Proteomic Testing for Systemic Therapy in Non-Small Cell Lung Cancer

Medical Policy #: 02.04.77
Original Effective Date: September 2019
Reviewed: September 2022
Revised: September 2020

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DESCRIPTION

Lung cancer is the leading cause of cancer death in the United States. In 2022, an estimated 236,740 new cases (117,910 in men and 118,830 in females) of lung and bronchial cancer will be diagnosed, and 130,180 deaths (68,820 in men and 61,360 in women) are estimated to occur because of the disease. Only 21.7% of all patients with lung cancer are alive 5 years or more after diagnosis. However, much progress has been made recently for lung cancer such as screening; this includes patients with non-small cell lung cancer (NSCLC) and those with small cell lung cancer (SCLC) (NCCN Non-Small Cell Lung Cancer Version 4.2022).

Diagnosis
The stage at which lung cancer is diagnosed has the greatest impact on prognosis. Localized disease confined to the primary site has a 59.8 % relative 5-year survival but accounts for only 18 % of lung cancer cases at diagnosis. Mortality increases sharply with advancing stage. Metastatic lung cancer has a relative 5-year survival of 6.3%. Overall, advanced disease, defined as regional involvement and metastatic, accounts for approximately 80% of cases of lung cancer at diagnosis. These statistics are mirrored for the population of NSCLC, with 85% of cases presenting as advanced disease and up to 40% of patients with metastatic disease.

Treatment
Treatment approaches are multimodal and generally include surgery, radiotherapy, and chemotherapy (either alone or in combination with another treatment, depending on disease stage and tumor characteristics). Per the National Comprehensive Cancer Network (NCCN) guidelines, the clinical management pathway for stage I or II NSCLC is dependent on surgical findings and may involve resection, radiotherapy, chemotherapy, or chemoradiation. First-line chemotherapy regimens for neoadjuvant and adjuvant therapy utilize platinum-based agents (e.g., cisplatin, carboplatin) in combination with other chemotherapeutics and/or radiotherapy. Treatment recommendations are based on the overall health or performance status of the patient, presence, or absence of metastases, as well as the presence or absence of a treatment-sensitizing genetic variant. These aspects inform the selection of targeted and systemic therapies.[7]

For individuals who experience disease progression following initial systemic therapy, subsequent treatment regimens are recommended, mainly featuring novel programmed death-ligand 1 (PD-L1) inhibitors. The NCCN also includes recommendations for targeted therapy or immunotherapy in patients with biomarkers, including sensitizing epidermal growth factor receptor (EGFR) mutations. For patients with sensitizing EGFR mutations, recommendations include first-line therapy with EGFR tyrosine kinase inhibitors (TKIs) afatinib, erlotinib, dacomitinib, gefitinib, erlotinib plus ramucirumab, erlotinib plus bevacizumab (nonsquamous), or osimertinib and subsequent therapy with osimertinib. The NCCN does not make any recommendations for the use of EGFR TKIs in the absence of a confirmed sensitizing EGFR mutation. Initial systemic therapy recommendations can be considered for multiple, symptomatic, systemic lesions

Genomic Alterations
Several common genetic alterations in NSCLC have been targets for drug therapy, the most well-established of which are TKIs targeting the EGFR and crizotinib targeting the anaplastic lymphoma kinase (ALK) gene rearrangement.

EGFR Variants
EGFR, a tyrosine kinase (TK) receptor, is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR-signaling either prevent ligand-binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small molecule TKIs). These targeted therapies dampen signal transduction through pathways

downstream to the EGFR, such as the RAS/RAF/MAPK cascade. RAS proteins are G proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and the stimulation of neovascularization.

