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Medical Policy Manual Laboratory, Policy No. 41

Analysis of Proteomic and Metabolomic Patterns for Cancer Detection, Risk, Prognosis, or Treatment Selection

Effective: February 1, 2023

Next Review: November 2023
Last Review: December 2022

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 describes the assaying of substrates and by-products of enzymatic reactions. Both of these types of tests are currently being studied in an effort to improve screening and early detection of cancer, to assess the risk of cancer development, or for cancer treatment selection.

MEDICAL POLICY CRITERIA

Note: This policy does not address proteomic and metabolomic tests for ovarian cancer, prostate cancer, or lung nodules, or urinary biomarker tests (see Cross References section).

Analysis of proteomic and metabolomic patterns for screening and detection of cancer, for assessing risk of cancer development, for cancer prognosis, or for cancer treatment selection is considered **investigational** for all indications.

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

CROSS REFERENCES

1. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
2. Detection of Circulating Tumor Cells in the Management of Patients with Cancer, Laboratory, Policy No. 46
3. Proteomics-based Testing Related to Ovarian Cancer, Laboratory, Policy No. 60
4. Protein Biomarkers for Screening, Detection, and/or Management of Prostate Cancer, Laboratory, Policy No. 69
5. Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance, Laboratory, Policy No. 72
6. Molecular Testing in the Management of Pulmonary Nodules, Laboratory, Policy No. 73

BACKGROUND

Genetic information does not completely 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% to 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 spectometry 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

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The commercially available proteomic test (VeriStrat®; Biodesix) is available underthe Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

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 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 the clinical utility of any metabolomic test.

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

Liesenfeld (2013) 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.

Madama (2021) published a systematic review of metabolomic profiling in lung cancer.[6] The authors noted that while more than 150 metabolites have been associated with lung cancer, patient selection for studies has been variable, and studies evaluating the use of profiling tests to predict lung cancer treatment response are lacking. A systematic review by Pillai (2021) on proteomic biomarkers for oral squamous cell cancer noted similar limitations, including a lack of validation for most biomarkers.

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.[7-24]

VERISTRAT®

VeriStrat®, a commercially available serum-based test, has been developed and proposed to be used as a prognostic tool to predict expected survival for standard therapies used in the

treatment of non-small cell lung cancer (NSCLC). The test is also proposed to have predictive value for response to epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR* TKIs). The test uses matrix-assisted laser desorption ionization mass spectrometry analysis, and a classification algorithm was developed on a training set of pretreatment sera from three cohorts totaling 139 patients with advanced NSCLC who were treated with second-line gefitinib.[25] The classification result is either “good” or “poor".

Testing for Prognosis

For individuals with newly diagnosed advanced NSCLC without prior systemic therapy, multiple studies have assessed the use of VeriStrat® score (good or poor) as a prognostic test to discriminate between overall survival (OS) and progression-free survival (PFS) outcomes.[25-33] Most studies were retrospective and intended to validate the extent to which the VeriStrat® proteomic classification correlated with OS or PFS. Grossi (2017) was an observational nonrandomized study with prospective sample collection for proteomic testing before NSCLC treatment and reported PFS as the primary outcome.[31] This is the only study that included a first-line treatment consistent with current guidelines-based recommendations; platinum-doublet-based chemotherapy with cisplatin or carboplatin in combination with pemetrexed.

The VeriStrat® classification was not used to direct the selection of treatment in any of the clinical trials from which the validation samples were derived. Testing for the presence of a sensitizing variant (*EGFR*) for targeted therapy with TKIs was variably performed in these studies. When testing was performed and results known as wild-type (negative) or positive, the analysis of OS and PFS was variably adjusted for variant status. The relationship between VeriStrat® classification and OS and PFS in populations with unknown variant status, when reported, was not analyzed. Disposition of populations with variant status “not reported” was generally not clear and could not be construed as “unknown” when wild-type or positive variant status was reported.

For individuals with advanced NSCLC who had recurrent disease or who had failed prior systemic therapy, multiple studies assessed the use of VeriStrat® as a prognostic test to discriminate between good and poor survival outcomes.[25, 34-36] All studies were retrospective and intended to validate the extent to which VeriStrat® proteomic classification correlated with OS or PFS. The VeriStrat® classification was not used to direct the selection of treatment in any of the clinical trials from which the validation samples were derived. None of the trials from which the samples for VeriStrat® proteomic classification were derived used a therapy consistent with current guidelines-based recommendations. The populations in all studies were unselected for *EGFR*-variant status.

