APPENDIX to Proteomic Pattern Analysis in Serum to Identify Cancer Policy

Prior Authorization Requirements

This service (or procedure) is considered **investigational** in all instances. If you would like to submit additional information please forward to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

The genetic basis of cancer has been the focus of intense research; however, genetic mutations do not reflect the complicated interactions between individual cells, tissue, and organs. Proteins are the functional units of cells and represent the end product of the interactions among the underlying genes. Research interest has been increasing in the field of proteomics (referring to the protein product of the genome), in an effort to improve on screening and detection efforts for malignancies.

Proteomics involve the use of mass spectrometry to study differences in patterns of protein expression. While patterns of protein expression have been proposed to yield more biologically relevant and clinically useful information than assays of single proteins, many limitations in the use of proteomics exist (Reymond, 2007). In contrast to genomics, in which amplification techniques like polymerase chain reaction (PCR) allow for the investigation of single cells, no technology is available at the protein level (Reymond, 2007). Other issues between studies have been lack of uniform patient inclusion and exclusion criteria, small patient numbers, absence of standardized sample preparations, and limited analytical reproducibility (Reymond, 2007).

The potential role for proteomics for cancer screening and detection has undergone considerable discussion (Reymond & Schlegel, 2007; Lin et al., 2009; Dziadziuszko & Hirsch, 2008;

Lomnytska & Souchelnytskyi, 2007; Unwim & Whetton, 2007). However, data in the peer-reviewed literature are inadequate to permit scientific conclusions regarding ovarian, prostate, or other malignancies.

Current diagnostic and follow-up serum biomarkers in clinical oncology (e.g., prostate-specific antigen [PSA, prostate cancer], CA-125 [ovarian cancer]) involve identifying and quantifying specific proteins, but limitations may include non-specificity and elevation in benign conditions. There are a variety of gene-based biomarkers that 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 have now been cleared by U.S. Food and Drug Administration (FDA) for use in women with adnexal masses (Ova1™ test and ROMA™ test) as an aid to further assess the likelihood that malignancy is present.

Ovarian cancer is the leading cause of death from gynecologic malignancy in the United States; most patients present with advanced disease, which has a 5-year survival rate from 15-45%. If the disease is diagnosed in Stage I, survival rates are 95%. Therefore, there is great interest in using a biomarker to detect ovarian cancer in its earliest stages, as current screening methods are inadequate.

Serum measurements of PSA are used as a screening method for detecting prostate cancer. Very low or very high serum PSA results are most reliable in determining cancer risk. Values often fall within a range that is nonspecific, and thus many patients end up undergoing biopsy for benign disease. Proteomics has been proposed as a technique to further evaluate cancer risk in this diagnostic gray zone. However, commercial testing is not available at this time.

Rationale

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 of a device 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 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.

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.

Ovarian Cancer

The American Cancer Society estimated that in 2013, about 22,240 new cases of ovarian cancer will be diagnosed and 14,030 women will die of ovarian cancer for ovarian cancer in the United States. The mortality rate (du Bois et al., 2009) 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 (Hosksins et al., 1997). To date, dozens of articles and several meta-analyses or systemic reviews (du Bois et al., 2009; Vernooij, et al., 2007; Giede et al., 2005) 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 (Vernooij, et al., 2007; Giede et al., 2005) 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 (Tingulstad et al., 2003) 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 (Giede et al., 2005).

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 (du Bois et al., 2009). 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.

The need for proper triage and specialty care for patients with ovarian cancer has recently been reinforced in a report by Grabowski and colleagues (2012). They describe 40 patients seen at a tertiary gynecologic oncology unit after primary operation for ovarian cancer. Based on clinical and pathologic information, 35 of these patients were subjected to repeat surgery. Half of the patients were found to require upstaging; 53% of patients had postoperative chemotherapy recommendations modified. These authors suggest that because many patients are not referred for specialty follow-up, results of poor quality staging may be underestimated in their study.

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. (2007) 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 (Van Holsbeke et al., 2010). About 6% have borderline tumors, 22%, invasive lesions, and 3%, metastatic disease.

