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

Policy # 00446
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of proteomic testing, including but not limited to the VeriStrat® assay, for all uses in the management of non-small-cell lung cancer to be investigational.*

Background/Overview
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. 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. 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.
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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%.

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

PIK3CA: phosphoinositide 3-kinase, catalytic subunit alpha; NSCLC: non-small-cell lung cancer.

**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 benefitting 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 T890M-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 unslected 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 unslected on the basis of EGFR variant status. By contrast, in the TAILOR trial (2013), standard chemotherapy was associated with longer OS than
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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 have PD-L1 expression on its cells.

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. Crizotinib is considered first-line therapy for advanced ALK-positive lung adenocarcinoma. 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. 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
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Spectrometry (MS) or protein microarray. For cancer, proteomic signatures in the tumor or in bodily fluids (i.e., 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. 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.

FDA or Other Governmental Regulatory Approval

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

Centers for Medicare and Medicaid Services (CMS)
Novitas Solutions established a local Medicare coverage determination for the VeriStrat test in June 2013, which serves as a national coverage determination because the test is only offered at a single lab within the local carrier’s coverage region. The coverage determination document noted: “The VeriStrat assay (NOC 84999) is a mass spectrophotometric, serum-based predictive proteomics assay for NSCLC patients, where ‘first line’ EGFR mutation testing is either wild-type or not able to be tested (e.g., if tissue might not be available).”

Rationale/Source
The evaluation of a predictive test focuses on 3 main principles: (1) analytic validity; (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease or the clinical phenotype of interest or stratifying patients for risk of a specific outcome); and (3) clinical utility (how the results of the predictive test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature to date.
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Clinical Context and Test Proposed
The proposed clinical utility for the current commercially available proteomic test is for predicting response to EGFR TKIs in individuals with NSCLC with wild-type or unknown EGFR variant status. It has specifically been used to select patients who should not receive EGFR TKIs in the second- or third-line setting.

Analytic Validity
In 2007, Taguchi et al described the development and testing of a predictive algorithm based on MALDI MS analysis of serum to identify patients with NSCLC who are likely to benefit from treatment with an EGFR TKI. This method forms the basis of the VeriStrat testing algorithm. The training set included 139 patients, and the validation set included 163 patients who received EGFR TKIs and 158 who did not. The authors examined the concordance of mass spectra independently acquired at 2 institutions to assess the reproducibility of the approach, with values available for 206 samples. The overall concordance with which the 206 available samples were labeled as “good,” “poor,” or “undefined” was 97.1%.

While most research has focused on the algorithm used to generate the VeriStrat algorithm, additional proteomic signatures have been developed as predictive or prognostic tests for NSCLC; studies that describe the analytic validity of these tests are briefly described. Salmon et al (2009) used a MALDI MS proteomic signature-associated algorithm to predict outcomes for patients with NSCLC treated with erlotinib, which was validated in a cohort of 82 NSCLC patients treated with erlotinib and 61 control patients. To quantify the relative variability of the features or peaks in m:z ratios, the authors generated coefficients of variation (CV) using 139 common peaks for all samples, and for samples with analysis replicated on 3 days. The mean CV was low (<5%) for all 3 days and for the overall sample, suggesting that their spectrometry was reproducible.

Wu et al (2013) used MALDI time of flight (TOF) MS protein profiles to generate a predictive algorithm for survival in patients with NSCLC treated with gefitinib or erlotinib, but did describe analytic validity parameters.

Section Summary: Analytic Validity
Methods for generating predictive algorithms for NSCLC outcomes from serum protein signatures by MS are not standardized. For the most widely studied test (the VeriStrat assay), which uses a predictive algorithm based on MALDI MS test, reproducibility is high. A separate MALDI MS-related predictive algorithm has also demonstrated good reproducibility. The analytic validity of future proteomic-based predictive algorithms will need to be determined as these tests are developed.

Clinical Validity
Proteomic Testing in NSCLC 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. Several studies have evaluated the ability of MALDI MS with a predictive algorithm (usually specifically referred to as the VeriStrat test) as a prognostic test, generally to discriminate...
between good and poor survival outcomes in patients treated with EGFR TKIs. Results of these studies are summarized in Table 2.

