MEDICAL POLICY

POLICY TITLE	PROTEOMICS-BASED TESTING RELATED TO OVARIAN CANCER
POLICY NUMBER	MP-2.270

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I. POLICY

All uses of the OVA1 and ROMA tests are **investigational,** including but not limited to

a. preoperative evaluation of adnexal masses to triage for malignancy, or
b. screening for ovarian cancer, or
c. selecting patients for surgery for an adnexal mass, or
d. evaluation of patients with clinical or radiologic evidence of malignancy, or
e. evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy, or
f. postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

POLICY GUIDELINES

OVA1 and ROMA tests are combinations of several separate lab tests and involve a proprietary algorithm for determining risk (ie, they are what the American Medical Association's CPT calls "Multianalyte Assays with Algorithmic Analyses" [MAAAs]).

Cross-reference:

MP-2.269 Serum Biomarkers for Human Epididymis Protein 4 (HEA)

II. PRODUCT VARIATIONS

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[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N]	Capital Cares 4 Kids	[N]	Indemnity
[N]	PPO	[N]	SpecialCare
[N]	HMO	[N]	POS
[Y]	SeniorBlue HMO**	[Y]	FEP PPO*
[Y]	SeniorBlue PPO**		

*Refer to FEP Medical Policy Manual MP-2.04.62 Proteomics-Based Testing Related To Ovarian Cancer. The FEP Medical Policy manual can be found at: www.fepblue.org

**Refer to Novitas Solutions Inc. Local Coverage Determination (LCD) for Biomarkers for Oncology (L34796).

III. DESCRIPTION/BACKGROUND

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A variety of gene-based biomarkers have been studied in association with ovarian cancer. Of particular interest have been tests that integrate results from multiple analytes into a risk score to predict the presence of disease. Two tests based on this principle (Ova1™ test and ROMA™ test) have now been cleared by FDA for use in women with adnexal masses as an aid to further assess the likelihood that malignancy is present.

Background

In 2009, more than 21,000 women in the U.S. were diagnosed with ovarian cancer and more than 14,000 died of this disease.(1) The mortality rate depends on three variables: (1) characteristics of the patient; (2) biology of the tumor (grade, stage, type); and (3) quality of treatment (nature of staging, surgery and chemotherapy used).(2) In particular, comprehensive staging and completeness of tumor resection appear to have a positive impact on patient outcome.

In 1997, the Society of Surgical Oncology recommended ovarian cancer surgery and follow-up treatment be performed by physicians with ovarian cancer disease expertise.(3) To date, dozens of articles have been published relevant to this recommendation looking at long-term outcomes, short-term outcomes, and process measures (eg, types of treatment such as complete staging or tumor debulking). At least two meta-analyses have concluded that outcomes are better in patients with ovarian cancer when they are treated by gynecologic oncologists.(4,5) Data have been most convincing for patients with advanced stage disease.

Adult women presenting with an adnexal mass have an estimated 68% likelihood of having a benign lesion.(6) About 6% have borderline tumors, 22%, invasive malignant lesions, and 3%, metastatic disease. Clinicians generally agree that women with masses that have a high likelihood of malignancy should undergo surgical staging by gynecologic oncologists.

However, women with clearly benign masses do not require referral to a specialist. Criteria and tests that help differentiate benign from malignant pelvic masses are thus desirable.

In 2005, the American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncologists (SGO) jointly released referral guidelines that address criteria for referring women with pelvic masses that are suspicious for ovarian cancer to gynecologic oncologists.(7) Separate criteria were developed for premenopausal and postmenopausal women. In premenopausal women, referral criteria included at least one of the following: elevated CA 125 (greater than 200 U/mL), ascites, evidence of abdominal or distant metastasis, or a positive family history. The referral criteria in postmenopausal women were similar, except that a lower threshold for an elevated CA-125 test was used (35 U/mL) and nodular or fixed pelvic mass was an additional criterion.

Two proteomic tests have now been cleared by the U.S. Food and Drug Administration (FDA) with the intended use to triage patients with adnexal masses. A suggested use of the test is to identify women with a positive test who have a higher likelihood of malignant disease and may benefit from referral to a gynecologic-oncology specialist. Patients with positive results may be considered candidates for referral to a gynecologic oncologist for treatment.

Regulatory Status

On July 16, 2009, the OVA1™ test (Vermillion Inc., Fremont, CA) was cleared for market by the U.S. Food and Drug Administration (FDA) as a 510(k) submission. On September 1, 2011, the Risk of Ovarian Malignancy Algorithm (ROMA™ test, Fujirebio Diagnostics Inc., Malvern, PA) was cleared by the U.S. Food and Drug Administration (FDA) as a 510(k) submission. Because the OVA1 test had been found to be a class II medical device by virtue of the July 2009 clearance, ROMA was found to be substantially equivalent to that predicate device.