A majority of patients can be treated without use of surgical oncology expertise. Referral guidelines have been published by the American College of Obstetricians and Gynecologists (ACOG, 2011) and the Society of Gynecologic Oncologists (SGO, 2009) 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 (Anderson et al., 2010), the use of an “ovarian crescent sign” on ultrasound (Van Holsbeke et al., 2010), the use of 3-dimensional ultrasound (Alcazar & Rodriquez, 2009) 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 (Goff et al., 2007). 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.

Two proteomic tests have now been cleared by the 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. As described above, this treatment may improve outcomes if the test is accurate at discriminating benign from malignant disease.

On July 16, 2009, the OVA1™ test (Vermillion, Inc. Fremont, CA) was cleared for market by the FDA as a 510(k) submission. No predicate was identified, and the review decision was based on the de novo 510(k) review process, which allows novel products with moderate or low-risk profiles and without predicates which would ordinarily require premarket approval as a class III device to be down-classified in an expedited manner and brought to market with a special control as a class II device. The intended use carried a boxed warning: “PRECAUTION: The OVA1™ test should not be used without an independent clinical/radiological evaluation and is **not** intended to be a screening test or to determine whether a patient should proceed to surgery.

Incorrect use of the OVA1™ test carries the risk of unnecessary testing, surgery, and/or delayed diagnosis."

On September 1, 2011, the Risk of Ovarian Malignancy Algorithm (ROMA™ 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.

In 2013, the American Cancer Society (ACS) stated that due to many marketed unproved lab tests that had not yet been shown to help find early cancers, the FDA told the companies to stop selling them. This occurred with two different tests looking at protein patterns: OvaSure and OvaCheck. Both were taken off the market at the request of the FDA.

Correlogic Systems, Inc. are in the process of developing proteomic blood tests for the detection of colorectal, breast (MammoCheck®) and prostate cancer (ProstaCheck®). These proteomic tests are not commercially available at this time

A TEC Assessment was completed in 2012 on "Multi-analyte testing for the evaluation of adnexal masses." 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.

Detailed information about the development of both of these proteomic tests can be found on the FDA web site describing the FDA clearance review process. In 2010, Fung ET. published a perspective on the descriptions of the developmental process for the OVA1 test. This publication clearly outlines the multiple steps used in test development, including decisions to:

- Improve and lock in analytical performance before initiating the clinical study
- Subsets of samples for training (to establish the multi-marker algorithm) and for validation (to establish performance)

- 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 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 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 by Moore and colleagues (2008) for ROMA. 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 (Moore et al., 2011). Separate cut-offs were again used for premenopausal and postmenopausal women.

Technical Performance

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 anti-mouse antibodies (HAMA). However, high levels of rheumatoid factor (more than 500 IU/mL) did appear to cause elevations in test values, and testing in patients with elevated rheumatoid factor is not recommended.

In conclusion, evidence on the technical performance of these tests has been evaluated by the FDA and is available through the FDA web site. 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 pre-surgical 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 non standardized 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 non-gynecological oncologists:

	Clinical Assessment Alone	**Clinical Assessment with OVA 1**
Sensitivity	72%*	92%
Specificity	83%	42%
Positive predictive value	61%	37%
Negative predictive value	89%	93%

* Confidence intervals not provided.

Diagnostic performance of the ROMA test was also evaluated in a prospective, blinded clinical trial using 13 demographically mixed subject enrollment sites with company sponsorship. 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% (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 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.

Of note, one recent European study (Van Gorp et al., 2012) demonstrated that in the hands of radiologists at a cancer institute, subjective assessment by ultrasound is superior to ROMA in discriminating benign from malignant adnexal masses. No similar study has been performed with the OVA1 test. Two additional studies have been performed looking at ROMA testing and have both questioned the value of HE4 in identifying ovarian cancers (Partheen et al., 2011; Van Gorp et al., 2011). Again similar studies have not been reported looking at individual components of the OVA1 test. Further prospective studies are needed for both assays to understand their proper role in patient care.

In conclusion, use of the ROMA and OVA1 proteomic tests in combination with clinical assessment appears to produce very modest changes in diagnostic performance for identifying adnexal masses negative for ovarian cancer.

