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

Table of Contents
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- Policy: Medicare
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Policy Number: 709
BCBSA Reference Number: 2.04.125
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
Proteomics-based Testing for the Evaluation of Ovarian Masses, #249
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer, #563

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.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

This is not a covered service.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

| Outpatient                  | Commercial Managed Care (HMO and POS)    | This is not a covered service. |
Commercial PPO and Indemnity

<table>
<thead>
<tr>
<th></th>
<th>This is not a covered service.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare HMO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>This is not a covered service.</td>
</tr>
</tbody>
</table>

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:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

Description

NON-SMALL-CELL LUNG CANCER

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 2015.¹ Non-small-cell lung cancer (NSCLC), which includes nonsquamous carcinoma (adenocarcinoma, large cell carcinoma, other cell types) and squamous cell carcinoma, causes about 85% of lung cancer cases. Treatment approaches generally include surgery, radiotherapy, and chemotherapy, either alone or in combination, depending on the disease stage and tumor characteristics. However, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication, and up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have brief responses, with a median time to progression of 3 to 5 months.² Second-line chemotherapy after platinum-based chemotherapy is associated with small improvements in time to progression. Genetic abnormalities in NSCLC and the development of therapies targeted to those abnormalities have prompted interest in tests to predict response to targeted therapies.

Genetic 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 epidermal growth factor receptor (EGFR) and crizotinib targeting the ALK gene rearrangement.

EGFR Variants

EGFR, a receptor tyrosine kinase (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 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 stimulation of neovascularization.

Variants in 2 regions of the EGFR gene, including small deletions in exon 19 and a point variant 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 mutations in lung adenocarcinoma patients in the United States is approximately 15%.^3^

### ALK Variants

In 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.^4^ 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

Other genetic variants, identified in subsets of patients with NSCLC, are summarized in Table 1. The role of testing for these variants to help select targeted therapies for NSCLC is less well-established than for EGFR variants.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Function</th>
<th>Estimated Variants Prevalence in NSCLC</th>
<th>Patient and Tumor Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>Encodes RAS proteins; mutations associated with constitutively activated protein</td>
<td>20%-30%</td>
<td>• Adenocarcinomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Heavy smokers</td>
</tr>
<tr>
<td>ROS1</td>
<td>Encodes a receptor TK in the insulin receptor family</td>
<td>0.9%-3.7%</td>
<td>• Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Never smokers</td>
</tr>
<tr>
<td>RET</td>
<td>Proto-oncogene that encodes a receptor TK growth factor</td>
<td>0.6%-2%</td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>Oncogene that encodes a receptor TK that is activated in response to binding of hepatocyte growth factor</td>
<td>2-4% of previously untreated NSCLC; 5%-20% of patients with acquired resistance to EGFR TKIs</td>
<td>Patients with acquired resistance to EGFR TKIs</td>
</tr>
<tr>
<td>BRAF</td>
<td>Serine-threonine kinase downstream from RAS in RAS-RAF-ERK-MAPK pathway</td>
<td>1%-3% of adenocarcinomas</td>
<td>Heavy smokers</td>
</tr>
<tr>
<td>HER</td>
<td>HER (EGFR) family of TK receptors; dimerizes with EGFR family members when activated</td>
<td>1%-2% of NSCLC</td>
<td>• Adenocarcinomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Nonsmoking women</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Intracellular signaling pathway</td>
<td>≈4% of NSCLC</td>
<td></td>
</tr>
</tbody>
</table>

EGFR: epidermal growth factor receptor; NSCLC: non-small-cell lung cancer; TK: tyrosine kinase; TKI: tyrosine kinase inhibitor.

### 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 the Food and Drug Administration (FDA) originally approved gefitinib in 2004, a phase 3 trial suggested gefitinib was not associated with a survival benefit. In May 2005, 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,
FDA approved gefitinib as first-line treatment for patients with metastatic NSCLC for patients with *EGFR*-mutated tumors. Erlotinib and afatinib also have approval by FDA.

In 2016, 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.

A 2013 meta-analysis of 23 trials assessing 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. 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 5 phase 3 randomized controlled trials, the American Society of Clinical Oncology recommended 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 in *EGFR* variant–negative patients is controversial. The TITAN trial (2012) 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. Karamepeazis 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 (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 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 results of the IUNO RCT, 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. The benefits of cetuximab in NSCLC have been questioned by the National Comprehensive Cancer Network. Panitumumab is not generally used in NSCLC.