In 2014, Sun et al published a meta-analysis of studies that compared outcomes based on VeriStrat classification for patients with NSCLC treated with EGFR TKIs. Eleven cohorts were identified, which were reported in 6 published studies, including those by Taguchi et al (2007), Carbone et al (2010), Kuiper et al (2012), Akerley et al (2013), Gautschi et al (2013), and Stinchcombe et al (2013), as well as 1 conference abstract. In pooled analysis, VeriStrat “good” status was associated with improved overall survival (OS) compared with VeriStrat “poor” status, and had a combined hazard ratio (HR) of 0.40 (95% confidence interval [CI], 0.32 to 0.49; p<0.001). Similarly, VeriStrat “good” status was associated with longer progression-free survival (PFS), and had a combined hazard ratio of 0.49 (95% CI, 0.38 to 0.60; p<0.001). There was low heterogeneity across studies.
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Table 2: Clinical Validity Results of Proteomic Testing in NSCLC for Disease Prognosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>N</th>
<th>Patient Population</th>
<th>Summary of Outcomes: OS for “Good” vs “Poor” Assay</th>
<th>Summary of Outcomes: PFS for “Good” vs “Poor” Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taguchi et al (2007)**</td>
<td>Retrospective</td>
<td>67</td>
<td>Late stage or recurrent NSCLC treated with erlotinib</td>
<td>Unadjusted HR of death, 0.50 (95% CI, 0.24 to 0.78; p=0.005)</td>
<td>Unadjusted TTT: HR=0.56 (95% CI, 0.28 to 0.89; p=0.02)</td>
</tr>
<tr>
<td></td>
<td>(Italian B validation set)</td>
<td></td>
<td>ECOG PS: 29.8% grade 0; 46.3% grade 1; 23.9% grade 2</td>
<td>Adjusted HR of death, 0.75 (95% CI, 0.55 to 0.99)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Histology: 56.7% adenoc; 22.4% squamous; 20.9% NOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taguchi et al (2007)**</td>
<td>Retrospective</td>
<td>96</td>
<td>ECOG 3503 trial patients: stage IIIb or IV or recurrent NSCLC treated with first line erlotinib</td>
<td>Unadjusted HR of death, 0.4 (95% CI, 0.24 to 0.70; p=0.001)</td>
<td>Unadjusted TTT: HR=0.53 (95% CI, 0.33 to 0.85; p=0.007)</td>
</tr>
<tr>
<td></td>
<td>(ECOG 3503 validation set)</td>
<td></td>
<td>ECOG PS: 39.2% grade 0; 43.8% grade 1; 26.0% grade 2</td>
<td>Adjusted HR of death, 0.53 (95% CI, 0.30 to 0.94; p=0.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Histology: 64.6% adenoc; 11.5% squamous; 1% LCC; 22.9% NOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amann et al (2010)</td>
<td>Retrospective</td>
<td>88</td>
<td>ECOG 3503 trial patients: stage IIIb or IV or recurrent NSCLC treated with first line erlotinib</td>
<td>Unadjusted HR of death, 0.36 (95% CI, 0.21 to 0.60; p=0.001)</td>
<td>Unadjusted TTT: HR=0.51 (95% CI, 0.28 to 0.90; p=0.02)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>ECOG PS: 28.4% grade 0; 46.1% grade 1; 25.5% grade 2</td>
<td>Adjusted for EGFR status HR of death, 0.26 (95% CI, 0.06 to 1.16; p=0.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Histology: 64.7% adenoc; 10.8% squamous; 1% LCC; 16.7% NOS; 6.9% other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabbone et al (2010)</td>
<td>Retrospective</td>
<td>35</td>
<td>Stage IIIb or IV, recurrent, nonanaplastic NSCLC treated with erlotinib and bevacizumab</td>
<td>Unadjusted HR of death, 0.14 (61 wk vs 41 wk; 95% CI, 0.03 to 0.58)</td>
<td>PFS: HR=0.045 (36 wk vs 8 wk; 95% CI, 0.008 to 0.237)</td>
</tr>
<tr>
<td>Kuiper et al (2012)</td>
<td>Retrospective</td>
<td>50</td>
<td>Chemotherapy naive patients with pathologically documented, inoperable, locally advanced, recurrent, or metastatic NSCLC, treated with erlotinib and cetuximab</td>
<td>• HR for OS, 0.30 (95% CI, 0.12 to 0.74; p=0.009)</td>
<td>• PFS: HR=0.40 (95% CI, 0.17 to 0.94; p=0.035)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>ECOG PS: 40%; grade 0; 60% grade 1</td>
