CLINICAL MEDICAL POLICY	
Policy Name:	Multimarker Serum Testing Related to Ovarian Cancer
Policy Number:	MP-108-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	04/01/2023; 04/01/2022; 02/13/2021; 02/17/2020
Effective Date:	05/01/2023; 05/01/2022; 03/15/2021; 03/16/2020
Next Annual Review:	11/2023
Revision Date:	11/16/2022; 11/17/2021; 11/18/2020; N/A
Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
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Policy History

Date	Activity
05/01/2023	Provider Effective date
03/08/2023	PARP Approval
11/16/2022	QI/UM Committee review
11/16/2022	Annual Review: Per PA DHS TAG determination, the OVA1 test (CPT code 81503) may be considered medically necessary under specific circumstances. Adjusted 'Procedures' section to include medical necessity guidance. Added TAG determination Option #3. Updated 'Summary of Literature' and 'Reference Sources' sections.
05/01/2022	Provider Effective date
03/07/2022	PARP Approval
11/17/2021	QI/UM Committee review
11/17/2021	Annual Review: No changes to clinical criteria. Updated FDA information. Added TAG determination. Updated Summary of Literature and Reference sections.
03/15/2021	Provider Effective Date
02/02/2021	PARP Approval
11/18/2020	QI/UM Committee Review
11/18/2020	Annual Review: updated Summary of Literature and References, removed inactive Hayes documentation.
03/16/2020	Provider effective date
01/16/2020	PARP Approval
12/18/2019	QI/UM Committee review
12/18/2019	Initial policy developed

Disclaimer

Highmark Wholecare℠ medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

Policy Statement

Highmark Wholecare℠ does not provide coverage under medical-surgical benefits of the Company's Medicaid products for OVA1, Overa, and ROMA testing related to ovarian cancer.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

Definitions

Prior Authorization Review Panel (PARP) - A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

OVA1® - A qualitative serum test that combines the results of CA125 II, transferrin, apolipoprotein AI, transthyretin, beta-2 microglobulin into a single numerical result.

ROMA™ (Risk of Ovarian Malignancy Algorithm) - A qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA125 II and menopausal status into a numerical score.

OVERA® - A qualitative serum test that combines the results of transferrin, CA 125 II, apolipoprotein AI, FSH, and HE4 EIA into a single numerical result.

Adnexal mass - masses of the ovary, fallopian tube, or surrounding tissues

Procedures

1. The Ova1® Multi-Marker Ovarian Cancer Test (CPT code 81503) is a multivariate index assay (MIA) that assesses the likelihood of malignancy in patients with an adnexal mass for which surgery is planned, with the aim of helping community practitioners determine if the patient should be referred to a gynecologic oncologist for evaluation and surgery. ALL of the following criteria must be met for Ova1 to be considered medically necessary:
    A. The patient is 18 years of age or older; AND
    B. An ovarian adnexal mass is present; AND
    C. Surgery is planned for treatment of the mass; AND
    D. The patient has not yet been referred to a gynecologic oncologist; AND
    E. A referral to a gynecologic oncologist is being considered in the event of a positive test result.

    Ova1® Multi-Marker Ovarian Cancer test requires a Program Exception, with approval by a Medical Director on a case-by-case basis.

2. All other uses of multimarker serum testing related to ovarian cancer, including Overa, and ROMA tests, are considered experimental and investigational and therefore, not medically necessary. This includes, but is not limited to, the following uses:
    - For evaluation of an individual with either clinical or radiological evidence of malignancy
    - When screening for ovarian cancer
    - Preoperative evaluation of adnexal masses to triage for malignancy
    - Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment
    - Selection of individuals for surgery for an adnexal mass
    - Evaluation of individuals with nonspecific signs or symptoms suggesting possible malignancy

3. Post-payment Audit Statement
    The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare℠ at any time pursuant to the terms of your provider agreement.

