrasound, and cancer antigen 125 (CA-125) assay.\(^1\) However, these screening methods have low predictive value 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.\(^3\) However, not all pelvic masses are cancerous.

- 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.
Test Information

Introduction

OVA1, OVERA, and OVA1plus 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. This test examines the following 5 serum protein markers to assess risk:

- 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)
- Markedly elevated risk: (postmenopausal: >6.0; premenopausal: >7.0)

OVERA

The second-generation OVERA assay assesses a woman’s malignancy risk using combined results from the following 5 immunoassays:

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

The OVERA test is indicated for women who receive an intermediate risk score from OVA1 testing.

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.
Guidelines and Evidence

Introduction

The following 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:

- "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, 2020) stated the following regarding OVA1:

- "The 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."
- "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 (category 1)."

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

Introduction

Requests for OVA1, OVERA, and OVA1plus testing are reviewed using the following criteria.

OVA1

Coverage for OVA1 will be granted 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.
OVERA, Including as a Component of OVA1plus

This test is considered investigational and/or experimental.

- Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Billing and Reimbursement Considerations

OVERA billed with 0003U or any other procedure code will be considered investigational and experimental and will not be reimbursable.

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), medically necessity for each CPT code will be determined individually. Therefore, the OVA1 component (81503) of the process is reimbursable when medical necessity criteria are met, but the OVERA component (0003U) of the process will be considered investigational and experimental and will not be reimbursable.

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


