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

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).

Lung cancer is the leading cause of cancer death in the United States, with an estimated 221,200 new cases and 158,040 deaths due to the disease in 2015.

Non-small-cell lung cancer (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. Localized disease confined to the primary site has a 55.6% relative 5-year survival but accounts for only 16% of lung cancer cases at diagnosis. Mortality increases sharply with advancing stage. Metastatic lung cancer has a relative 5-year survival of 4.5%. 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 2,349 advanced NSCLC patients from 5 randomized chemotherapy trials. Women had a higher response rate to platinum-based chemotherapy than men. Greater overall survival (OS) than men were among those with adenocarcinoma histology. A small survival advantage exists for squamous cell carcinoma over non-bronchiolar non-squamous histology.

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). Treatment recommendations are based on the overall health or performance status of the patient as well as the presence or absence of a treatment-sensitizing genetic variant. The latter is used to select for targeted therapy or platinum-based chemotherapy.
Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer

The clinical management pathway and treatment options for advanced NSCLC after progression on first-line treatment or recurrence is based on objective response to prior therapy, duration of response, as well as the type of and duration of prior therapy (either targeted therapy or chemotherapy).

Genomic Alterations

Several common genetic alterations in NSCLC have been targets for drug therapy, the most well-established of which are tyrosine kinase inhibitors TKIs targeting the EGFR and crizotinib targeting the ALK gene rearrangement.

EGFR Variants

EGFR, a receptor TK, 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 EGF receptor, 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 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, in whom EGFR variants have been reported to be up to 30% to 50%. The reported prevalence of EGFR variants in lung adenocarcinoma patients in the United States is approximately 15%.

ALK Variants

In about 2% to 7% of NSCLC patients in the United States, tumors express a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 gene and the anaplastic lymphoma kinase gene (EML4-ALK), which is created by an inversion on chromosome 2p. 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 and tend to be associated with younger age of NSCLC onset, and typically do not occur in conjunction with EGFR variants.

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

Targeted Treatment Options

EGFR-Selective Small Molecule TKIs

Three orally administered EGFR-selective small molecule TKIs have been identified for use in treating NSCLC: gefitinib (Iressa®, AstraZeneca), erlotinib (Tarceva®, OSI Pharmaceuticals), and afatinib (Gilotrif™, Boehringer Ingelheim). Although originally the U.S. Food and Drug Administration (FDA) approved gefitinib, in 2004 a phase 3 trial suggested that gefitinib was not associated with a survival benefit. In 2003, FDA revised gefitinib labeling, further limiting its use to patients who had previously benefitted or were currently benefiting from the drug; no new patients were to be given gefitinib. However in July 2015, the FDA approved gefitinib for the first-line treatment of patients with metastatic NSCLC for patients with EGFR-mutated tumors. Erlotinib and afatinib also have approval by the FDA.

In 2015, osimertinib (Tagrisso®; AstraZeneca), an irreversible selective EGFR inhibitor that targets T790M variant-positive NSCLC, received FDA approval for patients with T790M variant-positive NSCLC who have progressed on an EGFR-TKI.
Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer

A 2013 meta-analysis which assessed 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 for maintenance therapy. Comparisons were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively. 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. Overall survival (OS) did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcome. Reviewers concluded that EGFR variant testing is indicated to guide treatment selection in NSCLC patients.

On the basis of the results of five phase 3 randomized controlled trials, the American Society of Clinical Oncology recommends that patients with NSCLC who are 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 in EGFR variant-negative patients is controversial. The TITAN trial demonstrated no significant differences in OS between erlotinib and chemotherapy as 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 reported similar efficacy between erlotinib and standard chemotherapy (pemetrexed) for second-line therapy in patients unselected on the basis of EGFR variant status. In contrast, in the TAILOR trial, standard chemotherapy was associated with longer OS than erlotinib for second-line therapy in patients with wild-type EGFR. Auliac et al 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 a Simon’s optimal 2-stage design, the erlotinib plus docetaxel strategy was rejected, with 18 of 73 patients in the erlotinib plus docetaxel arm achieving PFS at 15 weeks compared with 17 of 74 patients in the docetaxel arm.

In 2016, Cicenas et al reported on results of the IUNORCT, which compared maintenance therapy with erlotinib followed by second line chemotherapy if progression occurred to placebo followed by erlotinib if progression occurred in 643 patients with advanced NSCLC with no known EGFR variant. Because there were no significant differences between groups in terms of PFS, objective response rate, or disease control rate, maintenance therapy with erlotinib in patients without EGFR variants was not considered efficacious.

Anti-EGFR Monoclonal Antibodies

For the treatment of KRAS-mutated NSCLC, anti-EGFR monoclonal antibodies have been investigated as possible treatment options. Available anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Neither drug has an established role in the treatment of NSCLC either as a component of initial therapy or as second-line therapy.