4. Related Policies
    - MP-010-MD-PA Testing for Genetic Disease
    - MP-011-MD-PA BRCA1 and BRCA2 Genetic Mutation Testing
    - MP-074-MD-PA Oncologic Genetic Testing Panels

Governing Bodies Approval

On September 11, 2009, the FDA approved OVA1® and trade test to help detect ovarian cancer. The OVA1 test identifies some women who will benefit from referral to a gynecological oncologist for surgery. The FDA approved the OVA1 testing for use in women who are over age 18, have an ovarian adnexal mass, and surgery is being planned, and the patient has not yet been referred to an oncologist. It is not FDA-approved for use as a screening tool or stand-alone diagnostic assay. The FDA has approved the use of HE4 and CA-125 for estimating the risk for ovarian cancer in women with a pelvic mass.

The ROMA™ testing received approval from the FDA in September 2011 as a predicate device of the OVA1 and includes the same indications as the OVA1 test.

The Overa™ was FDA-approved in March 2016 as a second-generation test (also referred to as next-generation OVA1®). This test replaces two of the five biomarkers in OVA1 with human epididymis secretory protein 4 and follicle stimulating hormone.

The Pennsylvania Department of Human Services Technology Assessment Group (TAG) workgroup meets quarterly to discuss issues revolving around new technologies and technologies or services that were previously considered to be a program exception. During this meeting, decisions are made as to whether or not certain technologies will be covered and how they will be covered. TAG's decisions are as follow:

- Option #1: Approved - Will be added to the Fee Schedule
- Option #2: Approved as Medically Effective - Will require Program Exception
- Option #3: Approved with (or denied due to) Limited/Minimal Evidence of Effectiveness - Will require Program Exception
- Option #4: Denied - Experimental/Investigational

As of October 2022, the TAG workgroup assigned an Option #3 decision for Ova1® Multi-Marker Ovarian Cancer Test, specifically CPT 81503.

Program Exception
CPT code 81503 requires a Program Exception. The ordering physician must provide a supporting statement indicating why the requested therapy or device is medically necessary, and the alternative options have been or are likely to be ineffective, adversely affect patient compliance, or cause an adverse reaction.

Summary of Literature

According to the American Cancer Society, it is estimated that approximately 21,410 women will receive a new diagnosis of ovarian cancer and that about 13,770 - women will die from ovarian cancer. Ovarian cancer ranks as the fifth most lethal cancer, accounting for more deaths than any other female reproductive system cancer. Approximately half of the women diagnosed with ovarian cancer are 63 years of age or older, and the disease is more common in white women than in African-American women. (American Cancer Society, 2020).

There are over 30 kinds of ovarian cancer, and they are classified by the cell type from which they originate. There are three main kinds of tumor cells: epithelial tumors, germ cell tumors, and stromal tumors. Epithelial tumors can be benign or cancerous and constitute approximately 90 percent of ovarian cancers. Germ cell tumors are a rare form of ovarian cancer that begin in the egg-producing cells of the ovaries. These types of tumors typically occur in the younger female population. Stromal tumors are also known as sex cord-stromal tumors and begin in the ovarian tissue that contains hormone-producing cells.

While a specific cause of ovarian cancer is not known at this time, several risk factors in ovarian cancer include age, obesity, inherited genes (e.g., BRCA1 or BCRA2), family history, a personal history of breast cancer, hormone replacement therapy, reproduction, fertility treatment, having an Eastern European or Ashkenazi Jewish background, and birth control use. There is no known method for the prevention of ovarian cancer. Several things have been associated with lowering the chance of ovarian cancer such as having used birth control pills for five or more years, having had a tubal ligation, having both ovaries removed, or a hysterectomy, giving birth and breast feeding for a year or more. There are no effective screening methods for ovarian cancer (CDC, 2022).