Testing for Treatment Selection

<u>Randomized Controlled Trials</u>

No randomized controlled trials (RCT) designed to evaluate the use of the Veristrat® test were identified, however the use of the test has been explored in RCTs for treatment regimens.

In the PROSE trial, Gregorc (2014) prospectively evaluated the VeriStrat® test in an RCT comparing erlotinib with chemotherapy as a second-line treatment for patients with stage IIIB or IV NSCLC, stratified by performance status, smoking history, treatment center, and (masked) pretreatment VeriStrat® classification.[37] In a multivariate model to predict OS, which included clinical characteristics and *EGFR*-variant status, VeriStrat® classification was

significantly associated with OS (hazard ratio [HR] for VeriStrat® “good” vs “poor” 1.88, 95% confidence interval [CI] 1.25 to 2.84, p=0.003). In the entire analysis cohort, the median OS was 9.0 months in the chemotherapy group and 7.7 months in the erlotinib group; OS did not differ significantly by treatment group in adjusted or unadjusted analyses. Moreover, PFS did not differ significantly by treatment group in the unadjusted analysis but was improved for the chemotherapy group in adjusted analysis (HR 1.35, 95% CI 1.05 to 1.73, p=0.020). Stratification of patients by VeriStrat® classification changed the estimate of the effect of chemotherapy. In the VeriStrat® “good” group, there was no significant difference in OS between the two treatment groups, whereas, in the VeriStrat® “poor” group, OS was shorter for patients treated with erlotinib. The authors of the PROSE trial concluded that the VeriStrat® proteomic test predicted differential benefit for erlotinib compared with chemotherapy as second-line treatment of NSCLC, suggesting that patients classified as VeriStrat® “poor” would have better outcomes with chemotherapy than erlotinib.

Peters (2017) published a randomized, phase 3, open-label trial (EMPHASIS) exploring the differential effect of second-line erlotinib vs docetaxel in VeriStrat® “good” vs “poor” patients. Patients had stage IIIB or IV squamous cell NSCLC and had failed first-line platinum-based doublet chemotherapy. Recruitment for the trial ended early due to low enrollment and the release of results from other trials (e.g., PROSE). The EMPHASIS investigators analyzed trial findings and conducted an exploratory analysis combining EMPHASIS results with those from the squamous cell NSCLC cohort in the PROSE trial. Eighty patients were randomized, of whom 58 (72.5%) were categorized as VeriStrat® “good.” The primary endpoint was PFS and was analyzed on an intention-to-treat basis. After a median follow-up of 20.5 months, 73 patients had experienced disease progression (median PFS, 2.7 months). Median PFS was 1.6 months in the erlotinib group and 3.0 months in the docetaxel group; the difference between groups was not statistically significant (p=0.37). PFS did not differ significantly by VeriStrat® status, and there was no significant interaction between treatment and VeriStrat® status (p=0.80). This trial was restricted to squamous NSCLC histology, and the treatment decision model is not representative of current guideline recommendations.

Lee (2019) published results from a randomized, double-blind trial (TOPICAL) in patients (n=527) with previously untreated advanced-stage IIIB/IV NSCLC who were considered unfit for platinum doublet chemotherapy due to poor performance status (PS, PS 2: 56%, PS 3: 27%) and/or the presence of multiple comorbidities.[33] Patients were unselected for *EGFR* status and randomized for treatment with erlotinib or placebo and active supportive care. This treatment approach is not consistent with current guidelines that cite recent data indicating that NSCLC tumors that do not harbor a sensitizing *EGFR* variant should not be treated with an *EGFR* TKI in any line of therapy. For patients with comorbidities and PS 0-1, carboplatin-based regimens are often used. For patients with PS 2, several alternative systemic therapy regimens not involving platinum-based agents are also available, including paclitaxel, albumin-bound paclitaxel, docetaxel, gemcitabine, gemcitabine/docetaxel, gemcitabine/vinorelbine, and pemetrexed. Fifty-five percent of patients were categorized as VeriStrat® “good,” which included 164 patients in the erlotinib arm and 124 patients in the placebo arm. Forty-five percent of patients were classified as VeriStrat® “poor,” which included 115 patients in the erlotinib arm and 124 patients in the placebo arm. For patients with VeriStrat® “good” vs. “poor” scores, median OS was 4.6 months vs. 2.9 months in the placebo group (HR 0.54, 95% CI 0.41 to 0.78, p<0.001) and 4.9 months vs. 3.1 months in the erlotinib group (HR 0.60, 95% CI 0.47 to 0.77, p<0.001). The difference between groups was not statistically significant in the unadjusted analysis (HR 0.93, 95% CI 0.87 to 1.11, p=0.41). *EGFR*-variant status was known in 41.2% of patients, which includes *EGFR*-variant positive status in 21/288 (7.3%) with a