Variants in 2 regions of the EGFR gene, including small deletions in exon 19 and a point mutation in exon 21 (L858R), appear to predict tumor response to TKIs such as erlotinib. The prevalence of EGFR variants in NSCLC varies by population, with the highest prevalence in nonsmoking Asian women with adenocarcinoma; for that subpopulation, EGFR variants have been reported to as high as 30% to 50%. The reported prevalence of EGFR variants in lung adenocarcinoma patients in the U. S. is approximately 15%

ALK Variants
For 2% to 7% of NSCLC patients in the U.S., tumors express a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the ALK gene (EML4-ALK), which is created by an inversion on chromosome 2p.[6,] The EML4 fusion leads to ligand-independent activation of ALK, which encodes a receptor TK whose precise cellular function is not completely understood. EML4-ALK variants are more common in never smokers or light smokers, tend to be associated with younger age of NSCLC onset, and typically do not occur in conjunction with EGFR variants.

Testing for the EML4-ALK fusion gene in patients with adenocarcinoma-type NSCLC is used to predict response to the small molecule TKI crizotinib.

Other Genetic Variants
There are other genetic variants identified in subsets of patients with NSCLC. The role of testing for these variants is to help select targeted therapies for NSCLC, *see medical policy 02.04.78 Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small Cell Lung Cancer*

Proteomics Testing for Selecting Targeted Treatment for Non-Small Cell Lung Cancer
The term proteome refers to the entire complement of proteins produced by an organism, or cellular system and proteomics refers to the large-scale comprehensive study of a specific proteome. The proteome may differ from cell to cell and may vary over time and in response to selected stressors.

A cancer cell's proteome is related to its genome and genomic alterations. The proteome may be measured by mass spectrometry (MS) or protein microarray. For cancer, proteomic signatures in the tumor or bodily fluids (i.e., pleural fluid or blood) other than the tumor have been investigated as a biomarker for cancer activity.

Proteomic testing has been proposed as a way to predict survival outcomes, as well as the response to and selection of targeted therapy for patients with non-small cell lung cancer (NSCLC). One commercially available test the VeriStrat assay has been investigated as a predictive marker for response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).

The VeriStrat assay uses an 8-peak proteomic signature; 4 of the 8 have been identified as fragments of serum amyloid A protein 1. This protein has been found to be elevated in individuals with a variety of conditions associated with acute and chronic inflammation. The VeriStrat assay measures acute phase proteins and the acute phase response which indicates chronic inflammation and more aggressive cancer. This assay is intended to impact treatment strategy and facilitate disease state monitoring. The VeriStrat results are reported as good or poor: VeriStrat Good results indicate a disease state that is more likely to respond to standard of care treatment; VeriStrat Poor results indicate a chronic inflammatory disease state and these patients may benefit from an alternative treatment strategy including clinical trial, broad genomic profiling for rare mutations, faster time to treatment if active therapy is being considered or palliative care.

Non-Small Cell Lung Cancer

Clinical Context and Test Purpose
The purpose of proteomic testing in individuals with non-small-cell lung cancer (NSCLC) who are epidermal growth factor receptor (EGFR)-negative, or EGFR-status unknown NSCLC is to predict expected survival when receiving standard therapies for the treatment of NSCLC. More specifically, the testing could impact the decision point for the selection of treatment based on a prediction of response to EGFR tyrosine kinase inhibitors (TKIs). That is, the VeriStrat classification might be predictive of a differential response to EGFR TKIs.

Populations
The relevant populations of interest are individuals with wild-type or unknown EGFR variant status NSCLC who are newly diagnosed or who have progressed after first-line treatment.

Intervention
The test being considered is management with a serum proteomic test to predict survival and select systemic therapy.

Comparator
Per the National Comprehensive Cancer Network (NCCN) guidelines, the clinical management pathway for stage I or II NSCLC is dependent on surgical findings and may involve resection, radiotherapy, chemotherapy, or chemoradiation. First-line chemotherapy regimens for neoadjuvant and adjuvant therapy utilize platinum-based agents (e.g., cisplatin, carboplatin) in combination with other chemotherapeutics and/or radiotherapy. Treatment recommendations are based on the overall health or performance

status of the patient, presence, or absence of metastases, as well as the presence or absence of a treatment-sensitizing genetic variant. These aspects inform the selection of targeted and systemic therapies. (NCCN Version 4.2022 Non-Small Cell Lung Cancer).

