BlueCross BlueShield of Alabama

Name of Policy:
Analysis of Proteomic Patterns in Serum to Identify Cancer

Policy #: 176
Category: Medicine

Latest Review Date: August 2013
Policy Grade: **Effective 08/29/2013: Active Policy but no longer scheduled for regular literature reviews and updates.**

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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.*

Description of Procedure or Service:

The analysis of proteomic patterns in serum for early detection of cancer has been proposed. Several of these proteomic tests are being studied, particularly in ovarian and prostate cancer.

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.

Serum protein biomarkers

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.

Ovarian cancer is the leading cause of death from gynecologic malignancy in the United States; most patients present with advanced disease, which has a five-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. However, 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.

Proteomics

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. 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. 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.

Proteomic tests

Correlogic Systems, Inc. has developed a serum-based test using proteomics for the early detection of epithelial ovarian cancer called OvaCheck®. The test is based on proteomic patterns detected in the serum, which are further analyzed with the use of a mass spectrometer to profile a population of proteins based on their size and electrical charge. This type of analysis contains thousands of data points, which undergo further sophisticated computer analysis using artificial intelligence-based algorithms to identify a pattern that is consistent with ovarian cancer.

Policy:

Analysis of proteomic patterns in serum to identify cancer does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The potential role for proteomics for cancer screening and detection has undergone considerable discussion; however, data in the peer-reviewed literature are inadequate to permit scientific conclusions regarding ovarian, prostate, or other malignancies.

Ovarian Cancer

Petricoin and colleagues reported on the technical feasibility of proteomic screening in a test series of serum from 50 patients with and 50 patients without ovarian cancer. The spectra of proteins were analyzed by an iterative searching algorithm that identified a cluster pattern that segregated the patients with cancer from those without. This discovered pattern was then used to classify an independent set of 116 masked serum samples; 50 were from women with ovarian cancer and 66 were from unaffected women or those with nonmalignant conditions. Patients without cancer were considered at high risk, due either to familial breast or cancer syndrome or positivity of BRCA1 or BRCA2 mutations. All 50 with ovarian cancer were correctly identified, including the 18 with Stage I cancer. Of the 66 benign cases, 63 were identified as not being positive for cancer, yielding a sensitivity of 100% and a positive predictive value (PPV) of 94%. The authors noted that while a PPV of 94% may be acceptable for high-risk patients, in the larger population of average-risk patients, the PPV must be close to 100% to avoid a high number of false-positive results, which, in turn, would generate additional workup. One of the key outcomes of an ovarian cancer screening test is the ability to identify Stage I ovarian cancer that is potentially curable with surgery. The described study only included 18 patients with Stage I ovarian cancer. The authors stated that an important future goal is the confirmation of the diagnostic performance of proteomic screening for the prospective detection of Stage I ovarian cancer in trials of both high- and low-risk women.

It should also be noted that the technology used in the Petricoin et al. study is not the same as that proposed for the OvaCheck® test. According to the National Cancer Institute, "The two techniques use different mass spectrometry instrumentation and detection methods, as well as different sample handling and processing methods. Therefore the class of molecules analyzed by these two approaches, and thus the molecules that constitute the diagnostic patterns would be expected to be entirely different." Other comments and correspondence in the literature also question the statistical analysis used by Petricoin et al. and other technical issues. The results of the Petricoin et al. study have not been reproduced elsewhere.

Van Gorp et al noted that in ovarian cancer a great effort has been put into discovering new diagnostic and screening markers. Several proteins have been put forward as possible candidates to fulfill this task. However, none of the proteins turned out to be better than CA125 alone. In endometrial cancer many of the presumed tumor markers are not specific for endometrial cancer but are more tumor markers for cancer in general. The same problem was noticed in cervical cancer. Papers are now focusing more on therapy response and carcinogenesis. To date, proteomic studies have not been able to change clinical practice in gynecological oncology.

