Proteomic testing has been proposed as a way to predict survival outcomes and response to and selection of targeted therapy for patients with non-small-cell lung cancer (NSCLC). One commercially available test (the VeriStrat assay) has been investigated as a predictive marker for response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).

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

Policy
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.

Benefit Application

BlueCard/National Account Issues
State or federal mandates (eg, FEP) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only on the basis of their medical necessity.

Rationale
This evidence review was created in October 2014 and has been updated regularly with literature reviews of the MEDLINE database, most recently through September 1, 2016.

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.

NON-SMALL-CELL LUNG CANCER

Clinical Context and Test Proposed
The proposed clinical utility for the current commercially available proteomic test is for predicting response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in individuals with non-small-cell lung cancer (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 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 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.
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>VeriStrat-specific studies</td>
<td>Retrospective</td>
<td>67</td>
<td>Late-stage or recurrent NSCLC treated with single-agent gefitinib&lt;br&gt;ECOG PS: 29.8% grade 0; 40.3% grade 1; 23.9% grade 2&lt;br&gt;Histology: 56.8% adeno; 22.4% squamous; 20.9% NOS</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, 0.26 to 0.89; p=0.02)</td>
</tr>
<tr>
<td>Taguchi et al (2007)</td>
<td>Retrospective</td>
<td>06</td>
<td>ECOG 3503 trial patients: stage IIIb or IV or recurrent NSCLC treated with first-line erlotinib&lt;br&gt;ECOG PS: 30.2% grade 0; 43.8% grade 1; 26.0% grade 2&lt;br&gt;Histology: 54.6% adeno; 11.5% squamous; 1.0% LCC; 22.9% NOS</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>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&lt;br&gt;ECOG PS: 28.4% grade 0; 48.1% grade 1; 25.5% grade 2&lt;br&gt;Histology: 64.7% adeno; 10.3% squamous; 11.6% NOS; 3.8% other</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 0.80; p=0.002)</td>
</tr>
<tr>
<td>Carbone et al (2010)</td>
<td>Retrospective</td>
<td>35</td>
<td>Stage IIIb or IV, recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab&lt;br&gt;KPS: 75% KPS: 75%; 47.5% KPS 80%; 45% KPS 90%;&lt;br&gt;Histology: 75% adeno; 22.5% NOS; 2.5% other</td>
<td>HR of death, 0.14 (61 wk vs 41 wk; 95% CI, 0.03 to 0.59)</td>
<td>PFS: HR=0.045 (36 wk vs 8 wk; 95% CI, 0.096 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 sorafenib&lt;br&gt;ECOG PS: 45% grade 0; 50% grade 1&lt;br&gt;Histology: 68% adeno; 32% other&lt;br&gt;EGFR status: 62% WT; 14% mutated; 24% unknown</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=0.036)</td>
</tr>
<tr>
<td>Akerley et al (2013)</td>
<td>Retrospective</td>
<td>42</td>
<td>Stage IIIb or IV or recurrent nonsquamous NSCLC, with no prior chemotherapy for metastatic disease, treated with erlotinib and bevacizumab&lt;br&gt;ECOG PS: 48% grade 0; 48% grade 1&lt;br&gt;Histology: 84% adeno; 48% NOS; 4% other</td>
<td>Median OS 7.14 mo for assay “good” and 19.9 wk for assay “poor” (p=0.002)</td>
<td>Median PFS 18.9 wk for “good” and 0.3 wk for “poor” (p=0.004)</td>
</tr>
<tr>
<td>Gautschi et al (2013)</td>
<td>Retrospective</td>
<td>117</td>
<td>Pooled analysis of patients from SAKK 19/05 and NTRG 526 trials: untreated, advanced nonsquamous NSCLC, treated with first-line therapy with erlotinib and bevacizumab&lt;br&gt;ECOG PS: 52.6% grade 0; 42.5% grade 1; 14.9% grade 2</td>
<td>HR=0.48 (95% CI, 0.294 to 0.784; p=0.003)</td>
<td>Median OS was 13.4 mo for assay “good” and 8.2 mo for assay “poor”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS: HR=0.785 (95% CI, 0.482 to 1.22; p=0.253)</td>
<td>Median PFS 4 mo for assay “good” and 3.2 mo for assay “poor”</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>N</td>
<td>Patient Population</td>
<td>Summary of Outcomes: OS for “Good” vs “Poor” Assay</td>
<td>Summary of Outcomes: PFS for “Good” vs “Poor” Assay</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------</td>
<td>----</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Kashtgarpour et al (2016)</td>
<td>Retrospective</td>
<td>49</td>
<td>Advanced-stage squamous and nonsquamous 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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmon et al (2009)</td>
<td>Retrospective</td>
<td>35</td>
<td>Stage IIIB or IV, recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab</td>
<td>Adjusted&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HR of death, 1.024 (95% CI, 1.009 to 1.040; p=0.003)</td>
</tr>
<tr>
<td>(erlotinib/bevacizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>generation set)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>Adjusted&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HR of death, 1.012 (95% CI, 1.003 to 1.021; p=0.012)</td>
</tr>
<tr>
<td>(ECOG 3503 validation set)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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 pemetinib or erlotinib. Histology: 79.2% adenocarcinoma; 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 0.016; p=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. Variant status: 42.3% with EGFR TKI–sensitive variant; 57.7% with EGFR WT 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 (81 patients in validation set): OS=20.0 mo for assay “mutant” and 28.0 mo for assay “wild” (p=NS)</td>
<td>Following EGFR-TKI treatment (81 patients in validation set): PFS=10.0 mo for assay “mutant” and 2.3 mo for assay “wild” (p&lt;0.001)</td>
</tr>
</tbody>
</table>

