

Local Coverage Determination (LCD): Multimarker Serum Tests Related to Ovarian Cancer Testing (L38371)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
National Government Services, Inc.	MAC - Part A	06101 - MAC A	J - 06	Illinois
National Government Services, Inc.	MAC - Part B	06102 - MAC B	J - 06	Illinois
National Government Services, Inc.	MAC - Part A	06201 - MAC A	J - 06	Minnesota
National Government Services, Inc.	MAC - Part B	06202 - MAC B	J - 06	Minnesota
National Government Services, Inc.	MAC - Part A	06301 - MAC A	J - 06	Wisconsin
National Government Services, Inc.	MAC - Part B	06302 - MAC B	J - 06	Wisconsin
National Government Services, Inc.	A and B and HHH MAC	13101 - MAC A	J - K	Connecticut
National Government Services, Inc.	A and B and HHH MAC	13102 - MAC B	J - K	Connecticut
National Government Services, Inc.	A and B and HHH MAC	13201 - MAC A	J - K	New York - Entire State
National Government Services, Inc.	A and B and HHH MAC	13202 - MAC B	J - K	New York - Downstate
National Government Services, Inc.	A and B and HHH MAC	13282 - MAC B	J - K	New York - Upstate
National Government Services, Inc.	A and B and HHH MAC	13292 - MAC B	J - K	New York - Queens
National Government Services, Inc.	A and B and HHH MAC	14111 - MAC A	J - K	Maine
National Government Services, Inc.	A and B and HHH MAC	14112 - MAC B	J - K	Maine
National Government Services, Inc.	A and B and HHH MAC	14211 - MAC A	J - K	Massachusetts

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
National Government Services, Inc.	A and B and HHH MAC	14212 - MAC B	J - K	Massachusetts
National Government Services, Inc.	A and B and HHH MAC	14311 - MAC A	J - K	New Hampshire
National Government Services, Inc.	A and B and HHH MAC	14312 - MAC B	J - K	New Hampshire
National Government Services, Inc.	A and B and HHH MAC	14411 - MAC A	J - K	Rhode Island
National Government Services, Inc.	A and B and HHH MAC	14412 - MAC B	J - K	Rhode Island
National Government Services, Inc.	A and B and HHH MAC	14511 - MAC A	J - K	Vermont
National Government Services, Inc.	A and B and HHH MAC	14512 - MAC B	J - K	Vermont

LCD Information

Document Information

LCD ID

L38371

Original Effective Date

For services performed on or after 07/01/2020

LCD Title

Multimarker Serum Tests Related to Ovarian Cancer Testing

Revision Effective Date

N/A

Proposed LCD in Comment Period

N/A

Revision Ending Date

N/A

Source Proposed LCD

DL38371

Retirement Date

N/A

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

CPT codes, descriptions and other data only are copyright 2020 American Medical Association. All Rights Reserved. Applicable FARS/HHSARS apply.

Notice Period Start Date

05/14/2020

Notice Period End Date

06/30/2020

Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not

recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein.

Current Dental Terminology © 2020 American Dental Association. All rights reserved.

Copyright © 2013 - 2021, the American Hospital Association, Chicago, Illinois. Reproduced by CMS with permission. No portion of the American Hospital Association (AHA) copyrighted materials contained within this publication may be copied without the express written consent of the AHA. AHA copyrighted materials including the UB-04 codes and descriptions may not be removed, copied, or utilized within any software, product, service, solution or derivative work without the written consent of the AHA. If an entity wishes to utilize any AHA materials, please contact the AHA at 312-893-6816. Making copies or utilizing the content of the UB-04 Manual, including the codes and/or descriptions, for internal purposes, resale and/or to be used in any product or publication; creating any modified or derivative work of the UB-04 Manual and/or codes and descriptions; and/or making any commercial use of UB-04 Manual or any portion thereof, including the codes and/or descriptions, is only authorized with an express license from the American Hospital Association. To license the electronic data file of UB-04 Data Specifications, contact Tim Carlson at (312) 893-6816. You may also contact us at ub04@aha.org.

CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA):

Section 1862(a)(1)(A) excludes expenses incurred for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Section 1833(e) prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

Section 1862(a)(7) excludes routine physical examinations, unless otherwise covered by statute.

Code of Federal Regulations:

42 CFR, Section 410.32, indicates that diagnostic tests may only be ordered by the treating physician (or other treating practitioner acting within the scope of his or her license and Medicare requirements) who furnishes a

consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem. Tests not ordered by the physician (or other qualified non-physician provider) who is treating the beneficiary are not reasonable and necessary (see Sec. 411.15(k)(1) of this chapter).

CMS Publications:

CMS Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 16:
20 Services Not Reasonable and Necessary

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This is a non-coverage policy for all multi marker serum tests related to ovarian cancer testing.