<td>• Median OS 13.7 mo for &quot;good&quot; and 5.6 mo for &quot;poor&quot;</td>
<td>• Median PFS 5.5 mo for &quot;good&quot; and 2.7 mo for &quot;poor&quot;</td>
</tr>
<tr>
<td>Akerley et al (2013)**</td>
<td>Retrospective</td>
<td>42</td>
<td>Stage IIIb or IV, recurrent, nonanaplastic NSCLC treated with erlotinib and bevacizumab</td>
<td>Median OS 71.4 mo for assay &quot;good&quot; and 19.9 wk for assay &quot;poor&quot; (p=0.002)</td>
<td>Median PFS 18.8 wk for &quot;good&quot; and 6.3 wk for &quot;poor&quot; (p=0.004)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ECOG PS: 25% grade 0; 74% grade 1</td>
<td>• Adjusted HR of death, 0.102 (95% CI, 0.009 to 1.04; p=0.003)</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Histology: 48%; adenoc; 48% NOS; 4% other</td>
<td>• HR for OS, 0.48 (95% CI, 0.294 to 0.784; p=0.003)</td>
<td>• HR of death, 0.75 (95% CI, 0.482 to 1.22; p=0.263)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Median OS was 13.4 mo for assay &quot;good&quot; and 6.2 mo for assay &quot;poor&quot;</td>
<td>• Median PFS 4 mo for assay &quot;good&quot; and 3.2 mo for assay &quot;poor&quot;</td>
<td></td>
</tr>
<tr>
<td>Keshgpourou et al (2016)**</td>
<td>Retrospective</td>
<td>49</td>
<td>Advanced-stage squamous and nonanaplastic NSCLC seen at a single clinic. Baseline histology and PS not reported.</td>
<td>HR=0.97 (95% CI, 0.48 to 1.97; p=0.94)</td>
<td></td>
</tr>
<tr>
<td>Non-VeriStrat proteomic testing algorithms</td>
<td>Retrospective</td>
<td>35</td>
<td>Stage IIIb or IV, recurrent, nonanaplastic NSCLC treated with erlotinib and bevacizumab</td>
<td>Adjusted HR of death, 1.024 (95% CI, 1.009 to 1.040; p=0.003)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ECOG PS: 35.0% grade 0; 63.6% grade 1; 1.4% grade 2</td>
<td>Adjusted HR of death, 1.012 (95% CI, 1.003 to 1.021; p=0.012)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Histology: 79.2% adenoc; 20.8% squamous</td>
<td>OS (predicted good vs predicted poor): HR=0.357 (95% CI, 0.186 to 0.688; p=0.002)</td>
<td>PFS (predicted good vs predicted poor): HR=0.06 (95% CI, 0.022 to 0.16; p&lt;0.001)</td>
</tr>
<tr>
<td>Salmon et al (2009)**</td>
<td>Retrospective</td>
<td>82</td>
<td>ECOG 3503 trial patients: stage IIIb or IV or recurrent NSCLC treated with first line erlotinib</td>
<td>OS (predicted good vs predicted poor): HR=0.357 (95% CI, 0.186 to 0.688; p=0.002)</td>
<td>PFS (predicted good vs predicted poor): HR=0.06 (95% CI, 0.022 to 0.16; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>(erlotinib and bevacizumab generation set)</td>
<td></td>
<td>ECOG PS: 52.9% grade 0; 42.5% grade 1; 4.6% grade 2</td>
<td>OS (predicted good vs predicted poor): HR=0.357 (95% CI, 0.186 to 0.688; p=0.002)</td>
<td>PFS (predicted good vs predicted poor): HR=0.06 (95% CI, 0.022 to 0.16; p&lt;0.001)</td>
</tr>
<tr>
<td>Wu et al (2013)**</td>
<td>Retrospective</td>
<td>44</td>
<td>Stage IIIb or IV NSCLC failed or intolerant to chemotherapy, treated with gefitinib or erlotinib.</td>
<td>OS (predicted good vs predicted poor): HR=0.357 (95% CI, 0.186 to 0.688; p=0.002)</td>
<td>PFS (predicted good vs predicted poor): HR=0.06 (95% CI, 0.022 to 0.16; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>(validation set)</td>
<td></td>
<td>Histology: 79.2% adenoc; 20.8% squamous</td>
<td>OS (predicted good vs predicted poor): HR=0.357 (95% CI, 0.186 to 0.688; p=0.002)</td>
<td>PFS (predicted good vs predicted poor): HR=0.06 (95% CI, 0.022 to 0.16; p&lt;0.001)</td>
</tr>
<tr>
<td>Yang et al (2015)**</td>
<td>Retrospective</td>
<td>123</td>
<td>Stage IIIb or IV NSCLC with a known EGFR variant status</td>
<td>Following EGFR TKI treatment (81 patients in validation set): OS=29.0 mo for assay &quot;mutant&quot; and 28.0 mo for assay &quot;wild&quot; (p=NS)</td>
<td>Following EGFR TKI treatment (81 patients in validation set): OS=29.0 mo for assay &quot;mutant&quot; and 28.0 mo for assay &quot;wild&quot; (p=NS)</td>
</tr>
</tbody>
</table>