VeriStrat® “good” score and 6/239 (2.5%) with a “poor” score. were *EGFR*-variant positive. Both VeriStrat® "good" vs. "poor" classification and *EGFR*-variant positive vs. wild-type status were found to have prognostic value for OS. Only VeriStrat® classification was found to have prognostic value for PFS. VeriStrat® classification did not have predictive value for response to erlotinib vs placebo. The authors indicate that the VeriStrat® assay was able to stratify patients within ECOG PS grades 0-1 and 2-3, however, CIs for these groups were not reported. *EGFR*-variant status was not reported according to respective treatment groups.

Several retrospective analyses of data from RCTs evaluating the efficacy of TKIs have examined VeriStrat® as a prognostic and/or predictive test. Carbone (2012) investigated the prognostic and predictive effects of VeriStrat® classification on response to treatment and survival in a subset of patients enrolled in a phase 3 trial of erlotinib vs placebo.[38] BR.21, a randomized, placebo-controlled study of erlotinib, enrolled 731 previously treated patients with advanced NSCLC. In the primary study, PFS and OS were prolonged by erlotinib. *EGFR* variants were prognostic for OS, but not predictive of erlotinib benefit, while increased *EGFR* copy number variants were both prognostic and predictive of erlotinib benefit. For the present trial, plasma from 441 patients was tested with the VeriStrat® test, of which 436 (98.9%) could be classified as “good” or “poor.” Among the 144 placebo patients, VeriStrat® test results were prognostic, with “good” patients (median OS 6.6 months, 95% CI 4.4 to 8.2 months) surviving significantly longer than “poor” patients (median OS 3.1 months, 95% CI 2.2 to 3.7 months, HR 0.44, 95% CI 0.31 to 0.63, p<0.001). Similar results were seen for PFS, with VeriStrat® “good” patients having longer PFS than “poor” patients (HR 0.59, 95% CI 0.42 to 0.86, p=0.002). Median survival was 10.5 months for VeriStrat® “good” patients treated with erlotinib and 6.6 months for those on placebo (HR 0.63, 95% CI 0.47 to 0.85, p=0.002), while for VeriStrat® “poor” patients, the median survival for erlotinib was 3.98 months and 3.09 months for placebo (HR 0.77, 95% CI 0.55 to 1.06, p=0.11). For 252 erlotinib-treated patients with data available to evaluate for objective response, VeriStrat® “good” patients (n=157 [62%]) had a significantly higher response rate (11.5%) than VeriStrat® “poor” patients (1.1%, p=0.002). In a Cox multivariate regression model to predict OS, the interaction between VeriStrat® status and treatment type was not statistically significant, indicating that both “good” and “poor” cohorts derived a similar survival benefit from erlotinib. The authors concluded that VeriStrat® status predicted response to erlotinib but did not predict differential benefit from erlotinib for OS or PFS.

Gadgeel (2017) retrospectively analyzed data from the LUX-Lung 8 trial, which compared second-line treatment with 1 of 2 TKIs (erlotinib, afatinib) in patients with advanced-stage IIIB or IV squamous NSCLC.[39] *EGFR*-variant status was not considered in study eligibility. Blood samples for VeriStrat® analysis were available for 691 (87%) of 795 randomized patients; of these, 12 had indeterminate results, and four could not be analyzed. The primary objective of the analysis was to evaluate whether VeriStrat® status pretreatment is associated with OS and in the afatinib vs erlotinib groups. In the cohort with VeriStrat® results (n=675), OS was significantly longer in the afatinib group (median, 7.8 months) than in the erlotinib group (median, 6.9 months, p=0.03). When stratified by VeriStrat® status, OS was significantly longer with afatinib than with erlotinib in the VeriStrat® “good” group (median, 11.5 months vs 8.9 months, HR 0.79, 95% CI 0.63 to 0.98) but not the VeriStrat® “poor” group (median, 4.7 months vs 4.8 months, HR 0.90, 95% CI 0.70 to 1.16). In the VeriStrat® stratified analysis, findings were similar for PFS. The study lacked a group receiving chemotherapy with which to compare the efficacy of TKIs.

