Medical Policy

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

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Policy Number: 709
BCBSA Reference Number: 2.04.125 (For Plan internal use only)

Related Policies

• Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease, #581
• Proteomics-based Testing for the Evaluation of Ovarian Masses, #249

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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

Prior Authorization Information

Inpatient

• For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient

• For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
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<th>Product</th>
<th>Outpatient</th>
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<tr>
<td>Commercial Managed Care</td>
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<tr>
<td>(HMO and POS)</td>
<td></td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.
Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
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<tr>
<td>81538</td>
<td>Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival</td>
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</tbody>
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Description
Non-Small Cell Lung Cancer
Lung cancer is the leading cause of cancer death in the U.S., with an estimated 228,820 new cases and 135,720 deaths due to the disease in 2020.1, NSCLC accounts for approximately 85% of lung cancer cases and includes nonsquamous carcinoma (adenocarcinoma, large cell carcinoma, other cell types) and squamous cell carcinoma.

Diagnosis
The stage at which lung cancer is diagnosed has the greatest impact on prognosis.2 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.

In addition to tumor stage, age, sex, and performance status are independent prognostic factors for survival particularly in early-stage disease. Wheatley-Price et al (2010) reported on a retrospective pooled analysis of 2349 advanced NSCLC patients from 5 randomized chemotherapy trials.3 Women had a higher response rate to platinum-based chemotherapy than men. Additionally, women with adenocarcinoma histology had greater overall survival than men. A small survival advantage exists for squamous cell carcinoma over non-bronchiolar nonsquamous histology.4

The oncology clinical care and research community use standard measures of performance status: Eastern Cooperative Oncology Group scale and Karnofsky Performance Scale.

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 (eg, 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.1

For patients 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.¹

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%.⁵

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 policy 2.04.45-Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer).

Targeted Treatment Options

EGFR-Selective Small Molecule Tyrosine Kinase Inhibitors
Orally administered EGFR-selective small-molecule TKIs approved by the U.S. Food and Drug Administration (FDA) for treating NSCLC include: gefitinib, erlotinib, afatinib, dacomitinib, mobocertinib, and osimertinib. Although the FDA approved gefitinib in 2004, a phase 3 trial has suggested gefitinib was not associated with a survival benefit. In 2003, the FDA revised gefitinib labeling, further limiting its use to patients who had previously benefited or were currently benefiting from the drug; no new patients were to
be given gefitinib. However, in 2015, the FDA approved gefitinib as a first-line treatment for patients with metastatic, sensitizing EGFR-variant positive NSCLC.

In 2015, osimertinib (Tagrisso), an irreversible selective EGFR inhibitor that targets T790M variant-positive NSCLC, received the FDA approval for patients with T790M variant-positive NSCLC who have progressed on an EGFR TKI.

A meta-analysis by Lee et al (2013) assessing 23 trials on the use of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC reported improved progression-free survival (PFS) in EGFR variant-positive patients treated with EGFR TKIs in the first- and second-line settings and as maintenance therapy. Comparators were chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings. Among EGFR variant-negative patients, PFS was improved with EGFR TKIs compared with placebo for maintenance therapy but not in the first- and second-line settings. OS did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcomes. Reviewers concluded that EGFR-variant testing is indicated to guide treatment selection in NSCLC patients.

On the basis of the results of 5, phase 3 randomized controlled trials, the American Society of Clinical Oncology recommended in 2011 that patients with NSCLC being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for EGFR variants to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.

The primary target population for TKIs in NSCLC is for EGFR variant-positive patients with advanced NSCLC. The use of TKIs in NSCLC for patients with non-sensitizing, wild-type EGFR-variant status is controversial. The TITAN trial as reported by Ciuleanu et al (2012) demonstrated no significant differences in OS between erlotinib and chemotherapy as a second-line treatment for patients unselected on the basis of EGFR-variant status, with fewer serious adverse events in erlotinib-treated patients. Karampeazis et al (2013) reported similar efficacy between erlotinib and standard chemotherapy (pemetrexed) for second-line therapy in patients unselected on the basis of EGFR-variant status. By contrast, in the TAILOR trial, as reported by Garassino et al (2013), standard chemotherapy was associated with longer OS than erlotinib for second-line therapy in patients with wild-type EGFR. Auliac et al (2014) compared sequential erlotinib plus docetaxel with docetaxel alone as second-line therapy among patients with advanced NSCLC and EGFR wild-type or unknown status. Based on Simon’s optimal 2-stage design, the erlotinib plus docetaxel strategy was rejected. Despite the rejection, it is worth noting that in the erlotinib plus docetaxel arm 18 of the 73 patients achieved PFS at 15 weeks; comparatively, in the docetaxel arm, 17 of 74 patients achieved PFS at 15 weeks.

Cicenas et al (2016) reported on results of the IUNO randomized controlled trial, which compared maintenance therapy using erlotinib followed by second-line chemotherapy if progression occurred with placebo followed by erlotinib if progression occurred in 643 patients who had advanced NSCLC and no known EGFR variant. Because there were no significant differences between groups in PFS, objective response rate, or disease control rate, maintenance therapy with erlotinib in patients without EGFR variants was not considered efficacious.

