I. 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. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference:
MP-2.270 Proteomics-Based Testing Related to Ovarian Cancer

II. PRODUCT VARIATIONS
This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO*  BlueJourney PPO*  FEP PPO**

*Refer to Novitas Solutions Local Coverage Determination (LCD) L35396 Biomarkers for Oncology.

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

Lung cancer is the leading cause of cancer death in the United States, with an estimated 221,200 new cases and 158,040 deaths due to the disease in 2015.\(^1\) 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 are tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) and crizotinib targeting the ALK gene rearrangement.

#### EGFR Mutations in NSCLC

The EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small molecule TKIs). These targeted therapies dampen signal transduction through pathways downstream to the EGFR, such as the RAS/RAF/MAPK cascade. RAS proteins are G-proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Mutations in 2 regions of the \(EGFR\) gene, including small deletions in exon 19 and a point mutation in exon 21 (L858R), appear to predict tumor response to TKIs such as erlotinib. The prevalence of \(EGFR\) mutations in NSCLC varies by population, with the highest prevalence in nonsmoking, Asian women, with adenocarcinoma, in whom \(EGFR\) mutations have been reported to be up to 30% to 50%. The reported prevalence of \(EGFR\) mutations in lung adenocarcinoma patients in the United States is approximately 15%.\(^3\)

#### ALK Mutations in NSCLC

In about 2% to 7% of NSCLC patients in the United States, tumors express a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 gene and the
anaplastic lymphoma kinase gene (EML4-ALK), which is created by an inversion on chromosome 2p. The EML4 fusion leads to ligand-independent activation of ALK, which encodes a receptor TK whose precise cellular function is not completely understood. EML4-ALK mutations 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 mutations.

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 Mutations in NSCLC

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

<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>
</table>
| KRAS | Encodes RAS proteins; mutations associated with constitutively activated protein | 20%-30% | • Adenocarcinomas  
• Heavy smokers |
| ROS1 | Encodes a receptor tyrosine kinase in the insulin receptor family | 0.9%-3.7% | • Adenocarcinoma  
• Never smokers |
| RET  | Proto-oncogene that encodes a receptor tyrosine kinase growth factor | 0.6%-2% | |
| MET  | Oncogene that encodes a receptor tyrosine kinase 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 activated | 1%-2% of NSCLC | • Adenocarcinomas  
• Nonsmoking women |

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

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 \textit{EGFR}-mutated tumors. Erlotinib and afatinib also have approval by FDA.

In 2016, osimertinib (Tagrisso; AstraZeneca), an irreversible selective EGFR inhibitor that targets \textit{T790M} mutation–positive NSCLC, received FDA approval for patients with \textit{T890M}–mutation-positive NSCLC who have progressed on an \textit{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 \textit{EGFR} mutation–positive patients treated with \textit{EGFR} TKIs in the first- and second-line settings and as maintenance therapy.\textsuperscript{5} Comparisons were chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings. Among \textit{EGFR} mutation–negative patients, PFS was improved with \textit{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 \textit{EGFR} mutation 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 who are being considered for first-line therapy with an \textit{EGFR} TKI (patients who have not previously received chemotherapy or an \textit{EGFR} TKI) should have their tumor tested for \textit{EGFR} mutations to determine whether an \textit{EGFR} TKI or chemotherapy is the appropriate first-line therapy.\textsuperscript{3} The primary role for TKIs in NSCLC is for \textit{EGFR} mutation–positive patients with advanced NSCLC. The use of TKIs in NSCLC in \textit{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 \textit{EGFR} mutation status, with fewer serious adverse events in erlotinib-treated patients.\textsuperscript{6} Karampeazis et al reported similar efficacy between erlotinib and standard chemotherapy (pemetrexed) for second-line therapy in patients unselected on the basis of \textit{EGFR} mutation status.\textsuperscript{7} In contrast, in the TAILOR trial, standard chemotherapy was associated with longer OS than erlotinib for second-line therapy in patients with wild-type \textit{EGFR}.\textsuperscript{8} Auliac et al compared sequential erlotinib plus docetaxel with docetaxel alone as second-line therapy among patients with advanced NSCLC and \textit{EGFR} wild-type or unknown status.\textsuperscript{9} 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 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 \textit{EGFR} mutation.\textsuperscript{10} There were no significant differences between groups in terms of PFS, objective response rate, or disease control rate; maintenance erlotinib in patients without \textit{EGFR} mutations is not considered favorable.
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. The benefits of cetuximab in NSCLC have been questioned by the National Comprehensive Cancer Network (NCCN). Panitumumab is not generally used in NSCLC.

