BlueCross BlueShield of Louisiana

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Proteomics-Based Testing for the Evaluation of Ovarian (Adnexal) Masses

Policy # 00281
Original Effective Date: 12/15/2010
Current Effective Date: 12/18/2013

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the proteomics-based OVA1™‡† test as an aid to further assess the likelihood that malignancy is present when the physician's independent clinical and radiological preoperative evaluations do not indicate malignancy in a patient with an ovarian (adnexal) mass to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility will be considered for the proteomics-based OVA1 test to be used for women with an ovarian (adnexal) mass when the all following criteria are met:

- The patient is older than age 18 years; and
- An ovarian adnexal mass is present; and
- Surgery is planned for treatment of the mass; and
- The patient has not yet been referred to a gynecologic oncologist.

Note: The test allows additional risk assessment in patients already believed to have benign disease using routine clinical and radiological parameters to estimate the risk that there is actually an underlying malignant process.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all other uses of the OVA1 test to be **investigational*,** including but not limited to:

- Screening for ovarian cancer, or
- Selecting patients for surgery for an adnexal mass, or
- Evaluation of patients with clinical or radiologic evidence of malignancy, or
- Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy, or
- Post-operative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

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Based on review of available data, the Company considers the use of the proteomics-based OVA1 test when patient selection criteria are not met to be **investigational.***

Background/Overview

The OVA1 test (Vermillion, Inc., Fremont, CA) is a qualitative serum test that combines immunoassay results for five analytes (CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, and transferrin) into a single numerical score. It is intended to be used in women with adnexal masses who are planning to have surgery by a non-gynecologic oncologist for disease considered benign using routine clinical and radiologic evaluation. In this patient subset, the test serves as an aid to further assess the likelihood that malignancy is present.

In 2009, it was estimated that more than 21,000 women in the U.S. were diagnosed with ovarian cancer and more than 14,000 died of this disease. The mortality rate depends on three variables: 1) characteristics of the patient; 2) the biology of the tumor (grade, stage, and type); and 3) the quality of treatment (nature of staging, surgery and chemotherapy used). 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 first recommended ovarian cancer surgery and follow-up treatment be performed by physicians with ovarian cancer disease expertise. To date dozens of articles and several meta-analyses or systemic reviews have been published relevant to this recommendation looking at long-term outcomes, short-term outcomes, and process measures (types of treatment such as complete staging or tumor debulking).

At least two meta-analyses have been performed concluding improved outcomes in patients with ovarian cancer when treated by gynecologic oncologists. Data are most convincing for patients with advanced stage disease. Median improvements in survival for patients treated by non-gynecologic oncologists versus gynecologic oncologists have been variable but impressive with increases recently reported to be up to 8 months (12 to 21 months). In at least some reports, important differences have also been observed showing improved survival in patients with early stage disease as well when treated by gynecologic oncologists.

A recent systematic review of 198 studies addressing the role of specialty treatment by gynecologic oncologists and evaluation of other practice-related factors (type of hospital, surgical volume, etc.) was more guarded in its analysis. This review noted that not all reports confirmed these findings of improved performance based on sub-specialty. It also noted that in some reports, only patients presenting with certain stages of disease (in most cases advanced stage although in some cases early stage) were studied and found to exhibit treatment differences. Nevertheless, this review also concluded that the use of sub-specialists and better education of treatment options for both primary care physicians and patients was warranted.

In an analysis of predictors of comprehensive surgical treatment (meticulous and extensive disease staging, efforts at debulking of the tumor with removal of all visible lesions, lymphadenectomy) in patients with ovarian cancer, Goff et al. observed that comprehensive treatment was linked not only to physician factors but also to a number of simple demographic factors including age, race, insurance status, and geographic

location (urban vs. rural). Optimization of treatment for ovarian cancer may clearly be complicated by these factors.

Adult women presenting with an adnexal mass have an estimated 68% likelihood of having a benign lesion. About 6% have borderline tumors, 22%, invasive lesions, and 3%, metastatic disease.

Obviously a majority of patients can be treated without use of surgical oncology expertise. To date no existing diagnostic modalities have been identified to discriminate reliably between benign and malignant lesions. Referral guidelines were published by the American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncologists (SGO) for women with pelvic masses that are suspicious for ovarian cancer who are being referred to gynecologic oncologists. In these guidelines, a decision to refer in postmenopausal women was based on the presence of at least one of the following indicators: elevated CA 125, ascites, a nodular or fixed pelvic mass, evidence of abdominal or distant metastasis, or a family history of one or more first-degree relatives with ovarian or breast cancer. A decision to refer in premenopausal women was based on at least one of the following: elevated CA 125, ascites, evidence of abdominal or distant metastasis, or a positive family history.

A validation study has been performed on these criteria, suggesting a high negative predictive value ([NPV] 90% or more) in both premenopausal and postmenopausal patients but a much lower positive predictive value ([PPV] as low as 34%).