adenoc: adenocarcinoma; cc: confidence interval; EGFR: European cooperative Oncology Group; EGFR: epidermal growth factor receptor; HR: hazard ratio; KPS: Karnofsky Performance Status; LCC: large cell carcinoma; MADLI: matrix-assisted laser desorption ionization/TOF MS technology

While most of the literature has focused on the use of MALDI MS techniques and predictive algorithms similar to those used in the VeriStrat assay, other MS techniques and predictive algorithms have been investigated. Jacot et al (2008) used surface-enhanced laser desorption ionization/TOF MS technology in

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combination with a predictive algorithm to discriminate between malignant and benign disease and between good and poor outcomes. Using data from a population of 87 patients with stage III or IV NSCLC receiving conventional first-line chemotherapy and with at least 1-year follow-up available, the authors developed a predictive survival classifier to differentiate between poor prognosis (n=33; OS <12 months) and good prognosis (n=54; OS >12 months). In multivariable analysis, the proteomic-based predictor was significantly associated with OS (HR=3.45; 95% CI, 1.22 to 6.13; p<0.001).

Proteomic Testing in NSCLC to Predict Response to Therapy

Based on the association between VeriStrat status and outcomes in patients treated with EGFR TKIs, it was postulated that VeriStrat testing may predict response to EGFR TKIs. There is some evidence on the role of MALDI MS algorithm–based classification for NSCLC as a predictive marker for response to treatment.

In the largest study to evaluate the VeriStrat test as a predictor of therapy response (the PROSE trial), Gregorc et al (2014) prospectively evaluated the VeriStrat test in a randomized controlled trial (RCT) comparing erlotinib 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. Standard chemotherapy was pemetrexed or docetaxel. Analysis was per protocol. Of 142 patients randomized to chemotherapy and 143 to erlotinib, and 129 (91%) and 134 (94%), respectively, were included in the per-protocol analysis (n=262). EGFR variant analysis was available for 193 (73%); 14 (5%) patients had sensitizing EGFR variants. Of the analysis sample, 184 (70%) and 79 (30%) had VeriStrat “good” and “poor” classifications, respectively. Across both groups, the VeriStrat “good” classification was associated with improved OS and PFS, as shown in Table 3.

Table 3: OS and PFS by VeriStrat Classification for All Patients in Gregorc et al (2014)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VeriStrat “Good”</th>
<th>VeriStrat “Poor”</th>
<th>VeriStrat “Good” vs “Poor”</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (95% CI), mo</td>
<td>Median (95% CI), mo</td>
<td>Hazard Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>11.0 (9.3 to 12.6)</td>
<td>3.7 (2.9 to 5.2)</td>
<td>2.0 (1.88 to 3.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFS</td>
<td>3.4 (2.4 to 4.6)</td>
<td>2.0 (1.6 to 2.4)</td>
<td>1.75 (1.34 to 2.29)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: confidence interval; OS: overall survival; PFS: progression-free survival.