For individuals who experience disease progression following initial systemic therapy, subsequent treatment regimens are recommended, mainly featuring novel programmed death-ligand 1 (PD-L1) inhibitors. The NCCN also includes recommendations for targeted therapy or immunotherapy in patients with biomarkers, including sensitizing epidermal growth factor receptor (EGFR) mutations. (NCCN Version 4.2022 Non-Small Cell Lung Cancer).

Outcomes
The outcomes of interest are overall survival (OS) and progression-free survival (PFS). The timing of testing is prior to treatment following a new diagnosis of NSCLC or with disease progression after first-line systemic therapy.

Review of Evidence

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Proteomic Testing in Non-Small Cell Lung Cancer for Disease Prognosis
The largest body of evidence on the clinical validity of proteomic testing for NSCLC relates to its ability to predict disease outcomes.

No published studies were identified that assessed the use of VeriStrat proteomic testing in newly diagnosed stage I or II NSCLC.

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 OS (primary outcome) and PFS (secondary outcome) outcomes. Most studies were retrospective and intended to validate the extent to which the 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. 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. 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.

Proteomic Testing in Non-Small Cell Lung Cancer to Predict Response to Therapy
No studies were identified that used VeriStrat proteomic testing to inform therapeutic options for patients with stage I or II NSCLC if surgery or surgery plus radiotherapy had been completed or who were upstaged as a result of surgical findings.

No studies were identified that used VeriStrat proteomic testing to inform therapeutic options for patients with stage I or II NSCLC who were considered medically inoperable.

Based on the association between VeriStrat status and outcomes in patients treated with EGFR TKIs, it was postulated that VeriStrat testing might predict response to EGFR TKIs.

No studies were identified that used VeriStrat proteomic testing to predict response to first-line targeted therapies or first-line chemotherapy in patients with newly diagnosed advanced NSCLC.

Randomized Controlled Trials
Lee et al (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 2: 56%; PS 3: 27%) and/or the presence of multiple comorbidities. 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 mutation 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.[1,] Fifty-five percent of patients were categorized as VeriStrat 'good,' which includes 164 patients in the erlotinib arm and 124 patients in the placebo arm. Forty-five percent of patients were classified as VeriStrat 'poor,' which includes 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; p0.001) and 4.9 months vs 3.1 months in the erlotinib group

(HR=0.60; 95% CI, 0.47 to 0.77; p<.001). The difference between groups was not statistically significant in the unadjusted analysis (HR=0.93; 95% CI, 0.87 to 1.11; p=.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 VeriStrat '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.

Retrospective Studies

Several retrospective analyses of data from RCTs evaluating the efficacy of TKIs have examined VeriStrat as a prognostic and/or predictive test.

Buttigliero et al (2018) retrospectively examined VeriStrat as a prognostic and/or predictive test in a randomized controlled phase 3 RCT (MARQUEE trial) of previously treated patients with advanced nonsquamous NSCLC who were given erlotinib plus tivantinib or placebo. *EGFR*-variant status was not considered in trial eligibility, and patients previously treated with EGFR inhibitors were excluded from the trial. Of the 1048 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<.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<.001). There was a significant correlation between treatment and VeriStrat status (p=.037) in multivariate analysis considering *EGFR* variant status; this interaction was no longer significant (p=.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.

Gadgeel et al (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. *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 were indeterminate results, and 4 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=.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.

Section Summary
No published studies were identified that assessed the prognostic use of VeriStrat proteomic testing in newly diagnosed stage I or II NSCLC.

For individuals with newly diagnosed advanced NSCLC without prior systemic therapy, 5 retrospective studies assessed the use of VeriStrat ("good" or "poor") as a prognostic test to discriminate between OS (primary outcome) and PFS (secondary outcome) using available samples from previously conducted clinical trials as validation of the classification. Classification based on proteomic testing (ie, VeriStrat "good" vs "poor") was associated with survival outcomes in analyses that were primarily unadjusted for clinical and patient factors known to be associated with disease survival. The evidence is limited by heterogeneity in the patient population characteristics such as histology and the treatment regimens used. The treatment regimens using EGFR TKIs represent an outdated clinical decision model. The populations studied were unselected for *EGFR*-sensitizing variants or unknown variant status was excluded. The use of erlotinib (or other TKIs) in *EGFR* variant-negative or unknown population is no longer an accepted treatment approach. Combination EGFR plus VEGF inhibition therapy is not an accepted treatment approach. The disposition of indeterminate proteomic test results varied, and sample sizes in the classification groups were small. There is a single observational, nonrandomized study with prospective sample collection for proteomic testing before NSCLC treatment; it reported PFS as the primary outcome. 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). Participant recruitment was nonrandom from a single lung cancer treatment unit. Adjusted analyses for PFS and OS did not include age or other sensitizing variants (*EGFR, ALK*), although data were reported. Overall, sample sizes in classification groups were small and limited generalizability.