Programmed Death Ligand 1 Inhibitors

Some tumors, including some NSCLCs, express a programmed death ligand 1 (PD-L1) on the cell surfaces to interact with host T-cells and evade the immune system. Several humanized monoclonal antibodies have been developed to act as immune checkpoint inhibitors by interfering with this interaction to interact with the PD-L1, block the cancer/T-cell interaction, and thus act as immune checkpoint inhibitors. Pembrolizumab, nivolumab, and atezolizumab which inhibit the programmed death 1 receptor, and atezolizumab, which inhibits the PD-L1, are used in NSCLC that have PD-L1 expression on its cells. Durvalumab also targets the PD-L1 protein but is used in unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiotherapy.

Other Targeted Therapies
Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer

Crizotinib is a novel MET-, ROS-1-, and ALK-TKI, which is associated with improved PFS in patients with advanced NSCLC that is ALK gene rearrangement-positive. Crizotinib is considered first-line therapy for advanced ALK-positive lung adenocarcinoma.

Other small molecule TKIs, designed to selectively bind to and inhibit ALK activation, have FDA approval: ceritinib, alectinib, and brigatinib.

Proposed targeted therapies for other genetic alterations in NSCLC are trastuzumab for HER2 variants, crizotinib for MET amplification and ROS-1 rearrangement, vemurafenib and dabrafenib for BRAF mutations and cabozantinib for RET rearrangements.

Proteomics Testing in Selecting Targeted Treatment for NSCLC

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. 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. 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.

This 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 specificity for malignant biologic processes and conditions has not been determined. 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.

Although the VeriStrat MALDI-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 (SELDI/TOF) mass spectrometry, and alternative predictive algorithms, in the assessment of proteomic predictors of lung cancer risk.

Best practices for peptide measurement and guidelines for publication of peptide and protein identification have been published for the research community.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Proteomic testing for targeted therapy in non-small cell lung cancer is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.
Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer is covered

Not applicable.

When Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer is not covered

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.

BCBSNC does not provide coverage for investigational services or procedures.

Policy Guidelines

For individuals with newly diagnosed NSCLC and EGFR-negative 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, 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 overall survival (primary) progression-free survival (secondary) outcomes. All studies were retrospective and intended to validate the extent to which the VeriStrat proteomic classification correlated with overall survival or progression-free survival. 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 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 4 retrospective studies and a prospective study. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. All study populations were either unselected
Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer

for \textit{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 \textit{EGFR}-variant status reported outcomes for the proteomic score based on unknown \textit{EGFR}-variant status. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with NSCLC and \textit{EGFR}-negative 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 randomized controlled trial (RCT). Relevant outcomes are overall survival, 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 \textit{EGFR}-negative variant status populations. The evidence includes an RCT (PROSE) using proteomic testing to predict response to erlotinib compared with chemotherapy as second-line treatment for patients with stage IIIB or IV NSCLC, stratified by performance status, smoking history, treatment center, and (masked) pretreatment VeriStrat classification. In a multivariable model to predict overall survival, which included clinical characteristics and \textit{EGFR}-variant status, VeriStrat classification was significantly associated with overall survival (hazard ratio for VeriStrat “good” vs “poor,” 1.88; 95% confidence interval, 1.25 to 2.84; \textit{p}=0.003). However, 62% of the combined study population was \textit{EGFR}-negative. Currently, the use of erlotinib in patients unselected for the presence or absence of an \textit{EGFR}-sensitizing variant is not standard clinical practice. It is recommended that variant status is determined, if not previously ascertained, before selecting treatment after progression or recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with NSCLC and unknown \textit{EGFR} variant 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 3 retrospective studies and 2 RCTs. Relevant outcomes are overall survival, 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 overall survival or progression-free survival. 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 \textit{EGFR}-variant status. In the PROSE RCT, using a multivariable model to predict overall survival, which included clinical characteristics and \textit{EGFR}-variant status, VeriStrat classification was significantly associated with overall survival (hazard ratio for VeriStrat “good” vs “poor,” 1.88; 95% confidence interval, 1.25 to 2.84; \textit{p}=0.003). However, 32.6% of the combined study population had unknown \textit{EGFR} status. In the EMPHASIS RCT, there were no significant differences in progression-free survival or overall survival 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 \textit{EGFR}-sensitizing variant is not standard clinical practice. It is recommended that variant status is determined, if not previously ascertained, before selecting treatment after progression or recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

\textit{Applicable service codes: 0022U, 81538}
Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**

- Senior Medical Director Review 10/2014
- Specialty Matched Consultant Advisory Panel 3/2018

**Policy Implementation/Update Information**

- **11/25/14** New policy developed. 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. Senior medical director review. Reference added. (lpr)
- **5/26/15** Specialty Matched Consultant Advisory Panel review 4/29/2015. No change to policy. (lpr)
- **11/24/15** Updated the description and policy guidelines sections. Removed the regulatory status section. Added CPT code 81538 to the Billing/Coding section for effective date 1/1/2016. No change to policy statement. (lpr)
- **5/31/16** Specialty Matched Consultant Advisory Panel review 4/27/2016. No change to policy. (lpr)
- **12/15/17** Updated Description and Policy Guidelines sections. No change to policy statement. Reference added. (lpr)
Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.