In a multivariable model to predict OS, which included clinical characteristics and EGFR-variant status, VeriStrat classification was significantly associated with OS (HR for VeriStrat “good” vs “poor,” 1.88; 95% CI, 1.25 to 2.84; p=0.003). In the same model, the interaction term for VeriStrat classification and treatment type was significantly associated with OS (HR=1.98; 95% CI, 1.10 to 3.57; p=0.022).

In the entire analysis cohort, median OS was 9.0 months in the chemotherapy group and 7.7 months in the erlotinib group; OS did not differ significantly by treatment group in adjusted or unadjusted analyses. PFS did not differ significantly by treatment group in unadjusted analysis, but was improved for the chemotherapy group in adjusted analysis (HR=1.35; 95% CI, 1.05 to 1.73; p=0.020). Stratification of patients by VeriStrat classification changed the estimate of effect of chemotherapy. In the VeriStrat “good” group, there was no significant difference in OS between the 2 treatment groups, whereas in the VeriStrat “poor” group, OS was shorter for patients treated with erlotinib (see Table 4).
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Table 4: OS by Treatment Group Stratified by VeriStrat Classification in Gregorc et al (2014)

<table>
<thead>
<tr>
<th>Classification</th>
<th>N</th>
<th>Chemotherapy Median OS (95% CI), mo</th>
<th>Erlotinib Median OS (95% CI), mo</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VeriStrat “good”</td>
<td>184</td>
<td>10.9 (8.4 to 15.1)</td>
<td>11.0 (9.2 to 12.9)</td>
<td>1.05 (0.77 to 1.46)</td>
<td>0.714</td>
</tr>
<tr>
<td>VeriStrat “poor”</td>
<td>79</td>
<td>6.4 (3.0 to 7.4)</td>
<td>3.0 (2.0 to 3.8)</td>
<td>1.72 (1.08 to 2.74)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

CI: confidence interval; HR: hazard ratio; OS: overall survival.

The authors concluded that the VeriStrat proteomic test predicted differential benefit for erlotinib compared with chemotherapy for second-line treatment of NSCLC, suggesting that patients classified as VeriStrat “poor” would have better outcomes with chemotherapy than erlotinib.

Hornberger et al (2015) used data from the PROSE trial to estimate cumulative lifetime direct medical costs and costs per QALY gained with use of a VeriStrat-guided treatment strategy. In the study's base-case model, the use of a VeriStrat-guided strategy reduced the use of erlotinib from 88.7% to 61.4%, with an increase in OS of 0.091 year and an increase in QALY by 0.05 year per patient.

Carbone et al (2012) investigated the prognostic and predictive effects of VeriStrat classification on response to treatment and survival in a subset of patients enrolled in a phase 3 clinical trial of erlotinib versus placebo. BR.21, a randomized, placebo-controlled study of erlotinib, enrolled 731 previously treated patients with advanced NSCLC. In the primary study, PFS and OS were prolonged by erlotinib. *EGFR* variants were prognostic for OS, but not predictive of erlotinib benefit, while increased *EGFR* copy number was both prognostic and predictive of erlotinib benefit. For the present study, plasma from 441 patients was tested with the VeriStrat test, of which 436 (98.9%) could be classified as “good” or “poor.”

Among the 144 placebo patients, VeriStrat test results were prognostic, with “good” patients (median OS=6.6 months; 95% CI, 4.4 to 8.2 months) surviving significantly longer than “poor” patients (median OS=3.1 months; 95% CI, 2.2 to 3.7 months; HR=0.44, 95% CI, 0.31 to 0.63; p<0.001). Similar results were seen for PFS, with VeriStrat “good” patients having longer PFS than “poor” patients (HR=0.59; 95% CI, 0.42 to 0.86; p=0.002). Median survival was 10.5 months for VeriStrat “good” patients treated with erlotinib versus 6.6 months for those on placebo (HR=0.63; 95% CI, 0.47 to 0.85; p=0.002), while in VeriStrat “poor” patients, the median survival for erlotinib was 3.98 months and 3.09 months for placebo (HR=0.77; 95% CI, 0.55 to 1.06; p=0.11). For 252 erlotinib-treated patients with data available to evaluate for objective response, VeriStrat “good” patients (n=157 [62%]) had a significantly higher response rate (11.5%) than VeriStrat “poor” patients (1.1%; p=0.002). In a Cox multivariable regression model to predict OS, the interaction term between VeriStrat status and treatment type was not statistically significant, indicating that both “good” and “poor” cohorts derived similar survival benefit from erlotinib. The authors concluded that VeriStrat status predicted response to erlotinib, but did not predict differential benefit from erlotinib for OS or PFS.

