Policy Statement

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.

Policy Guidelines

The following CPT code is specific for the VeriStrat 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

For proteomic testing other than VeriStrat, there are no specific CPT codes. If the test includes multiple assays, uses an algorithmic analysis, and is reported as a numeric score or a probability, the unlisted multianalyte assay with algorithmic analysis code 81599 would be reported. Otherwise, the unlisted molecular pathology code 81479 would be used.

Description

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).

Related Policies

- Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer
- Multimarker Serum Testing Related to Ovarian Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 Amendments (CLIA). The commercially available proteomic test (VeriStrat®; Biodesix) is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.
Rationale

Background
Non-Small-Cell Lung Cancer
Lung cancer is the leading cause of cancer death in the United States, with an estimated 221,200 new cases and 158,040 deaths due to the disease in 2015.\(^1\) Non-small-cell lung cancer (NSCLC), which includes nonsquamous carcinoma (adenocarcinoma, large cell carcinoma, other cell types) and squamous cell carcinoma, causes about 85% of lung cancer cases. Treatment approaches generally include surgery, radiotherapy, and chemotherapy, either alone or in combination, depending on the disease stage and tumor characteristics. However, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication, and up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have brief responses, with a median time to progression of 3 to 5 months.\(^2\) Second-line chemotherapy after platinum-based chemotherapy is associated with small improvements in time to progression. Genetic abnormalities in NSCLC and the development of therapies targeted to those abnormalities have prompted interest in tests to predict response to targeted therapies.

Genetic Alterations
Several common genetic alterations in NSCLC have been targets for drug therapy, the most well-established of which are tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) and crizotinib targeting the ALK gene rearrangement.

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

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

Anaplastic Lymphoma Kinase Variants
In 2% to 7% of NSCLC patients in the United States, tumors express a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 gene and the anaplastic lymphoma kinase gene (EML4-ALK), which is created by an inversion on chromosome 2p.\(^4\) The EML4 fusion leads to ligand-independent activation of ALK, which encodes a receptor TK whose precise cellular function is not completely understood. EML4-ALK variants are more common in never-smokers or light smokers, tend to be associated with younger age of NSCLC onset, and typically do not occur in conjunction with EGFR variants.

Testing for the EML4-ALK fusion gene in patients with adenocarcinoma-type NSCLC is used to predict response to the small molecule TKI crizotinib.
Other Genetic Variants
Other genetic variants, identified in subsets of patients with NSCLC, are summarized in Table 1. The role of testing for these variants to help select targeted therapies for NSCLC is less well-established than for EGFR variants.

Table 1: Non-EGFR Variants in NSCLC

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

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

Targeted Treatment Options

Epidermal Growth Factor Receptor-Selective Small Molecule Tyrosine Kinase Inhibitors

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, the 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 the FDA.

In 2016, osimertinib (Tagrisso; AstraZeneca), an irreversible selective EGFR inhibitor that targets T790M variant-positive NSCLC, received the FDA approval for patients with T890M-variant-positive NSCLC who have progressed on an EGFR TKI.

A 2013 meta-analysis of 23 trials assessing use of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC reported improved progression-free survival (PFS) in EGFR variant-positive patients treated with EGFR TKIs in the first- and second-line settings and as maintenance therapy. Comparators were chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings. Among EGFR variant-negative patients, PFS was improved with EGFR TKIs compared with placebo for maintenance therapy but not in the first- and second-line settings. Overall survival (OS) did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcome. Reviewers concluded that EGFR variant testing is indicated to guide treatment selection in NSCLC patients.

On the basis of the results of 5 phase 3 randomized controlled trials, the American Society of Clinical Oncology recommended that patients with NSCLC being considered for first-line...
therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for EGFR variants to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.3

The primary target population for TKIs in NSCLC is for EGFR variant-positive patients with advanced NSCLC. The use of TKIs in NSCLC in EGFR variant-negative patients is controversial. The TITAN trial (2012) demonstrated no significant differences in OS between erlotinib and chemotherapy as second-line treatment for patients unselected on the basis of EGFR variant status, with fewer serious adverse events in erlotinib-treated patients.6 Karampeazis et al (2013) reported similar efficacy between erlotinib and standard chemotherapy (pemetrexed) for second-line therapy in patients unselected on the basis of EGFR variant status.7 By contrast, in the TAILOR trial (2013), standard chemotherapy was associated with longer OS than erlotinib for second-line therapy in patients with wild-type EGFR.8 Auliac et al (2014) compared sequential erlotinib plus docetaxel with docetaxel alone as second-line therapy among patients with advanced NSCLC and EGFR wild-type or unknown status.8 Based on a Simon’s optimal 2-stage design, the erlotinib plus docetaxel strategy was rejected, with 18 of 73 patients in the erlotinib plus docetaxel arm achieving PFS at 15 weeks compared with 17 of 74 patients in the docetaxel arm.

