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

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Origination: 12/2014  Next Review: 12/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic 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.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With non-small-cell lung cancer who are EGFR</td>
<td>• Management with a serum proteomic test to select targeted therapy</td>
<td>• Usual care</td>
<td>• Overall survival</td>
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<td>wild-type or have unknown EGFR status who have</td>
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<td>• Disease-specific survival</td>
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<td>disease progression after first-line treatment</td>
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Proteomic testing has been proposed as a way to predict 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 EGFR tyrosine kinase inhibitors (TKIs).

The evidence for the use of serum proteomic testing to select targeted therapy in individuals with NSCLC who are EGFR wild-type or have unknown EGFR status who
have disease progression after first-line treatment includes 1 prospective study evaluating the test’s use in predicting response to EGFR TKI therapy and 1 prospective study evaluating changes in treatment decision making, along with retrospective studies evaluating the prognostic ability of this testing. Relevant outcomes are overall survival and disease-specific survival. Although a limited body of literature exists for analytic validity of proteomic testing to predict response to EGFR TKIs for NSCLC in general, at least 1 study reports good test reproducibility for the most widely studied proteomic test, the VeriStrat assay. The evidence from retrospective studies supports 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 suggests that VeriStrat discriminates between patients who are likely to respond to EGFR TKI therapy. Although there is evidence from 1 prospective study to suggest that physician decision making is altered by the use of the VeriStrat test, there is no direct evidence to demonstrate that outcomes are improved for EGFR wild-type or EGFR-unknown NSCLC patients who are managed with proteomic testing. Therefore, at present, the evidence related to the clinical utility of proteomic testing to select targeted therapies in NSCLC is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**
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. However, 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 in NSCLC**
Several common genetic alterations in NSCLC have been targets for drug therapy, the most well-established of which is the use of TKIs targeting the EGFR.

**EGFR Mutations in NSCLC**
The 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.

Mutations in 2 regions of the \textit{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 \textit{EGFR} mutations in NSCLC varies by population, with the highest prevalence in non-smoking, Asian women, with adenocarcinoma, in whom \textit{EGFR} mutations have been reported to be up to 30% to 50%. The reported prevalence of \textit{EGFR} mutations in lung adenocarcinoma patients in the U.S. is approximately 15%.(3)

\textbf{ALK Mutations in NSCLC}

In about 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 gene and the anaplastic lymphoma kinase gene (\textit{EML4-ALK}), which is created by an inversion on chromosome 2p.(4) The \textit{EML4} fusion leads to ligand-independent activation of \textit{ALK}, which encodes a receptor TK whose precise cellular function is not completely understood. \textit{EML4-ALK} mutations 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 \textit{EGFR} mutations.

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

\textbf{Other Genetic Mutations in NCLSC}

Other genetic mutations have been identified in subsets of patients with NSCLC, which are summarized in \textbf{Table 1}. The role of testing for these mutations in selecting targeted therapies for NSCLC is less well-established than for \textit{EGFR} mutations.

\textbf{Table 1: Non-EGFR Mutations in NSCLC}

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Function</th>
<th>Estimated Mutation 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 \nHeavy smokers</td>
</tr>
<tr>
<td>ROS1</td>
<td>Encodes a receptor tyrosine kinase in the insulin receptor family.</td>
<td>0.9-3.7%</td>
<td>Adenocarcinoma \nNever smokers</td>
</tr>
<tr>
<td>RET</td>
<td>Proto-oncogene that encodes a receptor tyrosine kinase growth</td>
<td>0.6-2%</td>
<td></td>
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<tr>
<td>Gene</td>
<td>Description</td>
<td>Information</td>
<td></td>
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<tr>
<td>MET</td>
<td>Oncogene that encodes a receptor tyrosine kinase 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></td>
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<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></td>
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<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></td>
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</table>

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

**Current Targeted Treatment Options for NSCLC**

**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, the 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 mutation-positive NSCLC, received FDA approval for patients with T890M-mutation-positive NSCLC who have progressed on an EGFR TKI.