PD-L1 Inhibitors

Some tumors, including some NSCLCs, express a PD-L1 ligand 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 ligand, block the cancer/T-cell interaction, and thus act as immune checkpoint inhibitors. Pembrolizumab and nivolumab, which inhibit the PD-1 receptor, and atezolizumab, which inhibits the PD-L1 ligand, are used in NSCLC which have PD-L1 expression on its cells.

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.

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, Boulder, CO), 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) mass spectrometry (MS) analysis of pretreatment serum to generate a “good” or “poor” assessment for response to TKIs. 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 MS, and alternative predictive algorithms, in the assessment of proteomic predictors of lung cancer risk.\textsuperscript{14}

**Regulatory Status**

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 Act (CLIA). The commercially available proteomic test, the VeriStrat test, 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. Food and Drug Administration has chosen not to require any regulatory review of this test.

**IV. RATIONALE**

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 epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in individuals with non-small-cell lung cancer (NSCLC) with wild-type or unknown EGFR mutation status. It has specifically been used to select patients who should not receive EGFR TKIs in the 2nd or 3rd -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 epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).\textsuperscript{13} This method forms the basis of the VeriStrat testing algorithm. The training set included 139 patients, and the validation set included a group of 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 conducted a study that used 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 used MALDI time of flight (TOF) MS protein profiles to generate predictive algorithm for survival in patients with NSCLC treated with gefitinib or erlotinib, but does 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 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. Eleven cohorts were identified, which were reported in 6 published studies, including the studies by Taguchi et al, Carbone et al, Kuiper et al, Akerley et al, Gautschi et al, and Stinchcombe et al, 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 2: Clinical Validity of Proteomic Testing in NSCLC for Disease Prognosis