Recent publications have appeared describing the use of CA 125 with a symptom index, the use of an "ovarian crescent sign" on ultrasound, the use of three-dimensional ultrasound to provide increased diagnostic reliability in this decision-making process, and most recently the use of an algorithm based on use of key features identified by ACOG/SGO. Since many of these studies have been performed in referral centers, it is not clear how generalizable they are to use in the general population. Further independent validation of these various approaches is needed.

The OVA1 is a new proteomic test that has been developed specifically to triage patients thought to have benign adnexal masses with planned treatment by a non-gynecologic-oncologist physician. Patients with positive results should be considered candidates for referral to a gynecologic oncologist for treatment. As described above, this treatment is likely to produce improved patient outcomes.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
On July 16, 2009, the OVA1TM test (Vermillion, Inc. Fremont, CA) was cleared for market by the FDA as a 510(k) submission. On September 1, 2011, the Risk of Ovarian Malignancy Algorithm (ROMATM test, Fujirebio Diagnostics, Inc., Malvern, PA) was cleared by the 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. 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.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source

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

Technical performance of a device is typically assessed with two 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 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 two methods in a population of patients who are suspected of disease but who do not all have the disease.

Evidence related to improvement of clinical outcomes with use of this testing assesses the data linking use of a test to changes in health outcomes (clinical utility). 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.

Literature Review
To date there are three publicly available scientific documents describing the OVA1 test by Vermillion.

The first is the FDA decision summary describing the FDA's review of the OVA1 test data submitted to the agency and used to obtain market clearance. This clearance was based on a prospective, multicenter, double-blind clinical study of 747 patients from 27 demographically mixed sites. The endpoint of interest was pathological truth on resected tumor and results of pathology were compared to results of pre-surgical clinical diagnosis and to blinded results of OVA1 testing.

The second is a short description of the developmental process for the test published as an informal report in *Clinical Chemistry* in February 2010.

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The third is an abstract published in the *Journal of Gynecological Oncology* in parallel to a presentation at the closing plenary session held at the Annual Meeting of the Society of Gynecological Oncology on March 17, 2010.

The *Clinical Chemistry* report clearly outlines the rationale for this test. As the author notes, "…our colleagues, however, identified a critical unmet need in the area of ovarian tumor triage. Although ovarian tumors are relatively common, only a fraction of them are malignant. Being able to identify the malignant ones preoperatively would permit better preoperative management of women with ovarian tumors." He goes on to note that this information would allow better decision making about whether surgery should be performed by a generalist or a gynecologic oncology specialist.

The perspective also clearly outlines the multiple steps used in test development including decisions:

1. To improve and lock in analytical performance before initiating the clinical study,
2. To separate subsets of samples for training (to establish the multi-marker algorithm) and for validation (to establish performance), and
3. To develop and craft claims and labeling to assure the adjunctive use of the test results would be clearly understood.

Of interest, candidate biomarkers were selected based on initial studies using mass spectroscopy but to improve analytical performance were converted to standard immunoassays. Seven final markers were evaluated, none of which individually appeared to be highly specific for malignant ovarian disease. However, the choice of five of these (CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, and transferrin*)* produced a composite profile that did appear to have discriminatory ability. The test, as cleared by FDA, is performed on a blood sample which is to be sent to a reference laboratory for testing using the five immunoassays described above. Results of the five determinations are entered manually into an Excel®‡† spread sheet used by the OvaCalc software. This software contains an algorithm which combines the five 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.

The fourth document describing the OVA1 test is an editorial published in August 2010 in *Obstetrics and Gynecology* describing the decision-making process for use of the test. The editorial re-enforced two important points: 1) that the test should not be used for screening and 2) that if a careful clinical assessment of risk of malignancy warrants referral to a gynecologic oncologist, the OVA1 test should not be performed. In these cases, a negative test would not negate appropriate referral.

Finally, the fifth document, published in October 2010, is a commentary suggesting that in order to assure success in the introduction of new diagnostics (including obtaining regulatory approval), new proteomic tests need to have carefully identified intended uses that allow for both broad applicability, as well as

feasibility for establishing clinical utility using proper clinical trials. OVA1 was described as an example of a product meeting these criteria.

Technical Performance
Based on the FDA review, analytical performance for the test appears robust. Precision ranges from 1% to 7.4% depending on the sample levels studied and reproducibility 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.) In the absence of a standard for the risk score signal, accuracy was defined in terms of clinical performance.

Diagnostic Performance
Diagnostic performance of the OVA1 test was evaluated in a prospective, double-blind clinical study using 27 demographically mixed subject enrollment sites. 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 a variety of clinical assessments.” 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.

Using pathological diagnosis as truth; sensitivity, specificity, the PPV and the NPV were determined for clinical decision making alone (a diagnostic process referred to as “single or pre-surgical assessment”).