A 2013 meta-analysis of 23 trials of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC reported improved progression-free survival (PFS) in EGFR mutation-positive patients treated with EGFR TKIs in the first- and second-line settings and for maintenance therapy.(5) Comparisons were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively. Among EGFR mutation-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 mutation-positive or mutation-negative patients. Statistical heterogeneity was not reported for any outcome. The authors concluded that EGFR mutation testing is indicated to guide treatment selection in NSCLC patients.
On the basis of the results of 5 phase III randomized controlled trials (RCTs), 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 mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.

The primary role for TKIs in NSCLC is for EGFR mutation-positive patients with advanced NSCLC. The use of TKIs in NSCLC in EGFR mutation-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 mutation 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 mutation 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.

**Anti-EGFR Monoclonal Antibodies**

For the treatment of KRAS-mutated NSCLC, anti-EGFR monoclonal antibodies have been investigated as possible treatment options. Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Cetuximab may be used in combination with chemotherapy in patients with advanced or recurrent NSCLC as first-line and maintenance therapy. Panitumumab is not generally used in NSCLC.

**Other Targeted Therapies**

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 ALK-TKIs, such as ceritinib, are under investigation.

Proposed targeted therapies for other genetic alterations in NSCLC are trastuzumab for HER2 mutations, 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, 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 spectrometry 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® (Biodesix, Inc., Boulder, CO) has been developed that is proposed to predict response to TKIs. The test relies on a predictive algorithm based on matrix-assisted laser desorption ionization (MALDI) mass spectrometry (MS) analysis of pretreatment serum to generate a “good” or “poor” assessment for response to TKIs.(12) Veristrat has been proposed as a method 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 (SELDI/TOF) mass spectrometry, and alternative predictive algorithms, in the assessment of proteomic predictors of lung cancer risk.(13)

**Rationale**

This evidence review was created in October 2014 and has been updated periodically with literature reviews of the MEDLINE database, most recently through September 1, 2016. The following is a summary of the key literature to date.

The evaluation of a predictive test focuses on 3 main principles: (1) technical performance; (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).

**CLINICAL CONTEXT AND PROPOSED CLINICAL UTILITY**

The proposed clinical utility for the currently commercially-available proteomic test is for predicting response to EGFR TKIs in individuals with NSCLC with wild-type or unknown EGFR mutation status, and thus helping determine whether the use of an EGFR TKI in these individuals might help improve outcomes.

**ANALYTIC VALIDITY**

In 2007, Taguchi et al described the development and testing of a predictive algorithm based on matrix-assisted laser desorption ionization (MALDI) mass spectrometry (MS) analysis of serum to identify patients with NSCLC who are likely to benefit from treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).(12) This method forms the basis of the VeriStrat testing algorithm. The authors developed a prediction algorithm based on the MS
results from a training set that comprised 3 cohorts (N=139 patients) of NSCLC patients who were treated with the EGFR-TKI gefitinib and from whom pretreatment serum was available. The authors tested the algorithm on 2 independent validation patient cohorts who received gefitinib or erlotinib, the Italian B validation set and the Eastern Cooperative Oncology Group (ECOG) validation set (N=163 patients; pretreatment serum available in 140 patients), and 3 independent control patient cohorts who did not receive EGFR TKIs (N=158 patients). In the prediction development, each sample spectrum was characterized by a set of features based on mass-to-charge (m:z) ratio, and a classifier algorithm was developed using a k-nearest neighbor algorithm to map a subset of the features to “good” or “poor” outcome after EGRF-TKI treatment. To develop the discriminatory algorithm, the authors initially evaluated differences in m:z peaks for 5 clinical groups: (1) progressive disease—early (disease progression in <1 month); (2) progressive disease (disease progression in 1-2 months); (3) partial response; (4) stable disease—short (stable disease for ≤6 months); and (5) stable disease—long (stable disease for >6 months). The most spectrally distinct clinical groups were those from patients with disease progression in less than 1 month and those with stable disease for more than 6 months, so candidate m:z features were chosen to discriminate between those groups. After optimization, the final discriminatory algorithm consisted of 8 features.

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%.