In 2013, Stinchcombe et al retrospectively analyzed the role of VeriStrat in predicting treatment outcomes in patients enrolled in a multicenter RCT comparing gemcitabine, erlotinib, or a combination as first-line therapy for NSCLC. Enrolled patients were 70 years and older with a histologic or cellular diagnosis of...
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NSCLC, and no requirement for EGFR status. In the overall trial results, neither erlotinib nor the combination therapy demonstrated efficacy. Of 146 patients enrolled in the trial, 98 had available plasma samples for analysis. In the gemcitabine arm, VeriStrat “good” patients (n=20) had similar PFS and OS rates to VeriStrat “poor” patients. In the erlotinib arm, median PFS was 89 days in 26 VeriStrat “good” patients compared with 22 days in 12 VeriStrat “poor” patients (HR=0.33; 95% CI, 0.16 to 0.70; p=0.002). Similarly, in the erlotinib arm, median OS was 255 days in VeriStrat “good” patients compared with 51 days in VeriStrat “poor” patients (HR=0.40; 95% CI, 0.19 to 0.85; p=0.014). PFS and OS rates between erlotinib-only and gemcitabine-only groups did not differ significantly for either VeriStrat “good” or “poor” patients, although the point estimate for the hazard ratio favored erlotinib in the “good” group and favored gemcitabine in the “poor” group. In a multivariable model, the treatment arm (erlotinib vs gemcitabine) and the VeriStrat-treatment arm interaction term was significantly associated with PFS (adjusted HR=0.20; 95% CI, 0.09 to 0.45; p<0.001). In a similar model to predict OS, the VeriStrat-treatment arm interaction term was significantly associated with OS (adjusted HR=0.49; 95% CI, 0.27 to 0.88; p=0.017), although the treatment arm was not associated with OS.

Lazzari et al (2012) evaluated the association between VeriStrat classification and treatment course in a cohort of 111 patients with a cytologic or histologic diagnosis of advanced or inoperable NSCLC treated with gefitinib, most (72%) as a second- or third-line therapy. VeriStrat classification was performed at baseline, after 1 month of gefitinib therapy, and every 2 months concomitantly with computed tomography evaluation until withdrawal in a total of 476 plasma samples. At baseline, 69% of patients were classified as VeriStrat “good” and 28% as VeriStrat “poor.” During treatment, 98 (88%) of 111 patients kept the same VeriStrat classification, while 13 (11%) had 1 or more intraindividual changes in classification. At treatment withdrawal, the number of VeriStrat “good” patients decreased from 69% to 51%, whereas the number of VeriStrat “poor” profile patients increased from 28% to 43%; 6 (6%) patients were “indeterminate.” VeriStrat “good” classification was associated with longer PFS in univariate (HR=0.54; 95% CI, 0.35 to 0.83; p=0.004) and multivariate (HR=0.52; 95% CI, 0.30 to 0.92; p=0.025) models. Similarly, “good” classification was associated with longer OS in univariate (HR=0.35; 95% CI, 0.23 to 0.44; p<0.001) and multivariate (HR=0.44; 95% CI, 0.26 to 0.72; p=0.001) models. Patients who shifted from “good” to “poor” classification had a higher risk of developing new lesions than other patients (odds ratio, 2.9; 95% CI, 1.02 to 8.37; p=0.049).