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

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></td>
<td>Median OS (95% CI, mo)</td>
<td>Median OS (95% CI, mo)</td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>VeriStrat &quot;good&quot;</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 &quot;poor&quot;</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>

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 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.

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 non-small-cell lung cancer (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 tyrosine kinase inhibitor (TKI) therapy and retrospective studies evaluating the prognostic ability of this test. Relevant outcomes are overall survival and disease-specific survival. Although a limited body of evidence exists for the analytic validity of proteomic testing to predict response to EGFR TKIs for NSCLC in general, at least 1 study has reported good test reproducibility for the most widely studied proteomic test, the VeriStrat assay. Evidence from retrospective studies has supported the clinical validity of proteomic testing in determining the prognosis of patients with advanced NSCLC who are treated with EGFR TKIs, but, due to heterogeneity in the treatment regimens used, it is difficult to determine specific populations for whom proteomic testing is prognostic.

Evidence from 1 prospective study found that VeriStrat discriminates between patients who are likely to respond to EGFR-TKI therapy. However, in that same study, even those patients who were predicted to respond to EGFR-TKI therapy did not have a significant survival benefit with EGFR-TKI therapy. If EGFR-TKI therapy were used as a standard of care in patients who are EGFR-unknown or -negative in the second- or third-line setting, proteomic testing could be used to select patients who are least likely to benefit, and those patients could be offered chemotherapy as an alternative. RCT evidence has suggested that erlotinib is not beneficial for EGFR-unknown or -negative patients in the second-line setting.
setting, and clinical guidelines do not support its use. The evidence is insufficient to
determine the effects of the technology on health outcomes.

Codes

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81538</td>
<td>Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival (new code 01/01/16)</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td></td>
<td>Investigational for all relevant diagnoses</td>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
<td>Investigational for all relevant diagnoses</td>
</tr>
<tr>
<td>ICD-10-CM (effective 10/1/15)</td>
<td></td>
<td>Investigational for all relevant diagnoses</td>
</tr>
<tr>
<td>C34.10-C34.92</td>
<td></td>
<td>Malignant neoplasm of lung code range</td>
</tr>
<tr>
<td>ICD-10-PCS (effective 10/10/1/15)</td>
<td></td>
<td>Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.</td>
</tr>
<tr>
<td>Type of Service Place of Service</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Limitation

As established in the policy.

References