Salmon et al conducted a study that used MALDI MS proteomic signature-associated algorithm to predict outcomes for patients with NSCLC treated with erlotinib.(14) The predictive algorithm was generated with serum from 40 patients with stage IIIB or IV recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab (a monoclonal antibody that acts as an inhibitor of vascular endothelial growth factor A), 35 of whom had clinical information available. The algorithm was validated with a validation cohort comprised of patients (N=82) enrolled in the ECOG study 3503, a pilot study of erlotinib in patients with stage IIIB or IV or recurrent NSCLC, and a control cohort (N=61). 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 used MALDI time of flight (TOF) MS protein profiles to generate predictive algorithm for survival in patients with NSCLC treated with gefitinib or erlotinib.(15) The algorithm was developed with a training cohort of 24 patients based on 3 m:z peaks that were significantly different between patients with a good or poor clinical outcome. The prediction model was validated in a blinded test set of 44 (15 with poor outcome, 29 with good outcome) patients; a total of 93% (14/15) of poor
outcome patients and 93% (27/29) of good outcome patients were correctly identified. Within- and between-user reproducibility is not reported.

**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 was also demonstrated to have 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 related to 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.(16) Eleven cohorts were identified, which were reported in 6 published studies, including the studies by Taguchi et al,(12) Carbone et al,(17) Kuiper et al,(18) Akerley et al,(19) Gautschi et al,(20) and Stinchcombe et al,(21) described next, and 1 conference abstract. In pooled analysis, VeriStrat “good” status was associated with improved overall survival (OS) compared with VeriStrat “poor” status: 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): combined HR of 0.49 (95% CI, 0.38 to 0.60; p<0.001). There was low heterogeneity across studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type and Assay</th>
<th>N</th>
<th>Patient Population</th>
<th>Summary of Outcomes: OS</th>
<th>Summary of Outcomes: PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taguchi et al (2007):12 – Italian B validation set</td>
<td>Retrospective; VeriStrat</td>
<td>67</td>
<td>Late-stage or recurrent NSCLC treated with single-agent gefitinib</td>
<td><strong>Unadjusted</strong> OS (assay “good” vs “poor”): HR of death, 0.50 (95% CI, 0.24 to 0.78; p=0.005)</td>
<td><strong>Unadjusted</strong> Time to progression (assay “good” vs “poor”): HR=0.56 (95% CI, 0.28 to 0.89; p=0.02)</td>
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<tr>
<td>Taguchi et al (2007):11 – ECOG 3503 validation set</td>
<td>Retrospective; VeriStrat</td>
<td>96</td>
<td>ECOG 3503 trial patients: stage IIIb or IV or recurrent NSCLC treated with first-line erlotinib</td>
<td><strong>Unadjusted</strong> OS (assay “good” vs “poor”): HR of death, 0.4 (95% CI, 0.24 to 0.70; p&lt;0.001)</td>
<td><strong>Unadjusted</strong> Time to progression (assay “good” vs “poor”): HR=0.53 (95% CI, 0.33 to 0.85; p=0.007)</td>
