

Medical Policy Manual

Topic: Analysis of Proteomic Patterns for Early Detection of Cancer **Date of Origin:** 08/03/2004

Section: Laboratory

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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 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. 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 the 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.

Regulatory Status

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. At this time, Correlogic is conducting clinical trials on OvaCheck® at sites in the United States and abroad, and it is not commercially available.

Correlogic is also in the process of developing proteomic blood tests for the detection of colorectal, breast (MammoCheck®) and prostate cancer (ProstaCheck®).

Proteomic testing is not commercially available at this time.

MEDICAL POLICY CRITERIA

Analysis of proteomic patterns in serum for screening and detection of cancer is considered **investigational** for all indications, including but not limited to ovarian, prostate, breast, and gastrointestinal cancer.

SCIENTIFIC EVIDENCE^[1]

Literature Appraisal

The potential role for proteomics for cancer screening and detection has undergone considerable discussion^[2-5]; 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.^[6] 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 BRCA 1 or BRCA 2 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 of 94%. The authors noted that while a positive predictive value of 94% may be acceptable for high-risk patients, in the larger population of average-risk patients, the positive predictive value 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 study^[6] 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. The class of molecules analyzed by these two approaches, and thus the molecules that constitute the diagnostic patterns are entirely different.”^[7] Other comments and correspondence in the literature^[8] also question the statistical analysis used by Petricoin and other technical issues.^[9] The results of the Petricoin study have not been reproduced elsewhere.

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.^[10] 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 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.^[11] 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 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 breast, lung, colorectal, gastric, pancreatic, liver, cervical, endometrial, bladder, lymphoma/leukemia, melanoma, neuroblastoma, and astrocytomas.^[12-20]

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The 2013 NCCN guidelines on prostate^[21], ovarian^[22], and breast^[23] addressed in this policy do not comment on the use of proteomics.^[24]

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.

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CROSS REFERENCES

[Detection of Circulating Tumor Cells in the Management of Patients with Cancer](#), Laboratory, Policy No. 46

[Proteomics-based Testing Related to Ovarian Cancer](#), Laboratory, Policy No. 60

CODES	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
	84999	Unlisted chemistry procedure
HCPCS	None	