Exon 19 deletions and p.L858R point mutations in exon 21 are the most commonly described sensitizing EGFR mutations, or mutations in EGFR that are associated with responsiveness to EGFR TKI therapy. According to the NCCN, most recent data indicate that NSCLC tumors that do not harbor a sensitizing EGFR mutation should not be treated with an EGFR TKI in any line of therapy.

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 (ie, pleural fluid or blood) other than the tumor have been investigated as a biomarker for cancer activity.

A commercially available serum-based test (VeriStrat) has been developed and proposed to be used as a prognostic tool to predict expected survival for standard therapies used in the treatment of NSCLC. The test is also proposed to have predictive value for response to EGFR TKIs.$^{13}$ The test uses matrix-assisted laser desorption ionization MS analysis, and a classification algorithm was developed on a training set of pretreatment sera from 3 cohorts (Italian A, Japan A, Japan B) totaling 139 patients with advanced NSCLC who were treated with second-line gefitinib.$^{14}$ The classification result is either “good” or “poor”. Two validation studies using pretreatment sera from 2 cohorts of patients (Italian B, Eastern Cooperative Oncology Group 3503) totaling 163 patients have been reported (see Tables 2 and 3).

This assay uses an 8-peak proteomic signature; 4 of the 8 have been identified as fragments of serum amyloid A protein 1.$^{15}$ This protein has been found to be elevated in individuals with a variety of conditions associated with acute and chronic inflammation.$^{16,17,18,19,20}$ The specificity for malignant biologic processes and conditions has not been determined.$^{21}$ With industry support, Fidler et al (2018) used convenience biorepository samples to investigate 102 analytes for potential correlations between the specific peptide and protein biomarkers and VeriStrat classification.$^{22}$ The VeriStrat test is currently marketed as a tool to measure a patient’s “immune response to lung cancer.” Biodesix indicates that a VeriStrat “Good” result indicates “a disease state that is more likely to respond to standard of care treatment,” whereas a VeriStrat “Poor” rating indicates a chronic inflammatory disease state associated with aggressive cancer and patients that “may benefit from an alternative treatment strategy.” The Biodesix website does not indicate whether the VeriStrat test should be reserved for use in patients with advanced lung cancer.$^{13}$

Although the VeriStrat matrix-assisted laser desorption ionization MS-based predictive algorithm has the largest body of literature associated with it, other investigators have used alternative MS methods, such as surface-enhanced laser desorption ionization/time-of-flight MS, and alternative predictive algorithms, to assess proteomic predictors of lung cancer risk.$^{23}$

Best practices for peptide measurement and guidelines for publication of peptide and protein identification have been published for the research community.$^{24}$

**Summary**

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.

**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
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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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. The evidence includes an RCT (PROSE) using proteomic testing to predict response to erlotinib compared with chemotherapy as a second-line treatment for patients with stage IIB or IV NSCLC, stratified by performance status, smoking history, treatment center, and (masked) pretreatment VeriStrat classification. In a multivariate model to predict OS, which included clinical characteristics and EGFR-variant status, VeriStrat classification was significantly associated with OS (hazard ratio for VeriStrat “good” vs “poor,” 1.88; 95% confidence interval, 1.25 to 2.84; p=.003). However, 62% of the combined study population was EGFR-negative. A retrospective analysis was also performed on the MARQUEE trial, a phase 3 RCT in patients with stage IIB or IV nonsquamous NSCLC, comparing the patient response to erlotinib in conjunction with either tivantinib or a placebo; patients were stratified by EGFR and KRAS variant status, sex, smoking history, and treatment history. Protocol treatments were subsequently discontinued by 93% of patients, and the trial discontinued after prespecified interim futility analysis. In a multivariate model to predict OS, which included clinical characteristics and EGFR-variant status, VeriStrat classification was significantly associated with OS (hazard ratio for VeriStrat “good” vs “poor,” 0.52; 95% confidence interval, 0.40 to 0.67; p<.001). Ninety percent of the combined study population was EGFR-negative. An interaction between treatment and VeriStrat status was significant for multivariate analysis including EGFR status (p=.036) but not significant for multivariate analysis including both EGFR and KRAS variant status (p=.068). Currently, the use of erlotinib in patients unselected for the presence or absence of an EGFR-sensitizing variant is not standard clinical practice. It is recommended that variant status be determined, if not previously ascertained, before selecting treatment after progression or recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
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. The populations in all 3 studies were unselected for EGFR-variant status. In the PROSE RCT, using a multivariate model to predict OS, which included clinical characteristics and EGFR-variant status, VeriStrat classification was significantly associated with OS (hazard ratio for VeriStrat “good” vs “poor,” 1.88; 95% confidence interval, 1.25 to 2.84; p=.003). However, 32.6% of the combined study population had unknown EGFR status. In the EMPHASIS RCT, there were no significant differences in PFS or OS among patients with VeriStrat “good” status receiving erlotinib or chemotherapy or among patients with VeriStrat “poor” status receiving erlotinib or chemotherapy. The results of the EMPHASIS RCT were restricted to squamous NSCLC histology. Currently, the use of erlotinib in patients unselected for the presence or absence of an EGFR-sensitizing variant is not standard clinical practice. It is recommended that variant status be determined, if not previously ascertained, before selecting treatment after progression or recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Policy History**

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<td>Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.</td>
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<td>Annual policy review. Background section clarified programmed death ligand 1 inhibitors are not only used for cancers expressing PD-L1. 5/1/2017</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
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References