History/Background and/or General Information

Ovarian cancer accounts for 2.5% of all malignancies in women and 5% of all cancer deaths due to the disease's relatively high fatality rate.¹ The most common histologic subtype of ovarian cancer is epithelial ovarian cancer which is most commonly detected in advanced stage (65% of cases are stage II or IV) when the cure rate is only 18%.² The incidence rate of ovarian cancer has dropped 29%, from 16.6 (per 100,000) in 1985 to 11.8 in 2014 and the mortality rate for ovarian cancer has declined 33% from 1976 (10.0 per 100,000) to 2015 (6.7 per 100,000) due to reductions in incidence and improvements in treatment.³ Nevertheless, improving early detection and prevention is a research priority because local-stage disease (confined to the ovary) has a 5-year relative survival rate of 93%.¹ Currently, there is no strategy for early detection of ovarian cancer that reduces ovarian cancer mortality.²

Ovarian cancer is staged surgically and the prognosis of ovarian cancer is closely related to the stage of the tumor at the time of diagnosis. The early involvement of the gynecologic oncologist is associated with improved survival and outcomes due to increased adherence to guidelines including optimal cytoreductive surgery and chemotherapy.⁴⁻⁸ As a result, NCCN guidelines recommend that all patients with suspected ovarian malignancies undergo primary assessment and debulking by a gynecologic oncologist as this results in a survival advantage.⁹ The proportion of women with ovarian cancer who undergo this surgery by a gynecologic oncologist can be as low as 33%.^{10,11}

Per the American College of Obstetrics and Gynecology (ACOG), the evaluation of an adnexal mass should consider individual patient characteristics, physical examination findings, imaging results, and serum marker levels to help separate masses into the categories of probably benign, uncertain, and likely malignant, which can then guide appropriate management.¹² Per ACOG, the most extensively studied serum marker is cancer antigen 125 (CA 125), which is a protein associated with epithelial ovarian malignancies, but it is also frequently expressed at lower levels by nonmalignant conditions. In evaluating adnexal masses, CA 125 measurement is most useful in postmenopausal women and in identifying nonmucinous epithelial cancer. The CA 125 level is elevated in 80% of patients with epithelial ovarian cancer but in only 50% of patients with stage I disease.¹² Therefore, CA 125 is not considered to be an appropriate screening test for ovarian cancer.

Current NCCN guidelines recommend that patients with a suspicious pelvic mass and/or symptoms (bloating, pelvic/abdominal pain, difficult eating) have a CA 125 or other tumor markers as clinically indicated as part of the workup.⁹ ACOG guidelines (Level B evidence) state "the combination of an elevated CA 125 level and a pelvic mass in a postmenopausal woman is highly suspicious for malignancy, and patients with these findings should be referred to or treated in consultation with a gynecologic oncologist".¹²

Various serum based tests have been proposed to triage patients with adnexal masses. A suggested use of the tests

is to identify women who have a higher likelihood of malignant disease and may benefit from referral to a gynecologic oncologist. These tests are combinations of several individual serum laboratory tests known as multi-analyte assays with algorithmic analyses (MAAA) and are performed on a blood sample by a reference laboratory using a proprietary algorithm.

There are currently three FDA cleared tests: Ova1[®], Overa[®], and ROMA[™].

Ova 1[®]

The OVA1[®] test uses proprietary OvaCalc Software to incorporate the values for five analytes from separately run immunoassays into a single numerical score between 0.0 and 10.0. The five analytes are Cancer Antigen 125 (CA 125), Transferrin (TRF), Apolipoprotein A-1 (APO A-1), Beta-2 Microglobulin (B2M), and Prealbumin (TT). This score is then interpreted in the context of menopausal or premenopausal status.

According to the FDA 510K decision summary, the Ova1[®] test is intended for women greater than or equal to 18 years of age who present with an ovarian adnexal *mass for which surgery is planned and who are not yet referred to an oncologist*.¹³ The assay is intended for use as a prognostic indicator of a woman's likelihood that malignancy is present when the physician's independent clinical and radiological evaluation does not indicate malignancy. The test is not intended to be used as a screen or standalone diagnostic assay and is intended for use in conjunction with imaging studies and clinical assessments in women for whom surgical intervention is planned.