</tr>
<tr>
<td>Study</td>
<td>Test Type</td>
<td>Patients</td>
<td>Characteristics</td>
<td>Validation Method</td>
<td>Assay Status</td>
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<tr>
<td>Amann et al (2010)</td>
<td>Retrospective; VeriStrat</td>
<td>88</td>
<td>ECOG 3503 trial patients: stage IIB or IV or recurrent NSCLC treated with first-line erlotinib</td>
<td><strong>ECOG PS</strong>: 28.4% grade 0; 46.1% grade 1; 25.5% grade 2&lt;br&gt;<strong>Histology</strong>: 64.7% adenocarcinoma; 10.8% squamous; 1% LCC; 16.7% NOS; 6.9% other</td>
<td><strong>Unadjusted</strong>&lt;br&gt;OS (assay &quot;good&quot; vs &quot;poor&quot;); HR=0.357 (95% CI, 0.21 to 0.60; p=0.001)&lt;br&gt;<strong>Adjusted</strong> (for EGFR status)&lt;br&gt;OS (assay &quot;good&quot; vs &quot;poor&quot;); HR=0.51 (95% CI, 0.28 to 0.90; p=0.02)</td>
</tr>
<tr>
<td>Carbone et al (2010)</td>
<td>Retrospective; VeriStrat</td>
<td>35</td>
<td>Stage IIB or IV, recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab</td>
<td><strong>KPS</strong>: 7.5% KPS 70; 47.5% KPS 80; 45% KPS 90&lt;br&gt;<strong>Histology</strong>: 75% adenocarcinoma; 22.5% NOS; 2.5% other</td>
<td><strong>OS (assay &quot;good&quot; vs &quot;poor&quot;); HR=0.12 (95% CI, 0.07 to 0.21; p=0.02)</strong></td>
</tr>
<tr>
<td>Kuiper et al (2012)</td>
<td>Retrospective; VeriStrat</td>
<td>50</td>
<td>Chemotherapy-naïve patients with pathologically documented, inoperable, locally advanced, recurrent, or metastatic NSCLC, treated with erlotinib and sorafenib</td>
<td><strong>Histology</strong>: 88% adenocarcinoma; 32% other&lt;br&gt;<strong>EGFR status</strong>: 62% WT; 14% mutated; 24% unknown</td>
<td><strong>OS (assay &quot;good&quot; vs &quot;poor&quot;); HR=0.06 (95% CI, 0.008 to 0.237)</strong></td>
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<tr>
<td>Akerley et al (2013)</td>
<td>Retrospective; VeriStrat</td>
<td>42</td>
<td>Stage IIB/IV or recurrent nonsquamous NSCLC, with no prior chemotherapy for metastatic disease, treated with erlotinib and bevacizumab</td>
<td><strong>Histology</strong>: 68% adenocarcinoma; 32% other&lt;br&gt;<strong>EGFR status</strong>: 62% WT; 14% mutated; 24% unknown</td>
<td><strong>OS (assay &quot;good&quot; vs &quot;poor&quot;); HR=0.48 (95% CI, 0.294 to 0.784; p=0.0027)</strong></td>
</tr>
<tr>
<td>Gautschi et al (2013)</td>
<td>Retrospective; VeriStrat</td>
<td>117</td>
<td>Pooled analysis of patients from SAKK19/05 and NTR528 trials: untreated, advanced nonsquamous NSCLC, treated with first-line therapy with erlotinib and bevacizumab</td>
<td><strong>Histology</strong>: 89.7% adenocarcinoma; 10.2% other</td>
<td><strong>OS (assay &quot;good&quot; vs &quot;poor&quot;); HR=0.40 (95% CI, 0.17 to 0.94; p=0.035)</strong></td>
</tr>
<tr>
<td>Keshtgarpour et al (2016)</td>
<td>Retrospective; VeriStrat</td>
<td>49</td>
<td>Advanced-stage squamous and nonsquamous NSCLC seen at a single clinic who underwent VeriStrat testing. Baseline histology and PS not reported.</td>
<td></td>
<td><strong>OS (assay &quot;good&quot; vs &quot;poor&quot;); HR=0.97 (95% CI, 0.48 to 1.97; p=0.94).</strong></td>
</tr>
</tbody>
</table>