An adnexal mass (ie, masses of the ovary, fallopian tube, or surrounding tissues) is a very common gynecologic problem, and is found in females of all ages from fetus to the elderly. The principal goals of the evaluation of an adnexal mass are to determine whether the mass is "almost certainly benign," has a "reasonable chance of being malignant," and whether there is an urgent condition (eg, ectopic pregnancy, adnexal torsion) that requires prompt medical or surgical treatment (UpToDate, 2021). Most adnexal masses are detected incidentally on physical examination or at the time of pelvic imaging. Less commonly, a mass may present with symptoms of acute or intermittent pain. Management decisions often are influenced by the age and family history of the patient. Although most adnexal masses are benign, the main goal of the diagnostic evaluation is to exclude malignancy (ACOG, 2016).

Management of nonurgent adnexal mass conditions may involve:

- Expectant management is used when the mass is not suspicious for malignancy and there are no other indications for surgery or surveillance, no further follow-up is needed.
- Surveillance is an option if the suspicion of malignancy is low but has not been completely excluded. Surveillance usually includes one or more pelvic ultrasounds and/or measurement of serum tumor markers.
- Surgery may be performed when there is a high risk of malignancy, histologic diagnosis is desired, or the patient has persistent pain or other symptoms (UpToDate, 2021).

The current established tumor-marker testing is called CA-125. However, a variety of proteomic biomarkers have been developed. The OVA1, ROMA, and Overa biomarker tests have been FDA-approved as tools for determining if adnexal masses are cancer. These tests integrate results from multiple analytes into a risk score to predict the presence of cancer and are not to be used as stand-alone determinants.

The OVA1 and the Overa are utilized as an aid in additional assessment if a malignancy is present in situations in which the physician clinical and radiology results do not indicate cancer. The ROMA is also used with the physician clinical assessment in premenopausal or postmenopausal women with an adnexal mass to determine the likelihood of finding a malignancy. It has been proposed that these tests can identify those women who may benefit from a referral to a gynecologic specialist and/or surgical interventions. Additional uses of these biomarkers have been considered in other situations such as:

- Evaluation of patient with either clinical or radiologic evidence of malignancy
- Screening for ovarian cancer
- Preoperative evaluation of adnexal masses to triage for malignancy
- Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment
- Selection of individuals for surgery for an adnexal mass
- Evaluation of individuals with nonspecific signs or symptoms suggesting possible malignancy

The current National Comprehensive Cancer Network (NCCN) guidelines states that the Society of Gynecologic Oncology (SGO) and the FDA collectively advise that the OVA1 test should not be used as a screening tool to detect ovarian cancer in patients without any other signs of cancer, or as a stand-alone diagnostic tool. Based on data documenting an increased survival, the NCCN Guidelines Panel recommends that all patients with suspected ovarian malignancies (especially those with an adnexal mass) should undergo evaluation by an experienced gynecologic oncologist prior to surgery. Appropriate lab studies for patients presenting with clinical symptoms/signs of ovarian cancer include CBC and chemistry profile with liver function test. The Guidelines also suggest that specific biomarkers (serum HE4 and CA-125) along with an algorithm (ROMA) may be useful for determining whether a pelvic mass is malignant or benign (NCCN, 2022).

The NCCN Guidelines do include CA-125 testing as a possible element of preoperative workup, if clinically indicated. This recommendation is based on data showing that serum CA-125 levels correlate with extent of disease, and may have prognostic value, so may help in treatment planning. Serum CA-125 levels tend to correlate with the clinical course of disease, especially in those with elevated pretreatment levels, so can be useful for monitoring response to therapy and surveillance for recurrence (NCCN, 2022).

The American College of Obstetricians and Gynecologists (ACOG) published a Committee Opinion on the role of the obstetrician–gynecologist in the early detection of epithelial ovarian cancer in women at average risk. The opinion guidance states that the U.S. Food and Drug Administration has approved laboratory panels of multiple tumor marker (including CA-125) panels have not been rigorously evaluated among asymptomatic women without adnexal masses and have not been shown to improve early detection and survival rates for ovarian cancer in average-risk women (ACOG, 2021).

