Analysis of Proteomic and Metabolomic Patterns for Early Detection of Cancer

Effective: January 1, 2018

Next Review: November 2018
Last Review: November 2017

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

Proteomics is known as protein expression profiling, while metabolomics is the assaying of substrates and by-products of enzymatic reactions. Both of these types of tests are currently being used in an effort to improve screening and early detection of cancer through the measurement of these markers in the blood or urine; with a focus on breast, prostate and colon cancer.

MEDICAL POLICY CRITERIA

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Detection of Circulating Tumor Cells in the Management of Patients with Cancer, Laboratory, Policy No. 46
2. Proteomics-based Testing Related to Ovarian Cancer, Laboratory, Policy No. 60
BACKGROUND

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, and substrates and by-products of enzymatic reactions are indicators of cellular metabolic status. As such, research interest has been increasing in the fields of proteomics and metabolomics, in an effort to improve on screening and early 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 involves 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.

METABOLOMICS

Metabolomics is a newly emerging field that involves the characterization of small molecule metabolites in biological systems, primarily substrates and by-products of enzymatic reactions. It can provide information regarding the metabolic status and global biochemical events associated with a cellular or biological system.

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 or metabolite level. Another issue with proteomics and metabolomics is that studies involving these methods as screening or diagnostic tools have lack of uniform patient inclusion and exclusion criteria, small patient numbers, absence of standardized sample preparations, and limited analytical reproducibility.
REGULATORY STATUS

None of the tests addressed in this policy have been submitted to the U.S. Food and Drug Administration (FDA) for marketing clearance but, if available, are offered as laboratory-developed tests by Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories.

EVIDENCE SUMMARY

The potential role for proteomics and metabolomics for cancer screening and detection has undergone considerable discussion\[^{[1-4]}\]; however, data in the peer-reviewed literature are inadequate to permit scientific conclusions regarding ovarian, prostate, colon cancer or other malignancies.

Metabolomics is still considered an emerging field and all of the published studies focus on improving the analytical and clinical validity of these tests for various oncological indications. To date, there have been no studies published on actual clinical utility of any metabolomic test.

SYSTEMATIC REVIEWS OF PROTEOMIC AND METABOLOMIC ANALYSES FOR VARIOUS TYPES OF CANCER

In 2013, Liesenfeld conducted a systematic review of mass spectrometry-based metabolomics in cancer research, including 106 studies reporting on 21 different types of cancer in seven different sample types.\[^{[5]}\] Only 15 out of 106 studies (14%) investigated samples from more than 100 cancer patients. Seventy-seven studies (73%) of the included studies examined the use of blood or urine with the intent of early diagnosis of cancer, with 20 studies on colon cancer, and thirteen on breast, lung and liver. The reviewers concluded that metabolomics is at a developmental stage and large-scale studies including prospective validation are needed.

OVARIAN CANCER

Petricoin (2002) 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 \(\text{BRCA1} \) or \(\text{BRCA2} \) 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 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**

In 2016, Huang investigated the relationship of the serum metabolome with prostate cancer risk.[10] The study included 380 cases diagnosed post-screening and 380 case controls. Sera were analyzed on a high-resolution accurate mass platform of ultrahigh-performance liquid and gas chromatography/mass spectroscopy. A total of 695 known metabolites were identified and 27 were associated with prostate cancer, but statistical methods, including Bonferroni correction, did not show any to be statistically significant.

Ornstein (2004) reported the results of serum proteomic profiling in 154 men with serum PSA ranging from 2.5 to 15.0 ng/mL.[11] 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 (2008) 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 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.[12] 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.

**COLON CANCER**

In 2016, Deng validated the PolypDx™ test for its ability to detect adenomatous polyps, including 1000 Chinese participants undergoing colonoscopy examination.[13] One-dimensional nuclear magnetic resonance spectra of urine metabolites were analyzed to determine the concentrations of three key metabolites used in PolypDx™, although 70 metabolites were
quantified in total. The predicted results were compared to standard colonoscopy. An area under curve (AUC) of 0.717 for PolypDx™ was calculated on Chinese dataset, which is slightly lower than the AUC on the Canadian dataset (0.752).[14] The sensitivity and specificity of PolypDx™ was calculated for this dataset, at 82.6% and 42.4%, respectively. When the specificity threshold was set similar to fecal-based tests, the sensitivity of the PolypDx™ test was determined to greater (19.1%) than three fecal-based tests (fecal guaiac HemiII®, fecal immune ICT® and fecal immune Magst®), whose sensitivities ranged from 2.5 to 11.9%. The authors reported that some of the desired metabolites “were often below the level of the detection” indicating that further study is needed to determine the most sensitive analytical technique and that significant research needs to be done in order to standardize the assay.