Black Box Warning: On December 10, 2011, the FDA published an amendment to the regulation for classifying ovarian adnexal mass assessment score test systems to restrict these devices so that a prescribed warning statement that addresses off-label risks be highlighted by a black box warning.(8) The warning is intended to mitigate the risk to health associated with off-label use as a screening test, stand-alone diagnostic test, or as a test to determine whether or not to proceed with surgery.

IV. RATIONALE

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Assessment of a diagnostic technology typically focuses on 3 parameters: (1) technical performance; (2) diagnostic performance (sensitivity, specificity, and positive [PPV] and negative predictive value [NPV]) in appropriate populations of patients; and (3) demonstration that the diagnostic information can be used to improve patient outcomes (clinical utility).

Technical performance: This is typically assessed with 2 types of studies, those that compare test measurements with a gold standard and those that compare results taken with the same device on different occasions (test-retest).

Diagnostic performance: This is evaluated by the ability of a test to accurately diagnose a clinical condition in comparison with the gold standard. The sensitivity of a test is the ability to detect a disease when the condition is present (true-positive), while specificity indicates the ability to detect patients who are suspected of disease but who do not have the condition (true-negative). Evaluation of diagnostic performance, therefore, requires independent assessment by the 2 methods in a population of patients who are suspected of disease but who do not all have the disease.

Clinical utility: This involves assessing the data linking use of a test to improvement in patient management and/or health outcomes. While in some cases, tests can be evaluated adequately using technical and diagnostic performance. When a test identifies a new or different group of patients with a disease; randomized trials are needed to demonstrate impact of the test on the net health outcome.

Technical Performance

Descriptions of the developmental process for the OVA1 test have been published in FDA documents and in a perspective by Fung in 2010. (9-11) Candidate biomarkers were selected based on initial studies using mass spectroscopy but were converted to standard immunoassays to improve analytical performance. Seven final markers were evaluated, none of which individually appeared to be highly specific for malignant ovarian disease. However, the choice of 5 of these (CA 125, prealbumin, apolipoprotein A-1, beta 2 microglobulin, and transferrin) produced a composite profile that did appear to have discriminatory ability. The test, as cleared by the U.S. Food and Drug Administration (FDA), is performed on a blood sample, which is to be sent to a reference laboratory for testing using the 5 immunoassays described above. Results of the 5 determinations are entered manually into an Excel® spreadsheet used by the OvaCalc software. This software contains an algorithm which combines the 5 discrete values into a single unitless numerical score from 0.0 to 10.0.

Details of the algorithm appear proprietary, but development is described as an empiric process, based on use of banked samples from academic partners, on a small prospective study of samples from Europe and using a designated subset of samples from the clinical study used to support submission to the FDA. It appears at an undisclosed point in the developmental process as a result of interaction with FDA; separate cut-points were developed for premenopausal and postmenopausal women.

A similar developmental process was described for ROMA by Moore et al. (12) They studied 9 biomarkers and chose human epididymis secretory protein 4 (HE4) and CA 125 because these markers in tandem produced the best performance. The algorithm developed was subsequently modified to include menopausal status and was independently validated. (13) Again, separate cut-offs were used for premenopausal and postmenopausal women.

The OVA1 is a qualitative serum test that combines immunoassay results for the 5 analytes described above (CA 125, prealbumin, apolipoprotein A-1, beta 2 microglobulin, and transferrin) into a single numerical score. Analytical performance for the test demonstrated good test precision (coefficient of variation [CV] ranging from 1% to 7.4%, depending on the sample levels studied) and good reproducibility (CV from 2.8% to 8.9%). The test appears linear, reagent and samples stable, and there was no observed interference evaluating common endogenous substances (hemoglobin, bilirubin, etc.)

The ROMA test is also a qualitative serum test that combines 2 analytes HE4 EIA and the ARCHITECT CA 125, along with menopausal status into a numerical score. Analytical performance for the ROMA also exhibited good precision with a total CV ranging from 0.49% to 7.72%, depending on both sample values and menopausal status. The reproducibility of the test was acceptable, with a CV that ranged from 0.98 to 25.9%, with highest values observed in patients with low scores, as expected. The reagents are variably stable, and users are instructed to follow package inserts for stability on each analyte used. The test was unaffected by interference with hemoglobin, bilirubin, lipids, or human antimouse antibodies (HAMA). However, high levels of rheumatoid factor (>500 IU/mL) did appear to cause elevations in test values, and testing in patients with elevated rheumatoid factor is not recommended.

Section Summary

Evidence on the technical performance of these tests has been evaluated by the U.S. Food and Drug Administration (FDA) and is available through the FDA website. This information generally indicates acceptable technical performance for use in clinical care.