Overa[®]

This is an assay that uses 5 protein biomarkers: Cancer Antigen 125 (CA 125), Transferrin (TRF), Apolipoprotein A-1 (APO A-1), Follicle-Stimulating Hormone (FSH), and Human Epididymis Protein 4 (HE4) the results of which are combined to calculate a single cancer risk score using proprietary software – OvaCALC. This score is then interpreted using menopausal or premenopausal status. According to the FDA 510K decision summary document, Overa[®] (referred to as OVA1 Next Generation or Multivariate Index Assay (MIA2G)) is intended for women greater than or equal to 18 years of age who present with an ovarian adnexal mass for which surgery is planned and who are not yet referred to an oncologist. The assay is intended for use as a prognostic indicator of a woman's likelihood that malignancy is present when the physician's independent clinical and radiological evaluation does not indicate malignancy.¹⁴

Risk of Ovarian Malignancy Algorithm (ROMA[™])

This is an assay that combines HE4, CA 125 and menopausal status into a numerical score. According to the initial FDA 510K clearance received, ROMA[™] is intended to aid in assessing whether a premenopausal or post-menopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. 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. ROMA[™] must be interpreted in conjunction with an independent clinical and radiological assessment.^{15,16}

Each of the above tests have black box warnings stating "PRECAUTION: Test should not be used without an independent clinical and imaging evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of this test carries a risk of unnecessary testing, surgery, and/or delayed diagnosis."

Summary of Evidence

A literature search was performed in PubMed. Studies identified for potential inclusion were obtained from searches in PubMed with no date limits. Search terms included "OVA1", "multivariate index assay", "adnexal mass", "Overa", "OVA1 next generation", "second generation multivariate index", "Risk of Ovarian Malignancy Algorithm", "ovarian mass assessment" or "adnexal mass assessment". Studies had to have been published in peer reviewed journals and include a patient population that met the FDA clearance criteria which includes over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist.

OVA1®

Fifteen studies were identified for OVA1®. Nine were excluded due to a variety of reasons including: OVA1® was not the index test, OVA1® performance assessed as an individual test; test not performed with the intended FDA-cleared intended usage as an adjunct test, the primary endpoint of the study was to examine how pelvic imaging influenced the OVA1® score, not the performance of the OVA1® test, cost-evaluation studies, and use of OVA1® for indications other than adnexal mass assessment.¹⁷⁻²⁵

Five of the six studies had limitations such as including patients who had been evaluated by a gynecologic oncologist prior to being tested and the studies contained overlapping patient populations.²⁶⁻³⁰ Therefore, the results may not be generalizable or broadly applicable. All the studies were funded by the test manufacturer.

There were 5 studies that evaluated the clinical validity of Ova1®.

The initial study was a prospective multi institutional cohort study of 590 women from 27 sites across the United States which sought to assess the effectiveness of OVA1® in identifying high-risk ovarian tumors.²⁶ Assessment by a non-gynecologic-oncologist physician plus Ova1® had a sensitivity of 92%, a Negative Predictive Value (NPV) of 93%, and a Positive Predictive Value (PPV) of 36% for predicting an ovarian malignancy. Over half the patients were enrolled by gynecologic oncologists, which may have biased these results. Given that this test is meant to determine the need for involvement of a gynecologic oncologist when it has already been predetermined that an adnexal mass requires surgery, including gynecologic oncologists in the trial was a significant limitation in determining the clinical validity of Ova1®. Additionally, the low PPV may be associated with increased false positives, creating potential patient anxiety/stress and unnecessary procedures. Lastly, not all results were reported separately for patients enrolled by non-gynecologic oncologists. This study was designated as "Level III Evidence" by the journal *Obstetrics and Gynecology*.

	Non-Gynecologic Oncologist - Physician Assessment plus Multivariate Index Assay	Gynecologic Oncologist - Physician Assessment plus Multivariate Index Assay
Sensitivity (%)	92	99
Specificity (%)	42	26
Positive Predictive Value (%)	36	43

Negative Predictive Value (%)	93	98
-------------------------------	----	----

Ueland, 2011

In a subsequent study of 494 patients, OVA1[®] demonstrated an overall sensitivity and NPV of 95.7% and 98.1% when combined with clinical impression, respectively.²⁸ Similar to the initial trial, the specificity and PPV were low (50.7% and 30.8%, respectively) and clinical assessment was by non-gynecologic oncologists in half the patients. OVA1[®] correctly identified ovarian malignancy in 91.4%, compared to 65.7% for CA 125. The study also found that both clinical impression and CA 125 were more accurate than OVA1[®] in correctly identifying benign disease. Menopausal status did not appear to have an impact on the OVA1[®] test performance; receiver operating characteristic (ROC) curves stratified by menopausal status showed similar discriminative ability at premenopausal area under the curve (AUC) of 0.906 (95% CI, 0.847-0.975) and a postmenopausal AUC of 0.898 (95% CI, 0.847-0.948).