<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>
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<td>Unadjusted</td>
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<tr>
<td>VeriStrat-specific studies</td>
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<tr>
<td>Taguchi et al (2007)13 – Italian B validation set</td>
<td>Retrospective; VeriStrat</td>
<td>67</td>
<td>Late-stage or recurrent NSCLC treated with single-agent gefitinib ECOG PS: 29.8% grade 0; 46.3% grade 1; 23.9% grade 2 Histology: 56.7% adeno; 22.4% squamous; 20.9% NOS</td>
<td>Unadjusted OS (assay “good” vs “poor”): HR of death, 0.50 (95% CI, 0.24 to 0.78; p=0.005)</td>
<td>Unadjusted Time to progression (assay “good” vs “poor”): HR=0.56 (95% CI, 0.28 to 0.89; p=0.02)</td>
</tr>
<tr>
<td>Taguchi et al (2007)13 – 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 ECOG PS: 30.2% grade 0; 43.9% grade 1; 26.9% grade 2 Histology: 64.6% adeno; 11.5% squamous; 1% LCC; 22.9% NOS</td>
<td>Unadjusted OS (assay “good” vs “poor”): HR of death, 0.75 (95% CI, 0.55 to 0.99)</td>
<td>Unadjusted Time to progression (assay “good” vs “poor”): HR=0.53 (95% CI, 0.33 to 0.85; p=0.007)</td>
</tr>
<tr>
<td>Amann et al20 (2010)</td>
<td>Retrospective; VeriStrat</td>
<td>88</td>
<td>ECOG 3503 trial patients: stage IIIb or IV or recurrent NSCLC treated with first-line erlotinib ECOG PS: 28.4% grade 0; 46.1% grade 1; 25.5% grade 2 Histology: 64.7% adeno; 10.8% squamous; 1% LCC; 16.7% NOS; 6.9% other</td>
<td>Unadjusted OS (assay “good” vs “poor”): HR of death, 0.36 (95% CI, 0.21 to 0.60; p=0.001)</td>
<td>Unadjusted Time to progression (assay “good” vs “poor”): HR=0.51 (95% CI, 0.28 to 0.90; p=0.02)</td>
</tr>
<tr>
<td>Carbone et al19 (2010)</td>
<td>Retrospective; VeriStrat</td>
<td>35</td>
<td>Stage IIIb or IV, recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab KPS: 7.5% KPS 70%; 47.5% KPS 80%; 45% KPS 90% Histology: 75% adeno; 22.5% NOS; 2.5% other</td>
<td>Unadjusted OS (assay “good” vs “poor”): HR of death, 0.26 (95% CI, 0.06 to 1.16; p=0.08)</td>
<td>PFS (assay “good” vs “poor”): HR=0.045 (36 wk vs 8 wk; 95% CI, 0.008 to 0.237)</td>
</tr>
<tr>
<td>Kuiper et al2(2012)</td>
<td>Retrospective; VeriStrat</td>
<td>50</td>
<td>Chemotherapy-naive patients with pathologically documented, inoperable, locally advanced, recurrent, or metastatic NSCLC, treated with erlotinib and sorafenib ECOG PS: 40% grade 0; 60% grade 1 Histology: 68% adeno; 32% other EGFR status: 62% WT; 14% mutated; 24% unknown</td>
<td>OS (assay “good” vs “poor”): HR for OS, 0.21 to 0.60; p=0.009</td>
<td>OS (assay “good” vs “poor”): HR=0.40 (95% CI, 0.17 to 0.94; p=0.035)</td>
</tr>
<tr>
<td>Akerley et al (2013)20</td>
<td>Retrospective; VeriStrat</td>
<td>42</td>
<td>Stage IIIb/IV or recurrent nonsquamous NSCLC, with no prior chemotherapy for metastatic disease, treated with erlotinib and bevacizumab ECOG PS: 26% grade 0; 74% grade 1 Histology: 48% adeno; 48% NOS; 4% other EGFR status: 84% WT; 10% mutated; 6% unknown</td>
<td>Median OS 71.4 for assay “good” and 19.9 wk for assay “poor” (p=0.0015)</td>
<td>Median OS 13.7 mo for “good” and 5.6 mo for “poor”</td>
</tr>
<tr>
<td>Gautschi et al (2013)21</td>
<td>Retrospective; VeriStrat</td>
<td>117</td>
<td>Pool analysis of patients from SAKK19/05 and NTRG2828 trials: untreated, advanced nonsquamous NSCLC, treated</td>
<td>OS (assay “good” vs “poor”): HR=0.48 (95% CI, 0.294 to 0.794; p=0.0027)</td>
<td>PFS (assay “good” vs “poor”): HR=0.78 (95% CI, 0.482 to 1.22; p=0.2532)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type and Assay</td>
<td>N</td>
<td>Patient Population</td>
<td>Summary of Outcomes: OS</td>
<td>Summary of Outcomes: PFS</td>
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<td></td>
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<td>with first-line therapy with erlotinib and bevacizumab</td>
<td>• Median OS was 13.4 mo for assay “good” and 6.2 mo for assay “poor”</td>
<td>• Median PFS 4 mo for assay “good” and 3.2 mo for assay “poor”</td>
</tr>
<tr>
<td>Salmon et al (2009)14 – erlotinib/bevacizumab</td>
<td>Retrospective; non-VeriStrat</td>
<td>35</td>
<td>Stage IIIB or IV, recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab generation set</td>
<td>Adjusted(^a) OS: HR of death, 1.024 (95% CI, 1.009 to 1.040; p=0.003)</td>
<td></td>
</tr>
<tr>
<td>Salmon et al (2009)(^a) 3503 (erlotinib-treated) validation set</td>
<td>Retrospective; non-VeriStrat</td>
<td>82</td>
<td>ECOG 3503 trial patients: stage IIIB or IV or recurrent NSCLC treated with first-line erlotinib</td>
<td>Adjusted(^d) OS: HR of death, 1.012 (95% CI, 1.003 to 1.021; p=0.012)</td>
<td></td>
</tr>
<tr>
<td>Wu et al (2013)(^b) validation set</td>
<td>Retrospective; non-VeriStrat</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 0.0158; p&lt;0.001).</td>
</tr>
<tr>
<td>Yang et al (2015)(^c) validation set</td>
<td>Retrospective; non-VeriStrat</td>
<td>123</td>
<td>Stage IIIB or IV NSCLC with a known EGFR mutation status Mutation status: 42.3% with EGFR TKI–sensitive mutation; 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 (n=81 patients in validation set): OS=29.0 mo for assay “mutant” and 28.0 mo for assay “wild” (p=NS)</td>
<td>Following EGFR TKI treatment (n=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>

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.
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. 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. 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>
<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>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; 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>Median OS (95% CI), mo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VeriStrat “good”</td>
<td>184</td>
<td>10.9 (8.4 to 15.1)</td>
<td>1.05 (0.77 to 1.46)</td>
</tr>
<tr>
<td>VeriStrat “poor”</td>
<td>79</td>
<td>6.4 (3.0 to 7.4)</td>
<td>1.72 (1.08 to 2.74)</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.