Diagnostic Performance

Risk scores for both tests are generated according to the specific algorithm used. In the absence of a standard for either of the risk score signals, accuracy has been defined in terms of clinical performance.

Diagnostic performance of the OVA1 test was evaluated in a single prospective, double-blind clinical study using 27 demographically mixed subject enrollment sites. The study was supported by the commercial sponsor of the test. Patients underwent a complete clinical evaluation prior to surgical intervention, and only patients with planned surgical intervention were included in the study. The presurgical process for identifying patients for surgery and for establishing a preliminary diagnosis as benign or malignant were not specifically described but were noted to be based on clinical assessment. The study did require at least one imaging test be performed within 12 weeks of surgery. Presumably, use of this somewhat nonstandardized diagnostic methodology provides information on how the test works in conjunction with real-world decision making. The study enrolled a total of 743 patients with 146 subjects used in the training set and 516 in the testing set. Seventy-four patients were excluded because of missing information or samples. All patients had adnexal masses and were scheduled for surgery. The final prevalence of cancer in the population was 27%.

Using pathologic diagnosis as the gold standard, test performance, when combined with presurgical assessment for benign disease, was as follows in the hands of nongynecologic oncologists:

	Clinical Assessment Alone, %	Clinical Assessment With OVA1, %
Sensitivity	72 [a]	92
Specificity	83	42
Positive predictive value	61	37
Negative predictive value	89	93

[a] Confidence intervals not provided.

Diagnostic performance of the ROMA test was also evaluated in a prospective, blinded clinical trial that was industry-sponsored. The study was conducted at 13 demographically mixed subject enrollment sites. 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, % (CI)	ICRA With ROMA Testing, % (CI)
Sensitivity	77 (66 to 86)	91 (81 to 96)
Specificity	84 (80 to 88)	67 (61 to 71)
Positive predictive value	46 (17 to 56)	33 (26 to 40)
Negative predictive value	96 (93 to 97	98 (95 to 99)

Both tests when added to pretesting 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.

Several prospective European studies published in 2012 and 2013 have evaluated the diagnostic accuracy of ROMA compared with other tools for distinguishing between benign and malignant pelvic masses. No similar studies have been published evaluating the diagnostic accuracy of the OVA1 test.

The study with the largest sample size was published by Karlsen et al. in 2012. (14) The study included 1218 women presenting with pelvic masses. Prior to diagnosis, HE4 and CA125 levels were obtained, and ROMA and the Risk of Malignancy Index (RMI, an index consisting of ultrasound findings, menopausal status and CA125 levels) were calculated. At a fixed sensitivity of 94.4%, the specificity of ROMA was 76.5% and the specificity of RMI was 81.5%. At a fixed specificity of 75%, the sensitivity of ROMA was 94.8% and the sensitivity of RMI was 96.0%. Accuracy of ROMA and RMI were not compared statistically, but appeared to be similar. In another study, Kaijser et al. evaluated 360 women with pelvic masses who were scheduled for surgery. (15) The study compared the diagnostic accuracy of ROMA and an ultrasound-based prediction model (LR2) developed by the International Ovarian Tumor Analysis Study (IOTA). Histology was used as the reference standard. The overall performance of LR2 (94% sensitivity, 82% specificity) was significantly better than ROMA (84% sensitivity, 80% specificity). In addition, a study by Van Gorp et al. found that,

in the hands of radiologists at a cancer institute, subjective assessment by ultrasound was superior to ROMA in discriminating benign from malignant adnexal masses. (16)

Section Summary

The number of studies comparing diagnostic accuracy of the ROMA and OVA1 proteomic tests is small, and, other than studies performed prior to FDA approval, most published studies have been conducted outside of the U.S. Studies have found that ROMA has similar or lower accuracy to other risk prediction measures that use components of the standard workup, such as the RMI and the LR2 measures. There are fewer published studies evaluating the diagnostic accuracy of OVA1.

Clinical Utility

A TEC Assessment was completed in 2012 on "Multi-analyte testing for the evaluation of adnexal masses." (17) The Assessment included evaluation of both the OVA1 and ROMA tests in regards to their impact on health outcomes. The following conclusions were made:

- The evidence regarding the effect of OVA1 and ROMA and effects on health outcomes is indirect, and based on studies of diagnostic performance of the tests in patients undergoing surgery for adnexal masses.
    - There are no prospective studies on the use of these tests in patients who present with an adnexal mass.
    - There are no studies that report the impact of testing on referral patterns or the impact on health outcomes
- Although the studies show improvements in sensitivity and worsening of specificity with the use of the tests in conjunction with clinical assessment, there are problems in concluding that this results in improved health outcomes. The clinical assessment performed in the studies is not well characterized.
- OVA1 appears to improve sensitivity for detection of malignancy, however specificity declines so much that most patients test positive.
- ROMA does not appear to improve the sensitivity of testing to a great extent.
- Underlying these issues is some uncertainty regarding the benefit of initial treatment by a gynecologic oncologist beyond the need for reoperation is some cases.