The objective of the third study was to determine the projected impact on referral patterns of patients undergoing surgery for an adnexal mass after initial evaluation by a nongynecologic oncologist using OVA1[®], CA 125, modified-ACOG referral guidelines, and clinical assessment using the combined datasets of the two previously reported studies.³⁰ The Dearing modified ACOG guidelines for consultation with a gynecologic oncologist were used for postmenopausal patients meeting one or more of the following criteria: an elevated CA 125 (>35 units/mL), nodular or fixed pelvic mass, ascites, or evidence of abdominal or distant metastasis. OVA1[®] demonstrated higher sensitivity (90.2%) compared with clinical assessment (73.2%), CA 125 (68.3%) and modified ACOG guidelines (79.3%). The authors also found that use of OVA1[®] as a risk stratification test was associated with a gynecologic oncology referral rate of 55.7% comparable to actual clinical practice (60.0%). The authors noted that "the factors affecting utilization of gynecologic oncology resources at the time of suspected ovarian cancer diagnosis appear to be multifactorial".

Stratification of test performance for detection of malignancy by menopausal status did not appear to have an impact on the test performance.

	Premenopausal	Postmenopausal
Sensitivity %	87.7	91.6
Specificity %	60.5	43.1
PPV %	25.6	41.9
NPV %	96.9	92.0

Bristow, 2013

Utilizing the same patient pool as the previously noted studies, Ware-Miller et al aimed to estimate the performance of OVA1[®] with ACOG guidelines and the effect of replacing CA 125 with the multivariate index assay.²⁷ This study demonstrated that replacing the CA125 with OVA1[®] in the ACOG guidelines increased the sensitivity from 77% to 94% and NPV from 87% to 93%. However, there was a concomitant decrease in the specificity from 68% to 35%,

and in the PPV from 52% to 40%. The ACOG guidelines with OVA1[®] identified 79% (15/19) of missed malignancies in premenopausal, and 67% (12/18) of malignancies missed in postmenopausal women compared with the ACOG criteria alone. This study was limited due to the fact that some patient included in the study were already under a gynecologic oncologist's care, results were not presented separately by physician specialty and there was no long-term follow-up on outcomes.

Longoria et al analyzed of the effectiveness of OVA1[®] in identifying early-stage ovarian malignancy compared to clinical assessment, CA 125, and modified ACOG guidelines among women undergoing surgery for an adnexal mass.²⁹ The performance of OVA1[®] demonstrated a high sensitivity in identifying early-stage ovarian malignancy when compared with clinical assessment, CA 125, and modified ACOG guidelines. The sensitivity was found to be 91.9% for OVA1[®] testing alone and 95.3% when OVA1[®] testing was combined with clinical assessment. The specificity with and without clinical assessment was 44.2% and 49.4%, respectively. Twenty-five percent of the patient population was enrolled by a gynecologic oncologist which may have inflated the prevalence of malignancy in the study population versus the OVA1[®] intended use population. This study was designated as "Level III Evidence" by the journal *Obstetrics and Gynecology*.

The sixth study by Eskander et al was a chart review assessing the ability of OVA1[®] to drive referrals of ovarian cancer patients to gynecologic oncologists prior to their first surgical intervention.³¹ Data for the study were retrospectively collected through an online medical chart review from 22 obstetrician/gynecologists. The study included 136 patients who had received an elevated-risk OVA1[®] score, with 122 of 136 patients undergoing surgery for the removal of an adnexal mass. Data were collected through chart extraction forms. Completed forms were aggregated for analysis and assessed for the rates at which obstetrician/gynecologists referred patients with an elevated OVA1[®] score to a gynecologic oncologist prior to surgery. Results showed that 80% of patients with an elevated OVA1[®] score were referred to a gynecologic oncologist prior to surgery, with postmenopausal and premenopausal patients showing similar referral rates of 82% and 78%, respectively. Additionally, an appropriate referral to a gynecologic oncologist was seen in 95% of patients with primary ovarian malignancies with an elevated OVA1[®] score. The study was limited by a small patient population and biases inherent to a retrospective chart review study, which could impact the rates of malignancy and referrals. Lastly, patient outcomes such as morbidity and mortality were not assessed, nor were other long-term outcomes.

Overa[®]

Only one study met inclusion criteria and it addressed clinical validity. There were no peer reviewed studies addressing analytical or clinical utility that met inclusion criteria.¹⁹

Clinical validity was evaluated in a non-concurrent prospective study of 493 preoperatively collected serum specimens from premenopausal and postmenopausal women presenting with an adnexal mass requiring surgical intervention from the same population from the aforementioned study by Bristow.²⁸ Overa[®] test scores were determined based on the analysis of archived serum specimens, and the patients were stratified into low or high risk groups for finding malignancy on surgery. The analysis examined whether patient referral to a gynecologic oncologist was supported when dual assessment was determined to be positive (either Overa[®] or clinical assessment was positive, or both were positive). A dual assessment was considered negative when both Overa[®] and clinical assessment were negative.

