MEDICAL POLICY	Ovarian Cancer: Multimarker Serum Testing (All Lines of Business Except Medicare)
Effective Date: 4/1/2022  4/1/2022 Medical Officer Date	Medical Policy Number: 43 Technology Assessment Committee Approved Date: 3/13; 2/14; 2/15; 2/16 Medical Policy Committee Approved Date: 3/17; 3/18; 8/19; 12/19; 6/2020; 03/2021; 3/2022

See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

Multianalyte serum biomarker testing, such as OVA1®, Overa™, OVA1plus® and ROMA® tests are considered **investigational and not covered** for the medical management of patients with a pelvic mass, including but not limited to, for determining malignancy in women with adnexal masses prior to surgery.

CPT CODES

All Lines of Business Except Medicare	
Not Covered	
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

DESCRIPTION

Ovarian Cancer

Most ovarian cancers are epithelial in origin, and their prognosis is related to the stage of the tumor at the time of diagnosis. If the cancer is detected while it is still localized to the ovary, the 5-year survival rate can be 90% to 95%. Therefore, early diagnosis may prove beneficial in decreasing the mortality of this disease. However, since ovarian cancer causes few or no symptoms early in its course, most women with this disease present at an advanced stage, when the 5-year survival rate is 20% to 35%. For this reason, much research has gone into developing a screening test for ovarian cancer.

Serum Biomarker Testing

Established methods of ovarian cancer screening include pelvic exams, pelvic ultrasound, and CA-125 tumor marker testing. However, the sensitivity of these available testing methods remains less than idea in detecting early stage ovarian disease. Serum protein biomarker tests have been suggested as a method for identifying malignancy in women presenting with adnexal mass. In women who are found to have a malignancy, the utility of testing may support routine referrals to clinical specialists, such as a gynecological oncologist.

Multiple proprietary tests have been cleared by the U.S. Food and Drug Administration (FDA):

OVA1®/OVERA™/OVA1plus® (ASPiRA LABS™)

The OVA1® test was originally offered by Quest Diagnostics and as of August 10, 2015, Quest Diagnostics no longer provides OVA1 testing, though it is offered through ASPiRA LABS™.[1] The OVA1® test is an in vitro diagnostic multivariate index assay (MIA) of protein biomarkers intended to further assess the likelihood of malignancy in women presenting with an ovarian adnexal mass prior to planned surgery. The OVA1 test combines results from 5 biomarkers: CA-125, prealbumin, apolipoprotein A-1, beta-2-

microglobulin, and transferrin. These 5 tests are combined into a single value between 0 and 10; a higher value corresponds to a higher risk of malignancy.

According to the manufacturer, the OVA1® test, "is a qualitative serum test that combines the results of five immunoassays into a single numerical result. It is indicated for women who meet the following criteria: over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. OVA1® is an aid to further assess the likelihood that malignancy is present when the physician's independent clinical and radiological evaluation does not indicate malignancy."[1]

OVERA, a second-generation Multivariate Index Assay (MIA2G), is a blood test intended for women with a pelvic mass who are planned for surgery. OVERA (MIA2G) incorporates different markers than OVA1 and a separate algorithm. OVERA (MIA2G) represents a significant improvement in positive predictive value, overall accuracy and a reduction in falsely elevated results and unnecessary referrals. With OVERA (MIA2G), healthcare providers can feel confident that they are using the best tool for ovarian cancer detection while minimizing the inefficiencies to the healthcare system and patient anxiety associated with falsely elevated results.

OVA1plus® is a reflex process which performs OVA1 and OVERA. It is intended for women with adnexal masses.

ROMA®

According to the manufacturer (Fujirebio®) the, "Risk of Ovarian Malignancy Algorithm (ROMA®) is a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA 125 II™ and menopausal status into a numerical score.

ROMA is intended to aid 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. ROMA is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. ROMA must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of serum biomarker testing as a predictive marker in women suspected of ovarian cancer. Below is a summary of the available evidence identified through February 2022.