No studies evaluating the clinical utility of OVA1 or ROMA were identified in subsequent literature searches. There is indirect evidence from studies of diagnostic accuracy that compare the ROMA test to other risk prediction measures that use components of the standard workup such as menopausal status, CA 125, and ultrasound results. These studies report that the accuracy of risk measures using readily available information are similar or superior to the ROMA test. This evidence suggests that the ROMA test would not improve the accuracy of triage compared to existing measures, and is unlikely to result in benefits such as reduced need for second-look operations.

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Direct evidence on the clinical utility of the proteomic tests is lacking. Indirect evidence suggests that, for patients who are considering treatment by a nongynecologic oncologist, use of proteomic tests will decrease the likelihood that an adnexal mass is categorized as benign when it is actually malignant. This might impact referral patterns to a gynecologic oncologist and decrease the likelihood that a patient will require a second follow-up procedure for comprehensive staging, lymphadenectomy, and/or tumor debulking, but empirical evidence of this is lacking. Indirect evidence from studies of diagnostic accuracy suggest that these proteomic tests are unlikely to improve the accuracy of referral, and unlikely to improve outcomes. Because of the unknown effect on referral patterns, the effect on health outcomes is uncertain. Further prospective studies are needed for both assays to understand their proper role in patient care.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Results of clinical input in 2012 revealed mixed support for the use of this test as a tool for triaging patients with an adnexal mass. Reviewers agreed that the evidence was insufficient to determine the impact of these tests on referral patterns. For indications other than triaging patients with an adnexal mass, there was a lack of support for use of these tests.

Summary

The OVA1 and ROMA tests have both been analytically validated and clinical performance has been reported in prospective multicenter clinical studies. Changes in the observed sensitivity and negative predictive value of testing compared to clinical assessment has been small and of uncertain diagnostic value. Studies on the diagnostic accuracy of these tests compared to other diagnostic tools have had mixed findings, but do not report that ROMA is superior to other risk prediction tools that use standard clinical information. No studies have been performed that directly evaluated the impact on referral patterns, and no studies have evaluated the impact on health outcomes. Clinical input from academic medical centers and specialty societies did not show consensus that this test improved outcomes when used as a tool to triage patients with adnexal masses. As a result of the evidence and clinical input, these tests are considered investigational pending more information about its performance and impact on outcomes.

Clinical Practice Guidelines and Position Statements

The American Congress of Obstetricians and Gynecologists addressed the use of the OVA1 test in their guidelines on the role of the obstetrician-gynecologist in the early detection of

epithelial ovarian cancer, last updated in 2011. (18,19) This document made the following statements:

- The OVA1 test appears to improve the predictability of ovarian cancer in women with pelvic masses
- This is not a screening test, but may be useful for evaluating women with a pelvic mass
- Clinical utility is not yet established

In May 2013, the Society for Gynecologic Oncology (SGO) issued the following statement on multiplex serum testing for women with pelvic masses (20):

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. It is important to note that no such test has been evaluated for use as, nor cleared by, the FDA as a screening tool for ovarian cancer. SGO does not formally endorse or promote any specific products or brands.

The National Institute for Health and Clinical Excellence (NICE) issued guidance in 2011 on the recognition and management of ovarian cancer.(21) These guidelines made the following recommendations:

- The evidence suggests that the combination of HE4 and serum CA125 is more specific, but less sensitive than either marker in isolation.
- There was no evidence to suggest that multiple tumour markers were much better than the two marker combination of serum CA125 and HE4.
- The routine use of CA 125 is recommended; the data on other serum markers is not substantial enough to recommend their use

The National Comprehensive Cancer Network (NCCN) guideline on ovarian cancer (2013, V.2) includes the following statement (22):

It has been suggested that specific biomarkers (serum HE4 and CA-125) along with an algorithm (Risk of Ovarian Malignancy Algorithm [ROMA]) 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.

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V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

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Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational therefore not covered:

CPT Codes®								
81500	81503							

IX. REFERENCES

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Other:

Novitas Solutions. Local Coverage Determination (LCD) L34796 Biomarkers for Oncology. Effective 7/24/14.

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X. POLICY HISTORY

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MP-2.270	**CAC 5/20/14** Policy criteria removed from MP-2.212 Tumor Markers and Tumor Related Molecular Testing. References updated and rationale added. No changes to policy statements. FEP variation added.

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