For individuals with advanced NSCLC that was recurrent or had advanced on prior systemic therapy, retrospective studies have assessed the use of VeriStrat ("good" or "poor") as a prognostic test to discriminate between OS (primary outcome) and PFS (secondary outcome) using available samples from previously conducted clinical trials as

validation of the classification. 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. One study used pre- and posttreatment proteomic test scores and added an indeterminate result to the "good" result data pool.

No published studies were identified that assessed the use of VeriStrat proteomic testing to inform treatment options in newly diagnosed stage I or II NSCLC.

No published studies were identified that assessed the use of VeriStrat proteomic testing to inform treatment options for newly diagnosed advanced NSCLC patients who had not received prior systemic therapy.

The available peer-reviewed clinical validity studies assess the predictive performance of VeriStrat-directed erlotinib therapy compared with chemotherapy in patients who were either EGFR wild type or had an unknown EGFR mutation status and had progressed after first-line treatment. The overall evidence base for predictive use is characterized by several study design limitations. For example, VeriStrat was not used to determine treatment in the available studies and the majority of the study authors reported that treatment selection was based on standard of care. In addition, a "VSGood" result claims to identify NSCLC patients who are EGFR wild-type but still likely to benefit from EGFR-TKI therapy. Yet the clinical validity studies did not consistently test for EGFR variants and, consequently, the true relationship between VeriStrat results, EGFR status, and survival cannot be definitively understood. For VeriStrat to demonstrate clinical validity in patients with NSCLC in light of the NCCN guideline changes and some of the original design limitations, additional studies supporting its performance are required.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

The proposed clinical utility of VeriStrat is for use by physicians to predict expected survival for standard therapies in the treatment of patients with NSCLC. Clinical utility is also proposed for physicians to use VeriStrat to select patients for systemic therapy based on the presence or absence of EGFR-sensitizing variants. Direct evidence from studies that demonstrate improved outcomes for patients managed with a strategy that includes proteomic testing compared with a strategy that does not, is not available for use of proteomic testing to select targeted therapy or other systemic therapy for NSCLC. Confidence that the proteomic classifier is independent of EGFR-variant status, as well as

other tumor and patient characteristics, has not been demonstrated and, thus, VeriStrat lacks clinical validity. The identity of the proteins that make up the MALDI-MS features was still being investigated at the time of publication of the studies for both prognostic and predictive uses, further challenging the specificity for malignant biologic processes and conditions.

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Absent direct evidence, a chain of evidence could be used to support the use of VeriStrat to select patients for EGFR TKI therapy. If EGFR TKI therapy were used as a standard of care in patients with unknown or negative *EGFR* status in the first-, second-, or third-line settings, proteomic testing could be used to select patients who are least likely to benefit. However, the IUNO trial did not find that erlotinib was efficacious in patients with NSCLC with no known *EGFR* variant, and the PROSE and EMPHASIS trials found that OS did not differ significantly for patients with advanced NSCLC treated with second line erlotinib or chemotherapy. There were mixed findings on PFS in the PROSE and EMPHASIS trials. Due to study findings and the lack of support from guidelines for EGFRTKIs in this setting, EGFR TKI therapy is no longer standard therapy for any *EGFR*-negative or -unknown patients. Platinum-based chemotherapy and immunotherapy (based on programmed death-ligand 1 testing) are the guidelines-based options for previously untreated advanced *EGFR*-negative or -unknown patients with NSCLC or those with recurrent NSCLC or who have progressed on prior systemic therapy.