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 an increase in QALY by 0.05 year per patient.

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. 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. 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. 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 of 111 patients (88%) 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 patients (6%) 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

The proposed clinical utility of VeriStrat is for selecting patients who are unlikely to benefit from EGFR TKIs in the 2ndline 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 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. 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.

Section Summary: Clinical Utility

No direct evidence for a serum proteomic test for the selection of a NSCLC treatment strategy was identified. In the absence of 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 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 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. If EGFR TKI therapy were used as a standard of care in patients who are EGFR unknown or negative in the 2nd or 3rdline 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 suggests that erlotinib is not beneficial for EGFR unknown or negative patients in the 2ndline setting, and clinical guidelines do not support its use. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 academic medical center and 2 community health systems, one of which provided 4 responses, while this policy was under review in 2017. Input was uniform that erlotinib is not considered routine for individuals with non-small-cell lung cancer (NSCLC) who are $EGFR$ negative or $EGFR$ status unknown in the second-line setting. Reviewers had limited confidence that there is adequate evidence that the use of Veristrat to guide treatment selection will improve outcomes for individuals with NSCLC who are $EGFR$ negative or $EGFR$ status unknown in the second-line setting.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines for the management of non-small-cell lung cancer (NSCLC; v. 4.2017)¹ recommend routine testing for epidermal growth factor receptor (EGFR) mutations in patients with metastatic nonsquamous NSCLC (category 1 recommendation) and consideration for EGFR mutation testing in patients with metastatic squamous NSCLC who are never smokers or with small biopsy specimens or mixed histology (category 2A recommendation).
EGFR positive:

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

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

EGFR negative or unknown:

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

For patients with advanced nonsquamous NSCLC who are PD-L1, ROS1, and EGFR 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.

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 tyrosine kinase inhibitor (TKI) therapy. The opinion 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 made the following recommendations about EGFR-TKI therapy as second- or third-line treatment in patients without a sensitizing EGFR mutation.
For second-line treatment, for patients with nonsquamous NSCLC, “docetaxel, erlotinib, gefitinib, or pemetrexed” are recommended (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 is 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. Based on excellent quality evidence (category A), the guidelines recommended EGFR mutation testing in patients with lung adenocarcinoma regardless of clinical characteristics (eg, 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. Based on review of the literature, guideline authors reported improved response rates, PFS, and toxicity profiles with first-line erlotinib or gefitinib compared with firstline platinum-based therapy in patients with EGFR mutations, especially exon 19 deletion and L858R. ACCP recommended “testing patients with NSCLC for 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 that “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).”

**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>
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<tbody>
<tr>
<td>Ongoing</td>
<td>NCT02055144 VeriStrat as Predictor of Benefit of First Line Non-Small Cell Lung Cancer (NSCLC) Patients From Standard Chemotherapy</td>
<td>100</td>
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<td>Unpublished</td>
<td>NCT01652469 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>
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</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

V. DEFINITIONS

NA

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.
MEDICAL POLICY

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<th>POLICY TITLE</th>
<th>PROTEOMIC TESTING FOR TargetED THERAPY IN NON-SMALL-CELL LUNG CANCER</th>
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<td>POLICY NUMBER</td>
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Investigation: therefore not covered when used for Proteomic testing:

<table>
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<tr>
<th>CPT Codes®</th>
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<tr>
<td>81538</td>
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IX. REFERENCES

following platinum-based chemotherapy (IUNO study). Lung Cancer. Dec 2016;102:30-37. PMID 27987585


MEDICAL POLICY

<table>
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Other Sources


X. POLICY HISTORY

<table>
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<tr>
<th>MP 2.337</th>
<th>CAC 3/29/16 New policy adopting BCBSA. Proteomic testing for targeted therapy in non-small-cell lung cancer is investigational. Medicare variation added – coverage is provided for this service. Coding reviewed.</th>
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<tbody>
<tr>
<td>Admin Update 1/1/2017</td>
<td>Variation reformatting.</td>
</tr>
<tr>
<td>CAC 3/28/17</td>
<td>Consensus Review. No change to policy statements. References and rationale updated. Coding reviewed.</td>
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Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.