Among the 493 study participants, 92 (19%) had a final pathology diagnosis of malignancy. The clinical performance of the Overa[®] assay, when combined with presurgical physician assessment demonstrated:

- Sensitivity of 93.5%
- Specificity of 64.8%

- PPV of 37.9%
- NPV of 97.7%

Overall, the addition of Overa[®] testing to presurgical physician assessment correctly identified 75% (P<0.001) of the malignancies missed by physician assessment alone.

This study had several limitations, including a small patient population and a retrospective study design. Additionally, preoperative physician assessment was not uniform across the patient population and this may have introduced bias into the study. Also the method used for combining clinical assessment and Overa[®] test results was to consider the test positive if either clinical assessment or Overa[®] test was positive. Thus, in practice, Overa[®] testing would not be necessary if clinical assessment alone indicated cancer. Using Overa[®] testing in this manner guarantees that Overa[®] testing will be more sensitive and less specific than clinical assessment alone, even if it has no better than chance capability of detecting ovarian cancer. Sensitivity improved from 74% to 94% and specificity decreased from 93% to 65%. Finally, this study was funded by the manufacturer. This single study provides very-low-quality evidence for the clinical validity of the Overa[®] test.

ROMATM

Wang et al 2014 published a meta-analysis of studies evaluating the diagnostic accuracy of the ROMATM algorithm and comparing it to the performance of single markers HE4 and CA 125.³² To be included in the meta-analysis, studies had to investigate both HE4 and CA 125 or calculate ROMATM, include women with ovarian cancer and benign gynecologic disease, use pathology diagnosis as the reference standard, and collect blood samples before treatment was initiated. A total of 32 studies met these inclusion criteria; six of these were conducted in the United States. Findings of the overall pooled analysis of diagnostic accuracy are presented in Table 1. Findings were similar when diagnostic performance in premenopausal women and postmenopausal women were evaluated separately. ROMATM had similar or higher sensitivity than HE4 and CA 125, and HE4 had the highest specificity.

Table 1. Diagnostic Performance of ROMATM compared with HE4 and CA 125 from Wang et al: Meta-analysis findings

	No. Studies	Sensitivity	Specificity
ROMA TM	14	85.3 (81.2-88.6)	82.4 (77.4-86.5)
HE4	28	76.3 (72.0-80.1)	93.6 (90.0-95.9)
CA 125	28	79.2 (74.0-83.6)	82.1 (76.6- 86.5)

Dayyani et al conducted a meta-analysis comparing ROMATM with HE4 and CA 125 in patients with suspected ovarian cancer.³³ Six studies met the inclusion criteria, four of which were included in the Wang et al meta-analysis. Two studies were published in 2014 or later. ROMATM had statistically higher area under the curve (AUC) values than either HE4 or CA 125 alone (0.921, vs 0.899, and 0.883 for HE4 and CA 125, respectively). Findings of the pooled analysis of diagnostic accuracy are shown in Table 2.

Table 2. Diagnostic Performance of ROMATM compared with HE4 and CA 125 from Dayyani et al: Meta-analysis findings ROMATM

	No. Studies	Sensitivity % (95% CI)	Specificity %, 95% CI
ROMA™	6	87.3 (75.2-94.0)	85.5 (71.9-93.2)
HE4	6	68.2 (69.3-90.1)	85.1 (71.6-92.8)
CA 125	6	79.6 (66.3-88.5)	82.5 (66.2- 91.9)

Since the publication of the Wang et al and Dayyani et al meta-analyses, multiple studies have described the use of ROMA™ in populations of women in whom decisions to pursue surgery had been made, including Al Musalhi et al³⁴ (n=213 cases), Cho et al³⁵ (n=90 cases), Terlikowska et al³⁶ (n=224 cases), and Minar et al³⁷ (n=267).

Diagnostic performance of the ROMA™ test was evaluated for FDA approval in a prospective, blinded clinical trial using thirteen demographically mixed subject enrollment sites with company sponsorship (K103358).¹⁶ Patients all presented with an adnexal mass and were scheduled to undergo surgery. An Initial Cancer Risk Assessment (ICRA) was performed to determine the detection of benign versus malignant lesions before testing. The prevalence of cancer was 15%.

Using pathologic diagnosis as the gold standard, test performance, when combined with presurgical assessment for benign disease, was as follows in the hands of a mixed population of generalist and specialist physicians:

	ICRA alone	ICRA with ROMA testing
Sensitivity	77%	91%
Specificity	84%	67%
PPV	46%	33%
NPV	96%	98%

Both tests, when added to pre-testing clinical assessment, produced a fall in the positive predictive value of diagnosis with a small increase in the negative predictive value. The changes observed in the negative predictive value were of uncertain statistical and clinical significance.