Evidence related to improvement of clinical outcomes (**Clinical Utility)**

No outcome studies have been performed using the OVA1 test or the ROMA test. It is not clear what impact use of either test would have on long-term healthcare outcomes. As is the case for false-positive cases identified and referred using existing clinical and radiologic diagnostic criteria, there is no evidence of harm to patients identified as false-positives.

The use of genomic testing to triage patients for malignancy may be only one of many factors in decision making about where treatment should be delivered. The clinical significance of the addition of these tests to currently used diagnostic modalities is unknown.

In an editorial on the OVA1 test (Muller CY., 2010) published in August 2010 in *Obstetrics and Gynecology* describing the decision-making process for use of the test, 2 important points were re-enforced: 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. These points have been highlighted in a recent FDA action establishing a black box warning for this category of product.

In conclusion, direct evidence on the clinical utility of the proteomic tests is lacking. For patients who are considering treatment by a non-gynecologic 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. Because of the unknown effect on referral patterns, the effect on health outcomes is uncertain.

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 (Federal Register, 2011). 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.

Prostate Cancer

Ornstein and colleagues in 2004 reported the results of serum proteomic profiling in 154 men with serum PSA ranging from 2.5 to 15.0 ng/mL. A total of 63 samples (30 malignant, 33 benign) were used as the training set to identify a proteomic pattern that could distinguish benign from malignant disease. The results of the training set were then applied to the remaining 91 samples (i.e., the “testing” set) in a blinded fashion. In this testing set of 63 negative biopsies and 28 positive biopsies, there was 100% sensitivity and 67% specificity. These data imply that if the results of proteomic profiling were used to deselect patients for biopsy; 42 of 63 (67%) patients without prostate cancer could have avoided biopsy. The authors noted that using a training set of only 63 samples may be inadequate and that “before this new technology can be applied in clinical practice, much larger and diverse training and testing sets will be needed.”

McLerran and colleagues in 2008 selected serum samples from biorepositories from patients with 1) prostate cancer with a Gleason score of 7 or higher; 2) prostate cancer with a Gleason score of less than 7; or 3) negative prostate biopsies with a PSA of 10 mcg/L or less and no history of cancer of any kind, a normal digital rectal examination, and no inflammatory disease. They also selected 2 control groups: one with a history of inflammatory disease but no cancer and one with no history of prostate cancer but a history of another type of cancer. Four hundred specimens were analyzed by mass spectrometry after random selection from the 5 groups of patients, with 125 from the group with high Gleason grade, 125 with low Gleason grade, 125 from the biopsy-negative group, and 50 from each of the control groups. The investigators sought to derive a decision algorithm for classification of prostate cancer from the mass spectrometry data but found that they were unable to separate the patients with prostate cancer from biopsy-negative controls. They also were not able to separate patients with high and low Gleason scores. The conclusion was made that in the validation process, this protein-expression profiling approach did not perform well enough to advance to the prospective study stage.

Miscellaneous Cancers

A number of preliminary proteomic studies are available for many cancers including lung, colorectal, gastric, pancreatic, liver, cervical, endometrial, bladder, lymphoma/leukemia, melanoma, and astrocytomas. (Reymond & Schlegel, 2007; Garrisi et al., 2008; Li et al., 2006; Leman et al., 2007; Belluco et al., 2007; Bast et al., 2007).

Summary

The OVA1 and ROMA tests have both been analytically validated and clinical performance has been reported in prospective multi-center clinical trials. Changes in the observed sensitivity and negative predictive value of testing has been small and of uncertain diagnostic value. No studies have been performed that directly evaluate the impact on referral patterns, and no studies have evaluated the impact on health outcomes. Since performance of the original trials prepared for FDA submissions, neither test has had evaluation of performance independently confirmed by independent investigators. 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. All other uses of this test, including use as a screening tool for ovarian cancer, are also considered investigational.

The clinical sampling for testing by serum proteomic studies for prostate cancer was noted to be inadequate and in need of further, much larger and diverse testing before this new technology could be applied.