Prostate Cancer

Ornstein and colleagues 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 selected serum samples from biorepositories from patients with 1) prostate cancer with a Gleason score of seven or higher; 2) prostate cancer with a Gleason score of less than seven; or 3) negative prostate biopsies with a prostate-specific antigen (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 two 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 five 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.

Masters noted in his study that proteomics has offered the hope of biomarker discovery to improve the management of prostate cancer. Markers are needed for screening and diagnosis, distinguishing latent from aggressive disease, defining the men who will benefit from therapy, differentiating localized from metastatic disease, predicting outcome and identifying new targets for therapy. There are many potential sources of proteins derived from the prostate, including urine, prostatic fluid (expressed or ejaculate), serum, and plasma or tissue, each with distinct advantages and limitations. Equally, there are many methodological platforms for proteomic studies of the prostate. Despite the promise, proteomics has yielded little of relevance to the

management of prostate cancer, and most of the work that has been published is either irreproducible or of no clinical value.

Summary
The use of proteomic pattern analysis for the early detection of cancer is currently 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 therefore considered investigational.

Practice Guidelines and Position Statements
The Society of Gynecologic Oncologists released the following statement in February 2004, which remains unchanged to date:

> "The Society of Gynecologic Oncologists (SGO) recognizes the importance of accurate early detection biomarkers for ovarian cancer. For this reason SGO reviewed the literature regarding OvaCheck, a serum based diagnostic test for ovarian cancer. In the opinion of SGO, more research is needed to validate the test's effectiveness before offering it to the public.
>
> SGO is committed to actively following and contributing to this vitally important research. As physicians who care only for women with gynecologic cancer, our hope is that these cancers can either be prevented or detected early. Because no test now exists to routinely detect ovarian cancer in its earliest and most curable stage, we will await the results of further clinical validation of OvaCheck with great interest."

National Comprehensive Cancer Network (NCCN) Guidelines
NCCN guidelines for the common cancers addressed in this policy do not comment on the use of proteomics.

Key Words:
Proteomics, ovarian cancer, OvaCheck™, Correlogic Systems, ProstaCheck, MammoCheck, NovellusDX

Approved by Governing Bodies:
Originally, the manufacturer had assumed that the test would not be subject to approval by the U.S. Food and Drug Administration (FDA), since the test would be performed exclusively at one reference laboratory and testing materials do not cross state lines (i.e., a "home brew" test). However, in 2004, the FDA determined that the software used to perform the analysis was considered a medical device and under the FDA premarket review jurisdiction. In 2010 Correlogic filed for bankruptcy and in 2011 its assets including the OvaCheck® test were acquired by Vermillion®. The test has since been taken off the market on FDA recommendation.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
BellSouth/AT&T contracts: Considers investigational
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity
Wal-Mart: Special benefit consideration may apply. Refer to member's benefit plan.
Pre-certification/Pre-determination requirements: Not applicable

Current Coding:

There is no specific code for this type of testing. One of the following codes might be used to report the test:

83788	Mass spectroscopy and tandem mass spectrometry (MS, MS/MS), analyte not elsewhere specified, qualitative, each specimen
83789	Mass spectroscopy and tandem mass spectrometry (MS, MS/MS), analyte not elsewhere specified, quantitative, each specimen
84999	Unlisted chemistry procedure

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Policy History:

Medical Policy Group, November 2006 **(4)**
Medical Policy Administration Committee, November 2006
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Medical Policy Group, November 2007 **(1)** Update with literature search, no new references added; no change to policy statement
Medical Policy Group, March 2009 **(1)** Update with literature search, no new references added; no change to policy statement

Medical Policy Group, March 2010 **(1)** Update to Key Points and References; no change to policy statement
Medical Policy Group, July 2011 **(1)** Update to Key Points and References; no change to policy statement
Medical Policy Panel, July 2012
Medical Policy Group, July 2012 **(1)** Update with literature search, no new references added; no change to policy statement
Medical Policy Panel, August 2013
Medical Policy Group, August 2013 **(1)** Update with literature search, no new references added; update to Key Words with addition of mammocheck, prostacheck and novellusDX; no change to policy statement

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