
Ovarian Cancer: Multimarker Serum Testing

MEDICAL POLICY NUMBER: 43

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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 Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. 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. 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.

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”).

PLAN PRODUCT AND BENEFIT APPLICATION

Commercial

Medicaid/OHP*

Medicare**

*Medicaid/OHP 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.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered “**not medically necessary**” for Medicare members.

COVERAGE CRITERIA

- I. Multianalyte serum biomarker testing, such as OVA1[®], Overa[™], OVA1plus[®] and ROMA[®] tests are considered **not medically necessary** 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.

Link to [Evidence Summary](#)

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be [accessed here](#).

POLICY GUIDELINES

BACKGROUND

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 ideal 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.

OvaWatchSM is a non-invasive test intended for use in assessing the risk of ovarian cancer for women with adnexal masses that have been considered indeterminate or benign in initial clinical assessment. This test reviews seven tumor biomarkers as well as age and menopausal status.

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.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

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 January 2023.

In 2022, 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 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 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 (V1.2023) 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.

EVIDENCE 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.

BILLING GUIDELINES AND CODING

CODES*		
CPT	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
	0375U	Oncology (ovarian), biochemical assays of 7 proteins (follicle stimulating hormone, human epididymis protein 4, apolipoprotein A-1, transferrin, beta-2 macroglobulin, prealbumin [ie, transthyretin], and cancer antigen 125), algorithm reported as ovarian cancer risk score
	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

*Coding Notes:

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company [Medical Policy](#), [Reimbursement Policy](#), [Pharmacy Policy](#) and [Provider Information website](#) for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. Quest Diagnostics™ Important Information about OVA1®.
<http://www.questdiagnostics.com/home/physicians/testing-services/by-test-name/ova1.html>. Accessed 2/2/2023.
2. Hayes. Molecular Test Assessment. OVA1 (ASPIRA Labs).
<https://evidence.hayesinc.com/report/gte.ova2060>. Published 2021. Accessed 2/2/2023.

3. Hayes. Molecular Test Assessment. Overa (ASPiRA Labs). <https://evidence.hayesinc.com/report/gte.overa4078>. Published 2022. Accessed 2/3/2023.
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 2/2/2023.
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 2/2/2023.
7. National Comprehensive Cancer Network. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (V1.2023). . https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed 2/2/2023.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
4/2023	Interim update. 4/1 code update.
6/2023	Changed denial from “investigational” to “not medically necessary.”