**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 and nivolumab, which inhibit the programmed death 1 receptor, and...
atezolizumab, which inhibits the PD-L1, are used in NSCLC that has progressed on platinum-based chemotherapy or targeted therapy for ALK or EGFR variants.

**Other Targeted Therapies**
Crizotinib is a novel MET, ROS1, and ALK TKI, and associated with improved progression-free survival in patients with advanced NSCLC who are ALK gene rearrangement–positive.\(^{11}\) Crizotinib is considered first-line therapy for advanced ALK-positive lung adenocarcinoma.\(^1\) Two other small molecule TKIs, designed to selectively bind to and inhibit ALK activation, have FDA approval: ceritinib and alectinib. Proposed targeted therapies for other genetic alterations in NSCLC are trastuzumab for HER2 variants, crizotinib for MET amplification and ROS1 rearrangement, vemurafenib and dabrafenib for BRAF variants, 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, which may vary over time and in response to selected stressors, and *proteomics* refers to the large-scale comprehensive study of a specific proteome.\(^{12}\) A cancer cell's proteome is related to its genome and to genomic alterations, but may not be static over time. The proteome may be measured with mass spectrometry (MS) or protein microarray. For cancer, proteomic signatures in the tumor or in bodily fluids (ie, pleural fluid or blood) other than the tumor have been investigated as a biomarker for cancer activity.

For NSCLC, 1 commercially available serum-based test (VeriStrat) has been developed and proposed to predict response to TKIs. The test relies on a predictive algorithm based on matrix-assisted laser desorption ionization (MALDI) MS analysis of pretreatment serum to generate a “good” or “poor” assessment for response to TKIs.\(^{13}\) VeriStrat has been proposed as a test to predict response to erlotinib in patients with NSCLC after failure of treatment with first-line therapy. Proposed uses have been in addition to EGFR testing, or in patients who do not have tumor samples available for EGFR testing.

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 MS, and alternative predictive algorithms, to assess proteomic predictors of lung cancer risk.\(^{14}\)

**Summary**
Proteomic testing has been proposed as a way to predict survival outcomes and 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).

For individuals with *EGFR*-negative or *EGFR*-status unknown NSCLC with disease progression after first-line treatment who receive management with a serum proteomic test to select targeted therapy, the evidence includes 1 prospective study evaluating the test’s use in predicting response to EGFR-TKI therapy and retrospective studies evaluating the prognostic ability of this test. Relevant outcomes are overall survival and disease-specific survival. Although a limited body of evidence exists for the analytic validity of proteomic testing to predict response to EGFR TKIs for NSCLC in general, at least 1 study has reported good test reproducibility for the most widely studied proteomic test, the VeriStrat assay. Evidence from retrospective studies has supported the clinical validity of proteomic testing in determining the prognosis of patients with advanced NSCLC who are treated with EGFR TKIs, but, due to heterogeneity in the treatment regimens used, it is difficult to determine specific populations for whom proteomic testing is prognostic. Evidence from 1 prospective study found that VeriStrat discriminates between patients who are likely to respond to EGFR-TKI therapy. However, in that same study, even those patients who were predicted to respond to EGFR-TKI therapy did not have a significant survival benefit with EGFR-TKI therapy. If EGFR-TKI therapy were used as a standard of care in patients who are *EGFR*-unknown or -negative in the second- or third-line setting, proteomic testing could be used to select patients who are least likely to benefit, and those patients could be offered chemotherapy as an
alternative. RCT evidence has suggested that erlotinib is not beneficial for EGFR-unknown or -negative patients in the second-line setting, and clinical guidelines do not support its use. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/2017</td>
<td>BCBSA National medical policy review. In the Background, in the discussion of osimertinib, NSCLC variant T890M changed to T790M. 8/1/2017.</td>
</tr>
<tr>
<td>5/2017</td>
<td>BCBSA National medical 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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<tr>
<td>3/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>2/2017</td>
<td>Non-coverage for Medicare Advantage members clarified based on Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000). 2/2017</td>
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<tr>
<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>12/2015</td>
<td>Policy updated to include Medicare LCD L35396. Effective 12/1/2015.</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
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