Single assessment was then compared to diagnosis using results of presurgical assessment with further evaluation of all patients thought on initial assessment to be negative for malignancy using the OVA1 test. This combined diagnostic process was referred to as “dual assessment” or “pre-surgical assessment and OVA1 test”. If either the pre-surgical assessment or the OVA1 test were positive, the patient was considered potentially positive for malignant disease and a candidate for referral to a specialist. If both results were negative, the patient would be viewed as at low risk of malignancy and treatment by a non-gynecological oncologist would be a reasonable option.

The FDA decision summary includes extensive analyses of results including analysis of presurgical assessment by gynecologic oncologists and non-gynecologic oncologists, and assessment in each of these two groups according to menopausal status. Since the test is intended to triage patients with planned surgery by non-specialists to determine if referral to a gynecologic oncologist is warranted, this data set is the most germane to understanding how the test is likely to work.

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Table 1: Single Assessment by Non-gynecologic Oncologists (Presurgical assessment in patients with adnexal masses)

	Patients with Ovarian Cancer	Patients without Ovarian Cancer	
Presurgical Assessment Positive	52	34	86
Presurgical Assessment Negative	20	163	183
	72	197	269

Prevalence of ovarian cancers = 27% (72/269)
Sensitivity = 72% (62 to 83%)
Specificity = 83% (77 to 88%)
PPV = 61% (50 to 71%)
NPV = 89% (84 to 94%)

Table 2: Dual Assessment by Non-gynecologic Oncologists (Presurgical assessment supplemented by OVA1 Test results in patients with adnexal masses but thought based on clinical and radiological findings to have benign disease)

	Patients with Ovarian Cancer	Patients without Ovarian Cancer	
Presurgical Assessment Positive or OVA1 Test positive	66	115	181
Presurgical Assessment and OVA test negative	6	82	88
	72	197	269

Prevalence of ovarian cancer = 27% (72/269)
Sensitivity = 91% (85 to 98%)
Specificity = 42% (35 to 48%)
PPV = 37% (29 to 43%)
NPV = 93% (88 to 98%)

As a comparison of Tables 1 and 2 demonstrates, the use of the OVA1 test in patients thought to be negative for malignancy on pre-surgical assessment clearly increased the sensitivity of testing (increase from 72% to 91%.) This allowed for identification of 14 out of 20 malignancies that would have been missed using single assessment alone.

Using the recommended diagnostic algorithm out of a population of 269 patients with 72 malignancies, only 6 malignancies would be missed--incorrectly identified as benign adnexal masses. The information provided by this 2-step diagnostic procedure has the potential to allow patients and primary care physicians to make better informed treatment choices.

For patients who are considering treatment by a non-gynecologic oncologist, use of this test would help to decrease the likelihood that as a result of misclassification of a malignant lesion as benign, the patient will require a second follow-up procedure to allow for the comprehensive staging, lymphadenectomy and/or tumor debulking that may be called for with malignant lesions.

This improved detection of malignancies is not without some loss of overall test performance. Only 1 out of every 6.9 additional patients referred for specialist care would actually have a malignancy. Of note, while the PPV in the total test population would fall significantly (61% to 37%), the NPV showed a statistically borderline improvement (89% to 93%). While use of the OVA1 test appears to increase identification of additional malignant tumors, it does so at a cost in global test performance. Using single assessment, 215 out of 269 patients (80%) are correctly categorized. Using dual assessment, this falls to 148 out of 269 patients (55%).

Evidence related to improvement of clinical outcomes (**Clinical Utility)**
Although no outcome studies have been performed using the OVA1 test, the test clearly appears to identify a subset of patients with adnexal lesions who would benefit from treatment by a gynecological oncologist. Identification of these additional true positive cases provides a clear potential to improve patient outcomes through more appropriate treatment choices.

As is the case for false positive cases identified and referred using existing clinical and radiological diagnostic criteria, there is no evidence of harm to patients identified as false positives.

While the ability to triage patients for malignancy with an increased yield of true positive results may be only one of many factors in decision making about where treatment should be delivered, it is a valuable piece of information that will contribute to better health care choices in dealing with a serious disease.

Summary
The OVA1 test has been analytically validated and clinical performance has been established in a prospective multi-center clinical trial. The plan for this trial (although not the trial itself) has been described in the peer-reviewed literature and a brief summary of results has appeared in a single abstract.

Extensive information about the trial is available through the posting of an FDA decision summary resulting from FDA clearance of the product in 2009. Use of the OVA1 test clearly improves the diagnostic sensitivity

and the preoperative detection of ovarian cancers. This increase in the identification of malignancies should result in more early referrals to gynecological oncologists with resulting improvement in clinical outcomes. Thus, use of the OVA 1 test is considered medically necessary as part of the preoperative evaluation of patients with ovarian masses by non-gynecologic oncologists whose initial evaluation does not indicate the mass is malignant.

All other uses of this test, including use as a screening tool for ovarian cancer, are considered investigational.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81500, 81503
HCPCS	No codes
ICD-9 Diagnosis	220, 236.2, 239.5, 789.33, 789.34
ICD-9 Procedure	No codes

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12/18/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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