The American Society of Clinical Oncology (ASCO) published a journal review which indicates that marker human epididymis protein 4 (HE4), when combined with the serum cancer antigen CA-125, may result in improved early diagnosis of ovarian cancer. HE4 appears to complement CA-125 by being more often elevated in early ovarian cancer. The review also advises that continued improvement in the survival of patients with ovarian cancer requires that physicians who care for women have a high index of suspicion, make liberal use of transvaginal ultrasound, and order tumor marker assays that may aid in early diagnosis. The combination of CA-125 and HE4 will improve the chances that early ovarian cancers will be identified and that patients will be referred in a timely manner to a gynecologic oncologist for surgical evaluation and treatment. However, the combination of CA-125 and HE4 appears indicated for use in

symptomatic patients or in patients with an adnexal mass, there is no evidence that it would be indicated as a screening test in asymptomatic patients (Hoskins, 2013).

The U.S. Preventive Services Task Force (2018) and the American Academy of Family Physicians (2018) recommend that, for asymptomatic women without a known high-risk hereditary cancer syndrome, screening for ovarian/fallopian tube cancer is not helpful and may lead to harm. Transvaginal ultrasound and serum CA-125 testing are available procedures that can be used to evaluate women with signs or symptoms of ovarian cancer and have been evaluated in screening studies.

A 2019 comparative study looked to identify the power of tumor markers for predicting ovarian cancer according to menopausal status. The medical records of 876 women with ovarian cysts were retrospectively reviewed. Cancer antigen 125 (CA 125), human epididymis protein 4 (HE4), and Risk of Ovarian Malignancy Algorithm (ROMA) were analyzed. Sensitivity, specificity, and the receiver operating characteristic (ROC) curve analyses of these tumor markers were evaluated. The conclusion was that the discrimination power of tumor markers for ovarian cancer was different according to menopausal status. In predicting ovarian malignancy, ROMA was neither superior to HE4 in premenopausal women nor superior to CA 125 in postmenopausal women (Han, 2019).

Hayes, Inc.

- Overa (ASPiRA Labs)
    - **D2 Rating** - For use of the Overa test to aid in assessing the likelihood that an adnexal mass is malignant prior to planned surgery. Peer-reviewed publications supporting the use of Overa are needed. The lack of studies supporting analytical validity, clinical validity, and clinical utility of Overa preclude recommendations for use at this time. Studies are needed to demonstrate the analytical and clinical performance of the commercially available test in addition to studies that demonstrate a clear benefit in patient outcomes and treatment-making decisions.

- OVA1 (ASPiRA Labs)
    - **D2 Rating** - For the use of the OVA1 test to assess malignancy risk in adnexal masses in women with planned surgery. Additional studies are needed to support the use of OVA1 as an adjunct screening test. Peer-reviewed publications with analytical validity outcomes are needed. While there is some evidence of clinical validity of the test, clinical utility studies are needed to demonstrate a clear benefit in patient outcomes and treatment-making decisions.

Coding Requirements

Procedure Code

CPT Code	Description
81503	Oncology (ovarian), biochemical assays of 5 proteins (CA 125, apolipoprotein A-1, beta-2 microglobulin, transferring and pre-albumin), utilizing serum, algorithm reported as a risk score (OVA1)

Non-covered Procedure Codes

CPT Code	Description
81500	Oncology (ovarian), biochemical assays of two proteins (CA 125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score (ROMA)
0003U	Oncology (ovarian) biochemical assays of 5 proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score

Informational

Table of Variables

Variables	OVA1	ROMA	OVERA (Next Generation OVA1®)
Manufacturer	Quest Diagnostics	Roche Diagnostics	Vermillion
FDA Approval	July 2009	September 2011	March 2016
Biomarkers Measured			
Transthyretin	X		
Apolipoprotein AI	X		X
Beta-2-microglobulin	X		
Transferrin	X		X
CA 125 II	X	X	X
HE4 EIA		X	X
FSH			X
Score Range	0-10	0-10	0-10
Risk Categorization			
Premenopausal	< 5.0: low ≥ 5.0: high	≥ 1.3: high	< 5.0: low ≥ 5.0: high
Postmenopausal	< 4.4: low ≥ 4.4: high	≥ 2.77: high	

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

Reference Sources

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