The available evidence does not demonstrate that the addition of a VeriStrat proteomic classification of "good" or "poor" to the standard clinical assessment of prognosis would influence treatment or define a treatment pathway. Similarly, there is no evidence to demonstrate the impact of the substitution of a VeriStrat proteomic classification in the standard of care treatment pathways. The negative predictive value of a VeriStrat "poor" score has not been demonstrated; there has been no validation in patients who received no or surgical therapy only.

Although studies of physician decision making using VeriStrat proteomic testing have been reported; they did not evaluate patient outcomes and did not evaluate the impact of *EGFR* testing on treatment recommendations (the number of patients who had previously received *EGFR* tests was not reported). Thus, these studies are insufficient to demonstrate clinical utility.

Previous NCCN guidelines for the treatment of NSCLC supported the use of proteomic tests to evaluate potential therapies in advanced NSCLC. However. likely due to technical advances, availability of next generation sequencing (NGS) testing for solid tumors, and treatment options, the current NCCN guideline Version 4.2022 Non-Small Cell Lung Cancer no longer incorporates these proteomic tests to include VeriStrat into their NSCLC evaluation algorithms.

Section Summary
Direct clinical utility studies were not identified in the scientific literature. In the absence of direct evidence, a chain of evidence could be developed to support the use of VeriStrat to select patients for EGFR TKI therapy. If EGFR TKI therapy were used as a standard of care in patients with EGFR-unknown or wild-type status in the first-, second-, or third-line settings, proteomic testing could be used to identify patients who are least likely to benefit. However, given the evidence from the available trials and the lack of support from guidelines for EGFR TKIs in this setting, EGFR TKI therapy is no longer standard therapy for any patient with wild-type or unknown EGFR-variant status. There are no studies that have directly evaluated the use of the proteomic classification to inform treatment selection based on current treatment pathways that consider other targeted therapy, chemotherapy, or immunotherapy options. Two studies by the same research group evaluated changes in treatment recommendations before and after receiving VeriStrat test results; patient outcomes were not reported.

Summary of Evidence
For individuals with newly diagnosed NSCLC and wild-type EGFR-variant status who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes retrospective studies and a prospective nonrandomized study. Relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related mortality and morbidity. No published studies were identified that assessed the prognostic use of VeriStrat proteomic testing in newly diagnosed stage I or II NSCLC. For individuals with newly diagnosed advanced NSCLC and EGFR-negative variant status without prior systemic therapy, 5 studies have assessed the use of VeriStrat ("good" or "poor") as a prognostic test to discriminate between OS (primary) and progression-free survival (PFS) (secondary) outcomes. All studies were retrospective and intended to validate the extent to which the VeriStrat proteomic classification correlated with OS or PFS. Only 1 of the 5 studies reported the percentage of participants who were EGFR-negative, but it did not report outcomes based on variant status. One observational, nonrandomized study with prospective sample collection for proteomic testing before NSCLC treatment reported the percentage of participants who were EGFR-negative, but it did not report outcomes based on variant status. This was also the only study that included a first-line treatment consistent with current guideline-based recommendations -- platinum-doublet-based chemotherapy plus cisplatin or carboplatin plus 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. Disposition of populations with variant status "not reported" was generally not clear and could not be construed as "unknown" when wild-type or positive were reported. No studies were identified that used VeriStrat proteomic testing to inform therapeutic options for patients with stage I or II NSCLC if surgery or surgery plus radiotherapy have been completed or who were upstaged as a result of surgical findings. No studies were identified that used VeriStrat proteomic testing to inform therapeutic options for patients with stage I or II NSCLC who were considered medically inoperable. No studies were identified that used VeriStrat proteomic testing to predict response to first-line targeted therapies or first-line chemotherapy in patients with newly diagnosed advanced NSCLC.

For individuals with newly diagnosed NSCLC and unknown EGFR-variant status who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes a randomized controlled trial (RCT), 4 retrospective studies, and a prospective study. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. All study populations were either unselected for EGFR-variant status or status was expressly reported as unknown in conjunction with negative or positive status reports. None of the studies that reported unknown EGFR-variant status reported outcomes for the proteomic score based on unknown EGFR-variant status.