In 2016, Cicenas et al reported results of the IUNO RCT, which compared maintenance therapy with erlotinib followed by second line chemotherapy if progression occurred to placebo followed by erlotinib if progression occurred in 643 patients with advanced NSCLC with no known EGFR variant.10 Because there were no significant differences between groups in terms of PFS, objective response rate, or disease control rate, maintenance therapy with erlotinib in patients without EGFR variants was not considered efficacious.

Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies
For the treatment of KRAS-mutated NSCLC, anti-EGFR monoclonal antibodies have been investigated as possible treatment options. Available anti-EGFR monoclonal antibodies include cetuximab and panitumumab. The benefits of cetuximab in NSCLC have been questioned by the National Comprehensive Cancer Network.1 Panitumumab is not generally used in NSCLC.

Programmed Death Ligand 1 Inhibitors
Some tumors, including some NSCLCs, express a programmed death ligand 1 (PD-L1) on the cell surfaces to interact with host T-cells and evade the immune system. Several humanized monoclonal antibodies have been developed to act as immune checkpoint inhibitors by interfering with this interaction. Pembrolizumab and nivolumab, which inhibit the programmed death 1 receptor, and atezolizumab, which inhibits the PD-L1, are used in NSCLC that have PD-L1 expression on its cells.

Other Targeted Therapies
Crizotinib is a novel MET, ROS1, and ALK TKI, and associated with improved progression-free survival in patients with advanced NSCLC who are ALK gene rearrangement-positive.11 Crizotinib is considered first-line therapy for advanced ALK-positive lung adenocarcinoma.1 Two other small molecule TKIs, designed to selectively bind to and inhibit ALK activation, have the FDA approval: ceritinib and alectinib.

Proposed targeted therapies for other genetic alterations in NSCLC are trastuzumab for HER2 variants, crizotinib for MET amplification and ROS1 rearrangement, vemurafenib and dabrafenib for BRAF variants, and cabozantinib for RET rearrangements.

Proteomics Testing in Selecting Targeted Treatment for Non-Small-Cell Lung Cancer
The term proteome refers to the entire complement of proteins produced by an organism or cellular system, which may vary over time and in response to selected stressors, and proteomics refers to the large-scale comprehensive study of a specific proteome.12 A cancer cell’s proteome is related to its genome and to genomic alterations, but may not be static over time.
The proteome may be measured with mass spectrometry (MS) or protein microarray. For cancer, proteomic signatures in the tumor or in bodily fluids (i.e., pleural fluid or blood) other than the tumor have been investigated as a biomarker for cancer activity.

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

Although the VeriStrat MALDI MS-based predictive algorithm has the largest body of literature associated with it, other investigators have used alternative MS methods, such as surface-enhanced laser desorption ionization/time-of-flight MS, and alternative predictive algorithms, to assess proteomic predictors of lung cancer risk.

Literature Review

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 not describe analytic validity parameters.16

**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 Non-Small-Cell Lung Cancer 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.17 Eleven cohorts were identified, which were reported in 6 published studies, including those by Taguchi et al (2007),13 Carbone et al (2010),18 Kuiper et al (2012),19 Akerley et al (2013),20 Gautschi et al (2013),21 and Stinchcombe et al (2013),22 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”</th>
<th>Summary of Outcomes: PFS for “Good” vs “Poor”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taguchi et al (2007)13 (Italian B validation set)</td>
<td>Retrospective</td>
<td>67</td>
<td>Late-stage or recurrent NSCLC treated with single-agent gefitinib</td>
<td>Unadjusted HR of death, 0.50 (95% CI, 0.24 to 0.78; p=0.005)</td>
<td>Unadjusted TTT: HR=0.56 (95% CI, 0.28 to 0.89; p=0.02)</td>
</tr>
<tr>
<td>Taguchi et al (2007)13 (ECOG 3503 validation set)</td>
<td>Retrospective</td>
<td>96</td>
<td>ECOG 3503 trial patients: stage IIIIB or IV or recurrent NSCLC treated with first-line erlotinib</td>
<td>Unadjusted HR of death, 0.4 (95% CI, 0.24 to 0.70; p&lt;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 al23 (2010)</td>
<td>Retrospective</td>
<td>88</td>
<td>ECOG 3503 trial patients: stage IIIIB or IV or recurrent</td>
<td>Unadjusted</td>
<td>Unadjusted</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>Carbone et al (2010)</td>
<td>Retrospective</td>
<td>35</td>
<td>Stage IIIb or IV, recurrent, non-squamous NSCLC treated with erlotinib and bevacizumab</td>
<td>HR of death, 0.36 (95% CI, 0.21 to 0.60; p=0.001)</td>
<td>TTT: HR=0.51 (95% CI, 0.28 to 0.90; p=0.02)</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</td>
<td>HR for OS, 0.30 (95% CI, 0.12 to 0.74; p=0.009)</td>
<td>PFS: HR=0.40 (95% CI, 0.17 to 0.94; p=0.035)</td>
</tr>
<tr>
<td>Akerley et al (2013)</td>
<td>Retrospective</td>
<td>42</td>
<td>Stage IIIb or IV or recurrent non-squamous NSCLC, with no prior chemotherapy for metastatic disease, treated with erlotinib and bevacizumab</td>
<td>Median OS 71.4 for assay “good” and 19.9 wk for assay “poor” (p=0.002)</td>
<td>Median PFS 18.9 wk for “good” and 6.3 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 SAKK19/05 and NTR528 trials: untreated, advanced non-squamous NSCLC, treated with first-line therapy with erlotinib and bevacizumab</td>
<td>HR=0.48 (95% CI, 0.294 to 0.784; p=0.003)</td>
<td>PFS: HR=0.768 (95% CI, 0.482 to 1.22; p=0.253)</td>
</tr>
<tr>
<td>Keshtgarpour et al (2016)</td>
<td>Retrospective</td>
<td>49</td>
<td>Advanced-stage squamous and non-squamous 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>
</tbody>
</table>
### Study Type