**Non-VeriStrat proteomic testing algorithms**

<table>
<thead>
<tr>
<th>Study</th>
<th>Test Type</th>
<th>Patients</th>
<th>Characteristics</th>
<th>Validation Method</th>
<th>Assay Status</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon et al (2009)¹⁴ – erlotinib/ bevacizumab generation set</td>
<td>Retrospective; non-VeriStrat</td>
<td>35</td>
<td>Stage IIB or IV, recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab</td>
<td><strong>Histology</strong>: 89.7% adenocarcinoma; 10.2% other</td>
<td></td>
<td>Median OS 71.4 for assay &quot;good&quot; and 19.9 wk for assay &quot;poor&quot; (p=0.0015) Median PFS 18.9 for VeriStrat &quot;good&quot; and 6.3 wk for VeriStrat &quot;poor&quot; (p=0.0035)</td>
</tr>
<tr>
<td>Salmon et al (2009)¹⁴ – ECOG 3503 (erlotinib-treated) validation set</td>
<td>Retrospective; non-VeriStrat</td>
<td>82</td>
<td>ECOG 3503 trial patients: stage IIB or IV or recurrent NSCLC treated with first-line erlotinib</td>
<td></td>
<td></td>
<td>Median OS 71.4 for assay &quot;good&quot; and 19.9 wk for assay &quot;poor&quot; (p=0.0015) Median PFS 18.9 for VeriStrat &quot;good&quot; and 6.3 wk for VeriStrat &quot;poor&quot; (p=0.0035)</td>
</tr>
<tr>
<td>Wu et al (2013)¹⁵ – validation set</td>
<td>Retrospective; non-VeriStrat</td>
<td>44</td>
<td>Stage IIB or IV NSCLC failed or intolerant to chemotherapy, treated with gefitinib or cetuximab</td>
<td></td>
<td></td>
<td>Median OS 71.4 for assay &quot;good&quot; and 19.9 wk for assay &quot;poor&quot; (p=0.0015) Median PFS 18.9 for VeriStrat &quot;good&quot; and 6.3 wk for VeriStrat &quot;poor&quot; (p=0.0035)</td>
</tr>
<tr>
<td>Yang et al (2015)</td>
<td>Retrospective; non-VeriStrat</td>
<td>Stage IIIb or IV NSCLC with a known EGFR mutation status</td>
<td>Following EGFR-TKI treatment (n=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>
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<td>Mutation status: 42.3% with EGFR TKI–sensitive mutation; 57.7% with EGFR WT</td>
<td>Following EGFR-TKI treatment (n=81 patients in validation set): PFS=10.0 mo for assay &quot;mutant&quot; and 2.3 mo for assay &quot;wild&quot; (p&lt;0.001)</td>
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<td>Previous EGFR treatment: 67.5% (30.9% as first-line, 26.8% as second-line, 9.8% as third-line or greater)</td>
<td>Following EGFR-TKI treatment (n=81 patients in validation set): PFS=10.0 mo for assay &quot;mutant&quot; and 2.3 mo for assay &quot;wild&quot; (p&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; ECOG: 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; MS: NOS: not otherwise specified; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free survival; PS: performance status; TKI: tyrosine kinase inhibitor; WT: wild-type.

a Adjusted based on age, performance status, sex, histology, smoking history, and MALDI MS classification.
b Adjusted based on age, number of involved sites, prior weight loss, histology, and MALDI MS classification.
c Adjusted based on age, sex, histology.
d Adjusted based on metastatic site and performance status.

In the Taguchi study, MALDI MS algorithm-predicted classification was not significantly associated with OS in any of the 3 control sets used. Similarly, in the Salmon study, MALDI MS algorithm-predicted classification was not prognostic of OS in the control set.

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 used surface-enhanced laser desorption ionization (SELDI)/TOF MS technology in combination with a predictive algorithm to discriminate between malignant and benign disease and between good and poor outcomes.(13) Using data from a population of 87 patients with stage 3 to 4 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 of VeriStrat status with outcomes in patients who were treated with EGFR TKIs but not in TKI-untreated patients, it was postulated that VeriStrat testing may be predictive of response to EGFR TKIs. There is some evidence related to 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 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 based on performance status, smoking history, treatment center, and (masked) pretreatment VeriStrat classification.(25) Standard chemotherapy was with pemetrexed or docetaxel. Analysis was per protocol. Of 142 patients randomly assigned to chemotherapy and 143 to erlotinib, and 129 (91%) and 134 (94%),
respectively, were included in the per-protocol analysis (total N=262). EGFR mutation analysis was available for 193 (73%); 14 patients (5%) had sensitizing EGFR mutations. Of the analysis sample, 184 (70%) and 79 (30%) had VeriStrat “good” and “poor” classifications, respectively. Across both groups, 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>HR for “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>HR (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;0.01</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;0.01</td>
</tr>
</tbody>
</table>

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

In a multivariable model to predict OS, which included clinical characteristics and EGFR-mutation 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).

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</th>
<th>Erlotinib</th>
<th>Hazard Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median OS (95% CI), mo</td>
<td>Median OS (95% CI), mo</td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<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 predicts differential benefit for erlotinib compared with chemotherapy for second-line treatment of NSCLC, suggesting that patients who are VeriStrat “poor” will have better outcomes with chemotherapy than erlotinib.
Carbone et al 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.\(^{(26)}\) Patients were enrolled in BR.21, a randomized placebo-controlled study of erlotinib in 731 previously treated patients with advanced NSCLC. In the primary study, PFS and OS were prolonged by erlotinib. \(EGFR\) mutations 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) surviving significantly longer than “poor” patients (median OS=3.1 months; 95\% CI, 2.2 to 3.7; 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; \(p=0.0016\)). 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 than VeriStrat “poor” patients (11.5\% vs 1.1\%; \(p=0.002\)). In a Cox multivariable regression model to predict OS, the interaction term between VeriStrat status and treatment type was nonsignificant, indicating that both “good” and “poor” cohorts derived similar survival benefit from erlotinib. The authors concluded that VeriStrat status predicts response to erlotinib, but does not predict differential benefit from erlotinib for OS or PFS.