For individuals with NSCLC and wild-type EGFR-variant status and disease progression after first-line systemic therapy who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes a RCT and a retrospective analysis. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. No studies were identified that reported or analyzed outcomes using the proteomic test as a prognostic tool in EGFR-negative variant status populations.

For individuals with NSCLC and unknown EGFR-variant status with disease progression after first-line systemic therapy who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes 2 RCTs and 3 retrospective studies. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. The use of VeriStrat as a prognostic test to discriminate between good and poor survival outcomes was assessed in 3 retrospective studies intended to validate the extent to which VeriStrat proteomic classification correlates with OS or PFS. The VeriStrat classification was not used to direct treatment selection in any of the trials from which the validation samples were derived. None of the clinical trials from which the samples for VeriStrat proteomic classification were derived used a therapy consistent with current guidelines-based recommendations.

Previous NCCN guidelines for the treatment of NSCLC supported the use of proteomic tests to evaluate potential therapies in advanced NSCLC. However. likely due to technical advances, availability of next generation sequencing (NGS) testing for solid tumors, and treatment options, the current NCCN guideline Version 4.2022 Non-Small Cell Lung Cancer no longer incorporates these proteomic tests to include VeriStrat into their NSCLC evaluation algorithms. Given that VeriStrat testing is not currently supported in clinical practice guidelines for the treatment of advanced NSCLC and the published evidence does not independently meet the criteria for this indication, the use of proteomic testing to include VeriStrat is considered not medically necessary.

Practice Guideline and Position Statements

American Society of Clinical Oncology (ASCO)

In 2021, the American Society of Clinical Oncology (ASCO) updated its clinical practice guidelines to include recommendations for patients with stage IV NSCLC. Separate guidelines were published for patients with and without driver mutations. The guideline

on treatment of NSCLC with driver mutations discusses treatments for patients with positive biomarkers (e.g., EGFR, ALK, ROS1 fusions, BRAF V600e mutations, RET fusions, MET exon 14 skipping mutations, and NTRK fusions). The guideline on treatment of NSCLC without driver mutations discusses therapy for patients with stage IV NSCLC without driver alterations in EGFR or ALK and with programmed death ligand 1 (PD-L1) tumor proportion score status that is known to the clinician.

Their recommendation does not include or indicate the use of proteomic testing or the use of VeriStrat in the management of non-small cell lung cancer.

In 2018, the American Society of Clinical Oncology (ASCO) updated their guideline on molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors in which they endorsed the molecular testing guidelines from the College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASCL) and the Association for Molecular Pathology (AMP) molecular testing guideline with minor modifications. Their recommendation does not include or indicate the use of proteomic testing or the use of VeriStrat in the management of non-small cell lung cancer.

National Comprehensive Cancer Network (NCCN)
Non-Small Cell Lung Cancer Version 4.2022 current NCCN guideline does not include or indicate specific recommendations for proteomic testing; there is no mention of proteomic testing or the use of VeriStrat in the management of non-small cell lung cancer.

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 (CLIA). The commercially available proteomic test (VeriStrat®; Biodesix) is available under the Clinical Laboratory Improvement Amendments (CLIA). 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.

PRIOR APPROVAL

Not applicable.

POLICY

See related medical policies

- 02.04.16 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
- 02.04.55 Epidermal Growth Factor Receptor (EGFR) Mutation Analysis Excluding Non-Small Cell Lung Cancer

- 02.04.63 Expanded Genetic Panels to Identify Targeted Cancer Therapy
- 02.04.78 Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small Cell Lung Cancer

The use of proteomic testing, including but not limited to the VeriStrat assay, is considered **not medically necessary** for all uses in the management of non-small cell lung cancer (NSCLC).

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81538 Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival

SELECTED REFERENCES

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POLICY HISTORY

Date	Reason	Action
September 2022	Annual Review	Policy Renewed
September 2021	Annual Review	Policy Renewed
September 2020	Annual Review	Policy Revised
September 2019		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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Des Moines, IA 50306-9232

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