A study by Moore et al evaluated ROMA™ in conjunction with clinical assessment, using either positive clinical assessment or positive ROMA™ as a positive test (similar to the recommended usage for OVA1®).³⁸ Using this method of combining tests guarantees a higher sensitivity and lower specificity for the combined test than for either test alone. Used in this way, ROMA™ would only need to be evaluated in patients with a negative clinical assessment. In this study, 461 women were enrolled, of whom a total of 86 (19%) had a malignancy. Combined assessment improved sensitivity from 77.9% to 89.7%, but worsened specificity from 84.3% to 67.2%.

It is important to note that all of the above literature assessed ROMA™ as a stand-alone test and did not evaluate diagnostic performance in conjunction with clinical assessment, as the test was intended to be used. Therefore, the ability to draw conclusions regarding the test's diagnostic performance is limited.

Evidence-Based Practice Guidelines, Position Statements, and Third Party Review

The American Congress of Obstetricians and Gynecologists (ACOG)

ACOG recommend at level C scientific evidence (based primarily on consensus and expert opinion) that physicians can use serum biomarker panels as an alternative to CA125 level alone when evaluating women with adnexal masses to determine the need for referral to or consultation with a gynecologic oncologist when an adnexal mass requires surgery. Consultation with or referral to a gynecologic oncologist is recommended at a level B scientific evidence (based on limited or inconsistent scientific evidence) for patients with an elevated score on a formal risk assessment test.¹²

The Society for Gynecologic Oncology (SGO)

In May 2013, the Society for Gynecologic Oncology (SGO) issued the following position statement on multiplex serum testing for women with pelvic masses³⁹:

"Blood levels of five proteins in women with a known ovarian mass have been reported to change when ovarian cancer is present. Tests measuring these proteins may be useful in identifying women who should be referred to a gynecologic oncologist. Recent data have suggested that such tests, along with physician clinical assessment, may improve detection rates of malignancies among women with pelvic masses planning surgery. Results from such tests should not be interpreted independently, nor be used in place of a physician's clinical assessment. Physicians are strongly encouraged to reference the American Congress of Obstetricians and Gynecologists' 2011 Committee Opinion "The Role of the Obstetrician-Gynecologist in the Early Detection of Epithelial Ovarian Cancer" to determine an appropriate care plan for their patients." SGO does not formally endorse or promote any specific products or brands.

A review by Hayes regarding the use of the OVA1® test to assess malignancy risk in adnexal masses in women with planned surgery was rated as "D2" (there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management).⁴⁰ The review concluded that "there is no peer-reviewed evidence for analytical validity, very-low-quality evidence for clinical utility, and low-quality evidence for clinical validity for the use of the OVA1® test. Individual study quality for publications supporting the OVA1® test ranged from poor to very poor. The lack of studies supporting analytical validity and clinical utility downgrades the overall body of evidence for OVA1®. Additionally, clinical validity studies evaluated had several limitations and consisted of low-quality and very-low-quality evidence".

The National Cancer Institute (NCI)⁴¹

[Level of evidence: 5](#)

Proteomics

Initially, mass spectroscopy of serum proteins was combined with complex analytic algorithms to identify protein patterns that might distinguish between ovarian cancer cases and controls.⁴² This approach assumed that pattern recognition alone would be sufficient to permit such discrimination, and that identification of the specific proteins responsible for the patterns identified was not required. This strategy was modified, using similar laboratory tools, to identify finite numbers of specific known serum markers that may be used in place of, or in conjunction with, CA 125 measurements for the early detection of cancer.⁴³ These studies^{44,45} have generally been small case-control studies that are limited by sample size and the number of early-stage cancer cases included. Further evaluation is needed to determine whether any additional markers identified in this fashion have clinical utility for the early detection of ovarian cancer in the unselected clinical population of interest.

National Comprehensive Cancer Network (NCCN)

The NCCN ovarian cancer guidelines (v1.2020) includes the following statement⁴⁶:

“It has been suggested that specific biomarkers (serum HE4 and CA 125) along with an algorithm (Risk of Ovarian Malignancy Algorithm [ROMATM]) may be useful for determining whether a pelvic mass is malignant or benign. The FDA has approved the use of HE4 and CA 125 for estimating the risk of ovarian cancer in women with a pelvic mass. Currently, the NCCN Panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass.”

Of note is the fact that the NCCN Ovarian Cancer panel has twice (2016, 2017) unanimously voted down the request by manufacturer to modify the wording in the guidelines to replace CA 125 by OVA1[®] and /or MIA or other tumor markers in the work up section of the guidelines, to revise the primary treatment section to include establishing a baseline CA 125 as clinically indicated either from OVA1[®] and or MIA result or separately and to change the wording in section M-5 to indicate that the guidelines recommend that anyone with an elevated OVA1[®] result undergo surgery by an experienced gynecologic oncologist.