In October of 2020 (updated in 2021), Hayes updated a genetic testing overview of the OVA1 test and maintained a **D2 rating** for the use of OVA1 testing to assess malignancy risk in adnexal masses in women with planned surgery.[2] This rating suggests there is insufficient evidence to assess the analytical and/or clinical validity of the test for the application assessed.

In January of 2020 (updated in 2021) Hayes updated a genetic testing overview of the Overa test and also assigned this test a **D2 rating** for the use of Overa to aid in assessing the likelihood that an adnexal mass is premalignant prior to planned surgery.[3]

In 2017, Hayes published a review of the literature regarding the use of the ROMA® test for assessment of adnexal masses.[4] Numerous studies were identified; however, Hayes reported, "the study abstracts present conflicting findings regarding the use of ROMA for the assessment of adnexal masses. Full-text review is required to confirm abstract content and, therefore, conclusions about the safety and effectiveness of this technology cannot be made until a full assessment has been completed."

In 2021, ECRI published a review of evidence regarding utility of OVA1 and ROMA testing in determining ovarian malignancy risk.[5,6] Studies published between 2011-2021 were included in the analysis. A total of 47 primary studies were included in for review, as well as 1 systematic review and 1 meta-analysis. Overall, the ECRI report concluded the evidence was inconclusive regarding the clinical utility of these test to improve patient outcomes as no study reported on the direct impact of testing on quality of life.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

The NCCN clinical practice guidelines (V1.2022) regarding ovarian cancer indicate the NCCN as well as the Society Gynecologic Oncology (SGO), the Food & Drug Administration (FDA), and the Mayo Clinic, "have stated that the OVA1 test should not be used as a screening tool to detect ovarian cancer."[7] In addition, the NCCN panel does not recommend the use of the ROMA test or other similar biomarker tests for determining the status of an undiagnosed pelvic mass.

POLICY SUMMARY

There is insufficient evidence regarding the use of multianalyte serum biomarker testing for the medical management of patients with a pelvic mass, including but not limited to, for determining malignancy in women with adnexal masses prior to surgery. There is a lack of studies which demonstrate the clinical utility of testing, or how testing may alter treatment decisions or improve health outcomes. No evidence-based clinical practice guidelines recommend the use of multianalyte serum biomarker testing in the management of ovarian cancer. Therefore, the use of this testing is considered investigational.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

REFERENCES

1. Quest Diagnostics™ Important Information about OVA1®. http://www.questdiagnostics.com/home/physicians/testing-services/by-test-name/ova1.html. Accessed 2/18/2022.
2. Hayes. Molecular Test Assessment. OVA1 (ASPiRA Labs). Updated 8/1/2021. https://evidence.hayesinc.com/report/gte.ova2060. Accessed 2/18/2022.
3. Hayes. Molecular Test Assessment. Overa (ASPiRA Labs). Updated 1/14/2021. https://evidence.hayesinc.com/report/gte.overa4078. Accessed 2/18/2022.
4. Hayes. Risk of Ovarian Malignancy Algorithm (ROMA) for Assessment of Adnexal Mass. Archived. Webpage removed. Accessed 2/18/2022.
5. ECRI. Risk of Ovarian Malignancy Algorithm (ROMA)(Fujirebio Diagnostics, Inc.) To Assess the Risk of Malignancy of an Ovarian Mass. Published 9/2021. https://www.ecri.org/components/ECRIgene/Documents/EG0079.pdf. Accessed 2/18/2022.
6. ECRI. Overa Multivariate Biomarker Test (Aspira Women's Health, Inc) for Assessing Risk of Malignancy of an Ovarian Mass. Published 5/2021. https://www.ecri.org/components/ECRIgene/Documents/EG0078.pdf. Accessed 2/18/2022.
7. National Comprehensive Cancer Network. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (V1.2022). . https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed 2/20/2022.