Section Summary: Clinical Validity
The literature related to the prognostic value of proteomic testing in patients with advanced NSCLC consists primarily of retrospective analyses of clinical trials of EGFR TKIs, with or without other therapies. Most studies demonstrated that classification based on proteomic testing is associated with survival outcomes. However, the evidence is limited by heterogeneity in the treatment regimens used and patient population characteristics. There is less evidence related to the role of proteomic testing to predict response to EGFR TKIs. The largest study (the prospective PROSE RCT) reported that proteomic testing with the VeriStrat assay predicted differential benefit for erlotinib compared with chemotherapy for second-line treatment of NSCLC. However, for the entire treatment population in the PROSE trial, there was no significant benefit with erlotinib treatment compared with chemotherapy, making the utility of VeriStrat in this population uncertain.
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Clinical Utility
The proposed clinical utility of VeriStrat is for selecting patients who are unlikely to benefit from EGFR TKIs in the second-line setting. Direct evidence from studies that demonstrate improved outcomes for patients managed with a strategy that includes proteomic testing would be helpful in demonstrating the clinical utility of proteomic testing to select targeted therapy for NSCLC.

Akerley et al (2013) prospectively evaluated whether treating physicians’ treatment recommendations changed after VeriStrat testing results were obtained for 226 physicians who provided pre- and posttest treatment plan information for 403 VeriStrat tests. Pre- and posttest result treatment recommendations were prospectively collected from ordering physicians. Of the 262 cases where pretreatment recommendations were for erlotinib only, for those patients who were classified as VeriStrat “poor,” physicians recommended erlotinib in 13.3% (vs 95.5% of VeriStrat “good” patients; p<0.001). Of the 45 physicians who were not considering erlotinib prior to testing, after testing physicians recommended erlotinib in 73.5% of patients with a VeriStrat “good” classification.

Section Summary: Clinical Utility
No direct evidence for a serum proteomic test for the selection of a NSCLC treatment strategy was identified. 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 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. However, given the evidence from the IUNO trial and the lack of support from guidelines for EGFR TKIs in this setting, EGFR-TKI therapy is no longer standard therapy for any EGFR-negative or -unknown patient in the second-line setting.

SUMMARY OF EVIDENCE
For individuals with epidermal growth factor receptor (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
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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.

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines on the management of non-small-cell lung cancer (NSCLC; v.4.2017) recommend routine testing for EGFR variants in patients with metastatic nonsquamous NSCLC (category 1 recommendation) and consideration for EGFR variant testing in patients with metastatic squamous NSCLC who were never smokers or with small biopsy specimens or mixed histology (category 2A recommendation).

EGFR-Positive Populations
Erlotinib, afatinib, or gefitinib are recommended as first-line therapy for patients with advanced or metastatic NSCLC with sensitizing EGFR variants (category 1 recommendation). If the variant is discovered during first-line chemotherapy, NCCN recommends completing planned chemotherapy, including maintenance therapy, or interrupting followed by erlotinib, afatinib, or gefitinib.

For EGFR-positive patients who have progression on a tyrosine kinase inhibitor (TKI), T790M testing is recommended. Treatment options following progression include local therapy, osimertinib (if T790M-positive; category 1 recommendation), or continuation of erlotinib, afatinib, or gefitinib, depending on the level and location of symptoms.

EGFR-Negative or –Unknown Populations
For patients with advanced nonsquamous NSCLC who are PD-L1- and ROS1-negative or -unknown, and without ALK rearrangements or sensitizing EGFR variants, systemic chemotherapy is recommended.

For patients with advanced nonsquamous NSCLC who are PD-L1-, ROS1-, and EGFR1-negative or -unknown, and without ALK rearrangements, who have progression on first-line systemic chemotherapy, with good performance status, treatment options include the following:

- Systemic immune checkpoint inhibitors (preferred):
  Nivolumab (category 1 recommendation); OR
  Pembrolizumab (category 1 recommendation); OR
  Atezolizumab (category 1 recommendation); OR

- Other systemic therapy:
  Docetaxel; OR
  Pemetrexed; OR
  Gemcitabine; OR
  Ramucirumab and Docetaxel.

The NCCN guidelines for the management of NSCLC v. 4.2017 no longer recommend that proteomic testing be used to determine whether erlotinib should be given to patients with unknown EGFR mutation status who have advanced NSCLC and disease progression.
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References

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Policy History
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05/20/2015 Medical Policy Implementation Committee approval. New policy.
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017 Medical Policy Committee review

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03/15/2017 Medical Policy Implementation Committee approval. Coverage changed to investigational.
Next Scheduled Review Date: 03/2018

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