National Institute for Health and Care Excellence

- There is currently not enough evidence to recommend the routine adoption of the IOTA ADNEX model, Overa[®], RMI I (at thresholds other than 200 or 250), ROMATM or IOTA Simple Rules in secondary care in the NHS to help decide whether to refer people with suspected ovarian cancer to a specialist multidisciplinary team (MDT).
- The NICE guideline on [ovarian cancer](#) recommends that people with an RMI I of 250 or more are referred to a specialist MDT. Evidence suggests that there is no substantial change in accuracy if the threshold for RMI I is lowered to 200.
- The IOTA ADNEX model, Overa[®], RMI I (at thresholds other than 250), ROMATM and IOTA Simple Rules show promise. Further research is recommended on test accuracy and the impact of the test results on clinical decision-making.⁴⁷

Analysis of Evidence (Rationale for Determination)

In summary, improving early detection and prevention of ovarian cancer is a priority in women's health. To date, none of the multimarker serum tests addressed in this policy have been shown to reliably screen, improve quality of life, or decrease mortality in women with ovarian cancer. Given that the literature has the limitations as outlined above and in conjunction with the position of the American College of Obstetrics and Gynecology, The Society for Gynecologic Oncology, and the National Cancer Institute, coverage of these tests must await larger, prospective, non-industry funded data on long term outcomes including quality of life, improvement in survival and impact on mortality in women with ovarian cancer.

General Information

Associated Information

N/A

Sources of Information

April 11, 2019 CAC Meeting

Bibliography

1. Howlader N NA, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2014, National Cancer Institute Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission. 2017.
2. Committee on Gynecologic Practice SoGO. Committee Opinion No. 716: The Role of the Obstetrician-Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk. *Obstet Gynecol.* 2017;130(3):e146-e149.
3. Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(4):284-296.
4. Carney ME, Lancaster JM, Ford C, Tsodikov A, Wiggins CL. A population-based study of patterns of care for ovarian cancer: who is seen by a gynecologic oncologist and who is not? *Gynecol Oncol.* 2002;84(1):36-42.
5. Engelen MJ, van der Zee AG, de Vries EG, Willemse PH. Debulking surgery for ovarian epithelial cancer performed by a gynaecological oncologist improved survival compared with less specialised surgeons. *Cancer Treat Rev.* 2006;32(4):320-323.
6. Mercado C, Zingmond D, Karlan BY, et al. Quality of care in advanced ovarian cancer: the importance of provider specialty. *Gynecol Oncol.* 2010;117(1):18-22.
7. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. *Gynecol Oncol.* 2007;105(3):801-812.
8. Chan JK, Kapp DS, Shin JY, et al. Influence of the gynecologic oncologist on the survival of ovarian cancer patients. *Obstet Gynecol.* 2007;109(6):1342-1350.
9. Armstrong DK. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. *NCCNorg.* 2020;Version 1.2020
10. Morgan RJ, Jr., Armstrong DK, Alvarez RD, et al. Ovarian Cancer, Version 1.2016, NCCN Clinical Practice

- Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(9):1134-1163.
11. Earle CC, Schrag D, Neville BA, et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. *J Natl Cancer Inst*. 2006;98(3):172-180.
 12. American College of Obstetrics and Gynecology Committee on Practice B-G. Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. *Obstet Gynecol*. 2016;128(5):e210-e226.
 13. Test FO. FDA 510(k) Number: k081754 https://www.accessdata.fda.gov/cdrh_docs/reviews/K081754.pdf.
 14. U.S. Food and Drug Administration. 510(k) Substantial Equivalence Determination Decision Summary: Overa™ Test (K150588). Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf15/k150588pdf.
 15. Oncologists. SoG. Multiplex Serum Testing for Women with Pelvic Mass (May 2013). Available from: <https://www.sgo.org/newsroom/position-statements-2/multiplex-serum-testing-for-women-with-pelvic-mass/>. 2013.
 16. (K103358).; USFaDAkSEDDSRRT. Available from: http://www.accessdata.fda.gov/cdrh_docs/reviews/K103358pdf.
 17. Amonkar SD, Bertenshaw GP, Chen TH, et al. Development and preliminary evaluation of a multivariate index assay for ovarian cancer. *PLoS One*. 2009;4(2):e4599.
 18. Yip P, Chen TH, Seshaiya P, et al. Comprehensive serum profiling for the discovery of epithelial ovarian cancer biomarkers. *PLoS One*. 2011;6(12):e29533.
 19. Coleman RL, Herzog TJ, Chan DW, et al. Validation of a second-generation multivariate index assay for malignancy risk of adnexal masses. *Am J Obstet Gynecol*. 2016;215(1):82 e81-82 e11.
 20. 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.
 21. 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 e61-65 e11.
 22. Kim KH, Zsebik GN, Straughn JM, Jr., Landen CN, Jr. Management of complex pelvic masses using a multivariate index assay: a decision analysis. *Gynecol Oncol*. 2012;126(3):364-368.
 23. Havrilesky LJ, Dinan M, Sfakianos GP, et al. Costs, effectiveness, and workload impact of management strategies for women with an adnexal mass. *J Natl Cancer Inst*. 2015;107(1):322.
 24. Forde GK, Hornberger J, Michalopoulos S, Bristow RE. Cost-effectiveness analysis of a multivariate index assay compared to modified American College of Obstetricians and Gynecologists criteria and CA-125 in the triage of women with adnexal masses. *Curr Med Res Opin*. 2016;32(2):321-329.
 25. Macuks R, Baidekalna I, Donina S. An ovarian cancer malignancy risk index composed of HE4, CA125, ultrasonographic score, and menopausal status: use in differentiation of ovarian cancers and benign lesions. *Tumour Biol*. 2012;33(5):1811-1817.
 26. 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.
 27. Bristow RE, Smith A, Zhang Z, et al. Ovarian malignancy risk stratification of the adnexal mass using a multivariate index assay. *Gynecol Oncol*. 2013;128(2):252-259.
 28. 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 e581-588.
 29. 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.
 30. 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 e71-79.
 31. 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.
 32. Wang J, Gao J, Yao H, Wu Z, Wang M, Qi J. Diagnostic accuracy of serum HE4, CA125 and ROMA in patients with ovarian cancer: a meta-analysis. *Tumour Biol*. 2014;35(6):6127-6138.
 33. Dayyani F, Uhlig S, Colson B, et al. Diagnostic Performance of Risk of Ovarian Malignancy Algorithm Against CA125 and HE4 in Connection With Ovarian Cancer: A Meta-analysis. *Int J Gynecol Cancer*. 2016;26(9):1586-1593.
 34. Al Musalhi K, Al Kindi M, Al Aisary F, et al. Evaluation of HE4, CA-125, Risk of Ovarian Malignancy Algorithm (ROMA) and Risk of Malignancy Index (RMI) in the Preoperative Assessment of Patients with Adnexal Mass.

- Oman Med J.* 2016;31(5):336-344.
35. Cho HY, Park SH, Park YH, et al. Comparison of HE4, CA125, and Risk of Ovarian Malignancy Algorithm in the Prediction of Ovarian Cancer in Korean Women. *J Korean Med Sci.* 2015;30(12):1777-1783.
 36. Terlikowska KM, Dobrzycka B, Witkowska AM, et al. Preoperative HE4, CA125 and ROMA in the differential diagnosis of benign and malignant adnexal masses. *J Ovarian Res.* 2016;9(1):43.
 37. Minar L, Felsing M, Cermakova Z, Zlamal F, Bienertova-Vasku J. Comparison of the Copenhagen Index versus ROMA for the preoperative assessment of women with ovarian tumors. *Int J Gynaecol Obstet.* 2018;140(2):241-246.
 38. Moore RG, Hawkins DM, Miller MC, et al. Combining clinical assessment and the Risk of Ovarian Malignancy Algorithm for the prediction of ovarian cancer. *Gynecol Oncol.* 2014;135(3):547-551.
 39. Oncology SoG. Position Statement: Multiplex Serum Testing for Women with Pelvic Mass. May 2013.
 40. Hayes. OVA1 (ASPiRA Labs). 2017:<https://evidence.hayesinc.com/report/gte.ova2060>.
 41. Institute NC. https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#cit/section_8.164.
 42. Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet.* 2002;359(9306):572-577.
 43. Zhang Z, Bast RC, Jr., Yu Y, et al. Three biomarkers identified from serum proteomic analysis for the detection of early stage ovarian cancer. *Cancer Res.* 2004;64(16):5882-5890.
 44. Badgwell D, Bast RC, Jr. Early detection of ovarian cancer. *Dis Markers.* 2007;23(5-6):397-410.
 45. Koehn H, Oehler MK. Proteins' promise-progress and challenges in ovarian cancer proteomics. *Menopause Int.* 2007;13(4):148-153.
 46. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist.* 2007;12(1):20-37.
 47. NICE guidelines. <https://www.nice.org.uk/guidance/dg31/chapter/1-recommendations>.
-

Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)

A57020 - Billing and Coding: Multimarker Serum Tests Related to Ovarian Cancer Testing

A58112 - Response to Comments: Multimarker Serum Tests Related to Ovarian Cancer Testing

Related National Coverage Documents

N/A

Public Version(s)

Updated on 05/07/2020 with effective dates 07/01/2020 - N/A

Keywords

N/A