<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>Non-VeriStrat proteomic testing algorithms</td>
<td>Retrospective 35</td>
<td>Stage III or IV, recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab</td>
<td>Adjusted&lt;sup&gt;c&lt;/sup&gt; HR of death, 1.024 (95% CI, 1.009 to 1.040; p=0.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-VeriStrat proteomic testing algorithms</td>
<td>Retrospective 82</td>
<td>ECOG 3503 trial patients: stage III or IV or recurrent NSCLC treated with first-line erlotinib</td>
<td>Adjusted&lt;sup&gt;d&lt;/sup&gt; HR of death, 1.012 (95% CI, 1.003 to 1.021; p=0.012)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-VeriStrat proteomic testing algorithms</td>
<td>Retrospective 44</td>
<td>Stage III or IV NSCLC failed or intolerant to chemotherapy, treated with gefitinib 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&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Non-VeriStrat proteomic testing algorithms</td>
<td>Retrospective 123</td>
<td>Stage III or IV NSCLC with a known EGFR variant status</td>
<td>Following EGFR-TKI treatment (81 patients in validation set): OS=29.0 mo for assay “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>
<td></td>
</tr>
</tbody>
</table>

Adeno: adenocarcinoma; CI: confidence interval; ECOG: European Cooperative Oncology Group; EGFR: epidermal growth factor receptor; HR: hazard ratio; KPS: Karnofsky Performance Status; LCC: large cell carcinoma; MALDI: matrix-assisted laser desorption ionization; MS: mass spectrometry; NOS: not otherwise specified; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free survival; PS: performance status; TKI: tyrosine kinase inhibitor; TTT: time to progression; WT: wild-type.

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

### Proteomic Testing in Non-Small-Cell Lung Cancer to Predict Response to Therapy

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 Non-Small-Cell Lung Cancer 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)26

<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)26

<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 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.22 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.23 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% 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
Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer

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, 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 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 from Blue Cross Blue Shield Association, input was received from 1 academic medical center and 2 community health systems, one of which provided 4 responses, 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 guidelines on the management of non-small-cell lung cancer (NSCLC; v.4.2017) recommend routine testing for epidermal growth factor receptor (EGFR) variants in patients with metastatic nonsquamous NSCLC (category 1 recommendation) and consideration for EGFR variant testing in patients with metastatic squamous NSCLC who were never smokers or with small biopsy specimens or mixed histology (category 2A recommendation).

**Epidermal Growth Factor Receptor-Positive Populations**

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

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

**Epidermal Growth Factor Receptor-Negative or -Unknown Populations**

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

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

- **Systemic immune checkpoint inhibitors (preferred):**
  - Nivolumab (category 1 recommendation); OR
  - Pembrolizumab (category 1 recommendation); OR
  - Atezolizumab (category 1 recommendation); OR
- **Other systemic therapy:**
  - Docetaxel; OR
  - Pemetrexed; OR
American Society of Clinical Oncology
In 2011, the American Society of Clinical Oncology (ASCO) issued a provisional clinical opinion on EGFR variant testing for patients with advanced NSCLC considering first-line EGFR-TKI therapy. The opinion concluded that such patients who have not previously received chemotherapy or an EGFR TKI should undergo EGFR variant 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 variant:

- 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 and 2 other medical associations published joint 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 variant testing in patients with lung adenocarcinoma regardless of clinical characteristics (e.g., 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 a review of the literature, ACCP reported improved response rates, progression-free survival, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with EGFR variants, 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 test in June 2013, which serves as a national coverage determination because the test is only offered at a single lab within the local carrier’s coverage region. The coverage determination document noted: “The VeriStrat® assay (NOC 84999) is a mass spectrophotometric, serum-based predictive proteomics assay for NSCLC patients, where ‘first line’ EGFR mutation testing is either wild-type or not able to be tested (e.g., if tissue might not be available).”

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>NCTNo.</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>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### References


### Documentation for Clinical Review

- No records required

### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td></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</td>
</tr>
<tr>
<td></td>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>All Diagnoses</td>
<td></td>
</tr>
</tbody>
</table>

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/30/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
## Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.