Buttigliero (2018) retrospectively examined VeriStrat® as a prognostic and/or predictive test in a randomized controlled phase 3 RCT (MARQUEE trial[40]) of previously treated patients with advanced nonsquamous NSCLC who were given erlotinib plus tivantinib or placebo.[41] *EGFR*-variant status was not considered in trial eligibility, and patients previously treated with *EGFR* inhibitors were excluded from the trial. Of the 1,048 patients assigned to treatment protocols, 976 (93%) patients discontinued treatment by protocol (duration of therapy, 0.1-92 weeks), which was discontinued for futility at an interim analysis. In this cohort, no significant difference was seen between the treatment arms for OS. Intention-to-treat analysis of VeriStrat® pretreatment status was performed on data for 996 patients.

When stratified by VeriStrat® status, PFS and OS were significantly longer for patients in the VeriStrat® "good" group than the VeriStrat® "poor" group for both treatment arms ($p<0.01$); no direct comparison of treatment arms within the VeriStrat® "good" or "poor" groups was performed. A prespecified Cox multivariate regression analysis of OS for the cohort demonstrated that there was a statistically significant difference between VeriStrat® "good" and "poor" groups ($p<0.001$). There was a significant correlation between treatment and VeriStrat® status ($p=0.037$) in multivariate analysis considering *EGFR* variant status; this interaction was no longer significant ($p=0.068$) when KRAS variant status was entered into the analysis. For patients who were *EGFR* wild-type (n=895 [90%]), OS was higher for both treatment arms in the VeriStrat® "good" group (tivantinib arm median 10.3 months, 95% CI 8.9 to 11.5 months; placebo arm median 9.2 months, 95% CI 7.8 to 10.2 months) than in the VeriStrat® "poor" group (tivantinib arm median 3.9 months, 95% CI 3.1 to 4.3 months; placebo arm median 3.8 months, 95% CI 2.9 to 5.4 months). The trial was restricted to nonsquamous NSCLC and lacked a group receiving chemotherapy with which to compare the efficacy of TKIs.

Clinical Utility

Two studies have evaluated the impact of VeriStrat® testing on physician treatment recommendations. Akerley (2013) reported on 226 physicians who provided pre- and post-test treatment plan information for 403 VeriStrat® tests.[42] In the 262 cases where pretreatment recommendations were for erlotinib only, for those patients who were classified as VeriStrat® "poor," physicians recommended erlotinib in 13.3%. In a larger study, Akerley (2017) reported on 2411 physicians who received 14327 VeriStrat® test results.[43] The investigators only included tests that were ordered for NSCLC, were ordered as the sole test, were not indeterminate, and were not ordered in patients with known *EGFR*-variant status. VeriStrat® findings were a classification of "good" for 1950 (78.2%) patients and "poor" for 544 (21.8%) patients. After receiving the test results, physicians changed their treatment recommendations in 28.2% of the cases; within this group, 13.2% were classified as VeriStrat® "good" and 81.6% as VeriStrat® "poor." Physicians initially considered treatment with an *EGFR* TKI in 484 (89.0%) of 544 classified as VeriStrat® "poor"; after receiving test results only, 49 (10%) were actually recommended *EGFR* TKI treatment.

PRACTICE GUIDELINE SUMMARY

No guidelines have been identified that currently recommend proteomic or metabolomic screening for cancers other than prostate. For example, National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma (v.1.2022) state:[44]

“Newer screening methods to identify patients with early pancreatic cancer rather than those with preinvasive lesions may prove to be beneficial in the future.”

SUMMARY

The use of proteomic and metabolomic pattern analysis for the early detection and treatment of cancer is currently in the early research phase. There is no research showing that the use of proteomic or metabolomic analysis for screening, detection, assessing risk of disease, or treatment selectin 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 this purpose. Therefore, the use of proteomic or metabolomic pattern analysis for the early detection of cancer, assessing risk of cancer development, cancer prognosis, or for cancer treatment selection is considered investigational.

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CODES

Codes	Number	Description
CPT	0067U	Oncology (breast), immunohistochemistry, protein expression profiling of 4 biomarkers (matrix metalloproteinase-1 [MMP-1], carcinoembryonic antigen-related cell adhesion molecule 6 [CEACAM6], hyaluronoglucosaminidase [HYAL1], highly expressed in cancer protein [HEC1]), formalin-fixed paraffin-embedded precancerous breast tissue, algorithm reported as carcinoma risk score
	0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas
	0174U	Oncology (solid tumor), mass spectrometric 30 protein targets, formalin fixed paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely, or uncertain benefit of 39 chemotherapy and targeted therapeutic oncology agents
	0249U	Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report
	81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
	84999	Unlisted chemistry procedure
HCPCS	None	

Date of Origin: *August 2004*