In 2013, Stinchcombe et al evaluated the role of VeriStrat in predicting treatment outcomes in a retrospective analysis of patients enrolled in a multicenter RCT comparing gemcitabine, erlotinib, or a combination as first-line therapy for NSCLC.\(^{(21)}\) Enrolled patients were age 70 and older with a histologic or cellular diagnosis of NSCLC, with no requirement for \(EGFR\) status. In the overall trial results, neither erlotinib nor the combination demonstrated efficacy. Of 146 patients enrolled in the trial, 98 had available plasma samples for the present analysis. In the gemcitabine arm, VeriStrat “good” patients (n=20) had similar PFS and OS to VeriStrat “poor” patients. In the erlotinib arm, median PFS was 89 days in VeriStrat “good” patients (n=26) compared with 22 days in VeriStrat “poor” patients (n=12) (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 between erlotinib-only and gemcitabine-only groups did not differ significantly for either VeriStrat “good” or “poor” patients, although the point estimate for HR 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 for VeriStrat-treatment interaction, 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 evaluated the association of VeriStrat with 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 drug. (27) VeriStrat classification was performed at baseline, after 1 month of gefitinib therapy, and every 2 months concomitantly with computed tomography scan 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 the treatment course, 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 compared with other patients (OR=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 NSCLC consists primarily of retrospective analyses of clinical trials of EGFR TKIs, with or without other therapies, in patients with advanced NSCLC. Most studies demonstrate 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 predicts 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 role of erlotinib in this population uncertain.

**CLINICAL UTILITY**

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. Based on prior studies, VeriStrat testing may help to select patients who
will have limited benefit from targeted therapy, for whom conventional chemotherapy would be a reasonable choice.

Akerley et al evaluated whether treating physicians’ treatment recommendations changed after VeriStrat testing results were obtained. Study authors considered all VeriStrat tests ordered from August 9, 2011, to November 26, 2012. Pre- and posttest result treatment recommendations were prospectively collected from ordering physicians. Over the duration of the study, 2854 tests were ordered by 724 physicians, of whom 226 provided pre- and posttest treatment information for 403 tests and were included in the analysis. In the posttest, physicians recommended erlotinib therapy for 90.3% of patients who were classified as VeriStrat “good,” compared with 9.6% of patients who were classified as VeriStrat “poor” (p<0.000). Of the 262 physicians whose 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, following testing physicians recommended erlotinib in 73.5% of patients with a VeriStrat “good” classification. This study suggests that physicians may alter treatment decisions based on the VeriStrat testing. However, it is limited by self-reported results and reporting bias. In itself, it does not provide information about the utility of VeriStrat testing in altering patient outcomes.

Several cost-utility studies have modeled cost and quality-adjusted life-year (QALY)‒related outcomes for a treatment strategy using a proteomic testing‒based approach. Nelson et al developed a cost-utility model to compare anticipated survival and cost-effectiveness of a VeriStrat-guided NSCLC treatment strategy for a hypothetical cohort of patients with NSCLC, compared with strategies of treating all patients with chemotherapy or all patients with an EGFR TKI. The study’s model estimated an incremental cost-effectiveness ratio of a VeriStrat-guided treatment strategy of $91,111 (vs EGFR TKI for all patients) per QALY. However, the strategy of treating all patients with chemotherapy was associated with the longest PFS. Hornberger et al used data from the PROSE trial to calculate estimates for 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 increase in QALY by 0.05 year per patient.

No empirical studies were identified that evaluate outcomes for a NSCLC treatment strategy guided by VeriStrat results.

SUMMARY OF EVIDENCE
For individuals with EGFR negative or EGFR status unknown non-small-cell lung cancer 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 1 prospective study evaluating changes in treatment
decision making, along with retrospective studies evaluating the prognostic ability of this testing. Relevant outcomes are overall survival and disease-specific survival. Although a limited body of literature exists for 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. It is possible that 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) guidelines for the management of NSCLC (v.5.2016) recommend routine testing for EGFR mutations in patients with metastatic nonsquamous NSCLC (category 1 recommendation) and consideration for EGFR mutation testing in patients with metastatic squamous NSCLC (category 2A recommendation). Erlotinib is recommended as first-line therapy for patients with advanced or metastatic NSCLC with sensitizing EGFR mutations.