Currently, the use of proteomic analysis is in clinical trials and testing is not commercially available. There are no published prospective trials that demonstrate that the use of proteomic analysis for screening or detection of disease improves clinical outcomes, and it is therefor considered investigational. Some of the cancer applications under study are: breast, lung, colorectal, gastric, pancreatic, liver, cervical, endometrial, bladder, lymphoma/leukemia, melanoma, neuroblastoma, and astrocytomas. Proteomic analysis is also being studied for medical indications other than cancer e.g. for the identification of disease, response to treatment and preventive care.

Clinical Practice Guidelines and Position Statements

The Society for Gynecologic Oncology (SGO) addressed the use of the OVA1 test in a bulletin issued in 2009. This document included the following statements:

- The OVA1 test may be a useful tool in identifying women who should be referred to a gynecologic oncologist for their ovarian cancer surgery.
- This test has not been approved for use as an ovarian cancer screening tool, nor has it been proven to result in early detection or reduce the risk of death from this disease.
- Results from the OVA1 test should not be interpreted independently, nor be used in place of a physician's clinical assessment.
- Physicians are strongly encouraged to reference the SGO/ACOG Pelvic Mass Guidelines to determine an appropriate care plan for their patients.

The American Congress of Obstetricians and Gynecologists in 2011 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. 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

The National Cancer Institute in 2013 included a discussion of proteomics in their publication on the Genetics of Breast and Ovarian Cancer. The following statement was included in their discussion on proteomics:

- These (proteomic) studies 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. Level of Evidence: 5

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

- The evidence suggests that the combination of HE4 and serum CA-125 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 CA-125 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 2012 version of the National Comprehensive Cancer Network (NCCN) guidelines addressed the use of the ROMA test in guidelines version V3.2012 on ovarian cancer. The following statement was included in this guideline:

- Although reports suggest that HE4 and CA-125 may be useful in detecting ovarian cancer, recent data show that several markers (including CA-125 and HE4, [ROMA test]) do not increase early enough to be useful in detecting early-stage ovarian cancer.
- Currently, the National Comprehensive Cancer Network (NCCN) panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass, because it increases cost without providing much benefit and because of concerns about false-positive results.
- Clinical Trials

As of August 2013, no clinical trials for analyzing proteomic patterns for early detection of cancer were identified.

A prospective longitudinal patient-based pilot study is currently recruiting patients for the use of mass spectroscopy to discover and validate serum proteomic expression profiles diagnostic of early lung cancer. The approach will compare the serum proteomic expression profiles of patients with non-small cell lung cancer compared to healthy heavy smoking adults, as well as differences before and after anatomic pulmonary resection with curative intent. The serum samples will be used to develop a training data set and then a test set for validation using a class prediction model. Candidate proteomic patterns will then serve as a basis for a larger prospective multicenter clinical trial. (NCT00175578).

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score
	81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score
HCPC	None	
ICD9 Procedure	None	
ICD10 Procedure	N/A	
ICD9 Diagnosis	All Diagnoses	
ICD10 Diagnosis	N/A	

Type	Number	Description
Place of Service	All Places of Service	

Tables

N/A

Definitions

- **Proteins** - The functional units of cells and represent the end product of the interactions among the underlying genes. Proteins perform a wide variety of functions including serving as enzymes, structural components or signaling molecules.
- **Proteomics** - The study of a set of proteins expressed by a cell and the changes in protein expressions patterns.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- N/A

Key / Related Searchable Words

- Adnexal masses
- Fujirebio Diagnostics
- MammoCheck
- OvaCheck
- Ova 1
- OVA1
- Ova1
- Ovarian cancer
- ProstaCheck
- Proteins
- Proteomics
- Roma test
- ROMA
- Vermillion

- 83788
- 83789
- 84999

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/15/2007	BCBSA Medical Policy adoption	Medical Policy Committee

Effective Date	Action	Reason
10/1/2010	Policy Revision with title change from Analysis of Proteomic Patterns in Serum to Identify Cancer	Medical Policy Committee
3/25/2011	Administrative Review	Administrative Review
2/22/2013	Coding Update	Administrative Review
9/27/2013	Policy revision with position change effective 12/19/2013	Medical Policy Committee
12/19/2013	Policy revision with position change.	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

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