In 2013, Eisner reported the initial validation study for the novel urine-based metabolomic diagnostic test, called PolypDx™, evaluating its ability to distinguish patients who require a colonoscopy from those who do not.[14] The test was developed using a group of 988 patients (633 normal and 355 who required colonoscopy) who were all at average or above-average risk for developing colorectal cancer. A metabolic profile of 72 metabolites for each subject was analyzed using ¹H-NMR and quantified using targeted profiling. Each subject then underwent a colonoscopy to determine whether he/she actually had an adenomatous polyp, a precursor to colorectal cancer. The metabolic profiles, colonoscopy outcomes, and medical histories were then analyzed to create a classifier that could predict whether a future patient requires a colonoscopy. Analyzed in this way, the investigators reported a sensitivity of 64% and a specificity of 65% for this test and its resulting classifier. As with the study above, many of the metabolites were often found to be below the level of detection, leaving only 27 metabolites to be used for analyses that were above the level of detection in at least 80% of the samples. Test performance is still being optimized for this assay, and further studies are needed. Other limitations include heterogeneous sample populations from multiple centers and a significantly higher number of adenocarcinoma among the cancer group, indicating poorly-matched baseline case-control populations.

**LUNG CANCER**

**Xpresys® Lung**

In 2015, Vanchani assessed the clinical utility of the Xpresys® Lung classifier in a multicenter prospective–retrospective analysis of a study including 475 patients with nodules 8–30 mm in diameter who had an invasive procedure to confirm diagnosis.[15] Based on the Xpresys® Lung test results, 32.0 % (CI 19.5–46.7) of surgeries and 31.8 % (CI 20.9–44.4) of invasive procedures (biopsy and/or surgery) on benign nodules could have been avoided. Patients with malignancy triaged to CT surveillance by the classifier would have been 24.0 % (CI 19.2–29.4). This rate is similar to that described in clinical practices (24.5 % CI 16.2–34.4). The potential harm of this test is that the percent of malignant lung nodules routed to CT surveillance is similar to that when compared to usual care (17.1 – 24.0% versus 24.5%, respectively). This study does not demonstrate true clinical utility, as it is reporting predicted potential changes in management, and not actual changes in management.

In 2015, Vachani also conducted a study addressing the clinical validity of an 11-protein version of the Xpresys® Lung test for individuals with pulmonary lung nodules.[16] This blinded, retrospective case-control study involved 141 lung nodule plasma samples and demonstrated an NPV of 90%, positive predictive values (PPV) of 26%, sensitivity of 92% and specificity of 20%. Results were independent of age, tobacco use, nodule size and diagnosis of chronic
obstructive pulmonary disease (COPD). As with the Li study described below, no clinical utility data was reported that addressed if the test altered medical management.

In 2013, Li and others described the result of the first validation study addressing a 13-protein version of the Xpresys® Lung test, which is proposed for the differentiation of benign and malignant pulmonary lung nodules.[17] This case-control study involved 143 serum samples from subjects with either benign or stage 1A lung cancer matched for nodule size, age, gender, and clinical site. The authors reported that the test was validated in a 104-subject group, resulting in a negative predictive value (NPV) of 90%. This result was independent of age, nodule size, or smoking history. No clinical utility data was reported that addressed if the test altered medical management in test subjects.

**EarlyCDT®-Lung**

In a 2017 prospective registry trial, Massion assessed the value of the EarlyCDT-Lung test in patients with an identified lung nodule.[18] A cohort of 1987 individuals were evaluated, and 451 had at least one nodule. Of those, 296 met inclusion criteria and received imaging, pathology, and testing with EarlyCDT-Lung. Patients with a positive EarlyCDT-Lung result had a twofold greater relative risk of developing lung cancer as compared with those with a negative test result. When EarlyCDT-Lung was added to risk models, diagnostic performance with high specificity (>92%) and positive predictive value (>70%) were improved.