For patients with advanced nonsquamous NSCLC without ALK rearrangements or sensitizing EGFR mutations who have disease progression during or after first-line therapy, the use of proteomic testing can be used to determine whether erlotinib should be used in patients with unknown EGFR mutation status. In addition, The use of proteomic testing to guide therapy is recommended if patients with unknown EGFR mutation status.

American Society of Clinical Oncology
In 2011, the American Society of Clinical Oncology (ASCO) issued a provisional clinical opinion on EGFR mutation testing for patients with advanced NSCLC who are considering first-line EGFR-TKI therapy.(3) The authors concluded that such patients who have not previously received chemotherapy or an EGFR TKI should undergo EGFR mutation testing to determine whether chemotherapy or an EGFR TKI is appropriate first-line treatment.

In 2015, ASCO issued a clinical practice guideline update on systemic therapy for stage IV NSCLC, which makes the following recommendations about EGFR-TKI
therapy as second- or third-line treatment in patients without a sensitizing \textit{EGFR} mutation\cite{31}:

- For second-line treatment, for patients with nonsquamous-NSCLC, docetaxel, erlotinib, gefitinib, or pemetrexed are acceptable (evidence quality: high; strength of recommendation: strong).
- For third-line treatment, for patients who have not received erlotinib or gefitinib and have performance status 0-3, erlotinib may be recommended.

**College of American Pathologists et al**
In 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR-TKI therapy.\cite{32} Based on excellent quality evidence (category A), the guidelines recommend \textit{EGFR} mutation testing in patients with lung adenocarcinoma regardless of clinical characteristics, such as smoking history.

**American College of Chest Physicians**
American College of Chest Physicians (ACCP) updated its evidence-based clinical practice guidelines on the treatment of stage IV NSCLC in 2013.\cite{33} Based on their review of the literature, guideline authors reported improved response rates, PFS, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with \textit{EGFR} mutations, especially exon 19 deletion and L858R. ACCP recommends “testing patients with NSCLC for \textit{EGFR} mutations at the time of diagnosis whenever feasible, and treating with first-line EGFR TKIs if mutation-positive.”

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**
Not applicable.

**MEDICARE NATIONAL COVERAGE**
Novitas Solutions established a local Medicare coverage determination for the VeriStrat 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 notes “The VeriStrat\textregistered 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).”\cite{34}

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**
Some currently unpublished trials that might influence this review are listed in Table 5.

**Table 5. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02055144</td>
<td>VeriStrat as Predictor of Benefit of First Line Non-Small Cell Lung Cancer (NSCLC) Patients From Standard Chemotherapy</td>
<td>100</td>
<td>May 2015 (ongoing)</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>-----</td>
<td>------------------</td>
</tr>
<tr>
<td>Unpublished</td>
<td>Testing of Drugs Erlotinib and Docetaxel in Lung Cancer Patients Classified Regarding Their Outlook Using VeriStrat® (EMPHASIS)</td>
<td>500</td>
<td>Dec 2015 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

References:
32. College of American Pathologists IAftSoLC, Association for Molecular Pathology (CAP,IASLC,AMP),. Molecular testing guidelines for selection of lung cancer patients for EGFR and ALK


### Billing Coding/Physician Documentation Information

**81538**  
Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival (new code 1/1/2016)

**84999**  
Unlisted chemistry procedure

**ICD-10 Codes:**

- **C34.10-C34.92**  
Malignant neoplasm of lung code range

Effective 01/01/16, there is a specific CPT code for this test:

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

Prior to 2016, there was no specific CPT code for this testing. It would likely have been reported using the unlisted chemistry procedure code 84999.

### Additional Policy Key Words

N/A

### Policy Implementation/Update Information

- **12/1/2014**  
New Policy. Proteomic testing considered investigational for all indications in the management of non-small cell lung cancer.

- **4/1/16**  
Added CPT code. No policy statement changes.

- **12/1/16**  
No policy statement changes.

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