In 2014, Jett published the results from the first 1699 patients for whom US physicians ordered EarlyCDT®-Lung test.[19] Six-month outcome analysis was based on 1613 patients. Six-month follow-up for the positives/negatives was 99%/93%. Sixty-one patients (4%) were identified with lung cancer, only 25 of whom tested positive by EarlyCDT®-Lung (sensitivity=41%). A positive EarlyCDT-Lung test on the current panel was associated with a 5.4-fold increase in lung cancer incidence versus a negative test result. Comparing performance of the seven-autoantibody panel (7AAB) and the six-autoantibody panel (6AAB), the 7AAB showed highly statistically significant (p < 0.0001) improved specificity over the 6AAB panel (91% versus 83%, respectively). The sensitivities of the 6AAB and 7AAB panels were not statistically different (46% versus 37%), respectively. The PPV offered by the 7AAB panel was nearly 2× better than the previous 6AAB panel (16% versus 9%, respectively). Eight out of fourteen NSCLCs (57%) detected as positive were early stage cancer (I or II). The investigators concluded that EarlyCDT®-Lung may be a complementary tool to CT for detection of early lung cancer.

In 2012, Chapman published the results of a case-control study involving 235 subjects with newly diagnosed lung cancer and 235 healthy controls used to evaluate both six- and seven-antigen versions of the EarlyCDT®-Lung test.[20] In addition, two prospective consecutive series of 776 and 836 individuals at an increased risk of developing lung cancer were also evaluated with both versions of the EarlyCDT®-Lung test. The six-antigen panel gave a sensitivity of 39% and a specificity of 89%, while the seven-antigen panel resulted in a sensitivity of 41% and a specificity of 91%. Once adjusted for occult cancers in the population, this resulted in a specificity of 93%.

In 2011, Lam published a case-control study describing the sensitivity of the EarlyCDT®-Lung test, which evaluated samples for tumor associated autoantibodies found in individuals with lung cancer, including 574 subjects from four separate cohorts.[21] Group one (n=122) included subjects with only small cell lung cancer (SCLC); group two (n=249) was composed of 97% of subjects with non-small cell lung cancer (NSCLC); group three (n=122) included only subjects
with NSCLC; and group four (n=81), was made up of 62% of subjects with NSCLC. For group one the results indicated a sensitivity of 57% for SCLC (specificity data not calculated). The sensitivity and specificity for group two was 34% and 87% for NSCLC. For group three sensitivity and specificity was 31% and 84% for NSCLC. Finally, in group four sensitivity and specificity was 35% and 89% for NSCLC and 43% and 89% for SCLC. No significant difference in positivity was reported for the EarlyCDT-Lung test with regard to different lung cancer stages.

Initial clinical validation of the EarlyCDT®-Lung test was reported by Boyle in 2011.[22] This study used the same three populations as the Murray study.[23] The optimal assay cut-off point was calibrated to target a 90% specificity, which provided the optimal overall accuracy based on Monte Carlo simulations. For the three separate populations, sensitivity was 36%, 39% and 37%. The specificity was 91%, 89%, 90%, approximating the 90% specificity of test calibration. Using a population prevalence of 2.0%, the positive predictive value (PPV) ranged from 7.0%-7.2% and the negative predictive value (NPV) was 98.6%. The area under the curve by ROC analysis was 0.63. There were no significant differences in accuracy of the test by lung cancer stage.

MISCELLANEOUS CANCERS

A number of preliminary proteomic studies are available for many cancers including breast, lung, colorectal, gastric, pancreatic, liver, cervical, endometrial, renal, bladder, lymphoma/leukemia, melanoma, neuroblastoma, meningiomas, nasopharyngeal carcinomas, and astrocytomas.[24-38]

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF RADIOLOGY (ACR)[39]

The 2012 ACR guidelines on ovarian cancer screening state that although there is increased interested in proteomic screening “there is currently insufficient evidence available for determining the value of biomarkers in population-level ovarian cancer screening”.

SUMMARY

The use of proteomic and metabolomic pattern analysis for the early detection of cancer is currently in the early research phase. There is no research showing that the use of proteomic or metabolomic analysis for screening or detection of disease improves clinical outcomes compared to standard screening and diagnostic tools. In addition, there are no research-based practice guidelines that recommend proteomic or metabolomic analysis for screening or detection of disease. Therefore, the use of proteomic or metabolomic pattern analysis for the early detection of cancer is considered investigational.

REFERENCES


### CODES

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