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

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

Background/Overview

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

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

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

such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

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

ALK Variants

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

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

Other Genetic Variants

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

Table 1: Non-*EGFR* Variants in NSCLC

Gene	Gene Function	Estimated Variants Prevalence in NSCLC	Patient and Tumor Characteristics
KRAS	Encodes RAS proteins; mutations associated with constitutively activated protein	20%-30%	• Adenocarcinomas • Heavy smokers
ROS1	Encodes a receptor TK in the insulin receptor family	0.9%-3.7%	• Adenocarcinoma • Never smokers
RET	Proto-oncogene that encodes a receptor TK growth factor	0.6%-2%	
MET	Oncogene that encodes a receptor TK that is activated in response to binding of hepatocyte growth factor	2-4% of previously untreated NSCLC; 5%-20% of patients with acquired resistance to EGFR TKIs	Patients with acquired resistance to EGFR TKIs
BRAF	Serine-threonine kinase downstream from	1%-3% of adenocarcinomas	Heavy smokers

	RAS in RAS-RAF-ERK-MAPK pathway		
HER	HER (EGFR) family of TK receptors; dimerizes with EGFR family members when activated	1%-2% of NSCLC	• Adenocarcinomas • Nonsmoking women
PIK3CA	Intracellular signaling pathway	≈4% of NSCLC	

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

Targeted Treatment Options

EGFR-Selective Small Molecule TKIs

Three orally administered EGFR-selective small molecule TKIs have been identified for use in treating NSCLC: gefitinib (Iressa®‡; AstraZeneca), erlotinib (Tarceva®‡; OSI Pharmaceuticals), and afatinib (Gilotrif™‡; Boehringer Ingelheim). Although the Food and Drug Administration (FDA) originally approved gefitinib in 2004, a phase 3 trial suggested gefitinib was not associated with a survival benefit. In May 2005, FDA revised gefitinib labeling, further limiting its use to patients who had previously benefitted or were currently benefiting from the drug; no new patients were to be given gefitinib. However, in July 2015, FDA approved gefitinib as first-line treatment for patients with metastatic NSCLC for patients with *EGFR*-mutated tumors. Erlotinib and afatinib also have approval by FDA.

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

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

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

The primary target population for TKIs in NSCLC is for *EGFR* variant–positive patients with advanced NSCLC. The use of TKIs in NSCLC in *EGFR* variant–negative patients is controversial. The TITAN trial (2012) demonstrated no significant differences in OS between erlotinib and chemotherapy as second-line

treatment for patients unselected on the basis of *EGFR* variant status, with fewer serious adverse events in erlotinib-treated patients. Karampeazis et al (2013) reported similar efficacy between erlotinib and standard chemotherapy (pemetrexed) for second-line therapy in patients unselected on the basis of *EGFR* variant status. 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*. Auliac et al (2014) compared sequential erlotinib plus docetaxel with docetaxel alone as second-line therapy among patients with advanced NSCLC and *EGFR* wild-type or unknown status. Based on a Simon's optimal 2-stage design, the erlotinib plus docetaxel strategy was rejected, with 18 of 73 patients in the erlotinib plus docetaxel arm achieving PFS at 15 weeks compared with 17 of 74 patients in the docetaxel arm.

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

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

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

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

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

Proteomics Testing in Selecting Targeted Treatment for NSCLC
The term *proteome* refers to the entire complement of proteins produced by an organism or cellular system, which may vary over time and in response to selected stressors, and *proteomics* refers to the large-scale comprehensive study of a specific proteome. A cancer cell's proteome is related to its genome and to genomic alterations, but may not be static over time. The proteome may be measured with mass spectrometry (MS) 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) has been developed and proposed to predict response to TKIs. The test relies on a predictive algorithm based on matrix-assisted laser desorption ionization (MALDI) MS analysis of pretreatment serum to generate a "good" or "poor" assessment for response to TKIs. VeriStrat has been proposed as a test to predict response to erlotinib in patients with NSCLC after failure of treatment with first-line therapy. Proposed uses have been in addition to *EGFR* testing, or in patients who do not have tumor samples available for *EGFR* testing.

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

FDA or Other Governmental Regulatory Approval

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

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

Rationale/Source

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) analytic validity (including test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive and negative predictive values) in relevant populations of patients; and (3) clinical utility (ie, demonstration that

the diagnostic information can be used to improve patient outcomes). The following is a summary of the key literature to date.

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Clinical Context and Test Purpose

The purpose of proteomic testing in individuals with NSCLC who are *EGFR*–negative or *EGFR*-status unknown NSCLC with disease progression after first-line treatment is to predict response to EGFR TKIs. Testing could impact the decision point of second-line treatment (ie, whether patients should receive *EGFR* treatment or chemotherapy). That is, those with VeriStrat "poor" findings might be less likely to respond to EGFR-TKIs, and thus chemotherapy would be a better choice.

The question addressed in this evidence review is: Does proteomic testing in patients with NSCLC who are *EGFR*-negative or *EGFR*-status unknown NSCLC with disease progression after first-line treatment improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with *EGFR*-negative or *EGFR*-status unknown NSCLC with disease progression after first-line treatment.

Intervention

The intervention of interest is management with a serum proteomic test to select second-line therapy.

Comparator

The comparator of interest is standard medical management.

Outcomes

The outcomes of interest are OS and PFS.

Timing

The timing of testing is after failing to respond to first-line therapy.

Setting

The test is available commercially though a single laboratory.

Analytic Validity

In 2007, Taguchi et al described the development and testing of a predictive algorithm based on MALDI MS analysis of serum to identify patients with NSCLC who are likely to benefit from treatment with an EGFR-TKI. While not a study specifically on analytic validity, the MALDI MS 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 206 available samples were labeled as “good,” “poor,” or “undefined”, and the overall concordance from such samples 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 using 139 common peaks for all samples, and for samples with analysis replicated on 3 days. The mean coefficient of variation was low (<5%) for all 3 days and for the overall sample, suggesting that their spectrometry was reproducible.

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

Clinical Validity
Proteomic Testing in NSCLC for Disease Prognosis
The largest body of evidence on the clinical validity of proteomic testing for NSCLC relates to its ability to predict disease outcomes. Several studies have evaluated the ability of MALDI MS with a predictive algorithm (usually specifically referred to as the VeriStrat test) as a *prognostic* test, generally to discriminate between good and poor survival outcomes in patients treated with EGFR-TKIs. Results of these studies are summarized in Table 2.

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

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/time of flight mass spectrometry (SELDI/TOF-MS) technology in combination with a predictive algorithm to discriminate between malignant and benign disease and between good and poor outcomes.[13] Using data from a population of 87 patients with stage 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).

Table 2. Clinical Validity Results of Proteomic Testing in NSCLC for Disease Prognosis

Study	Study Type	N	Patient Population	Summary of Outcomes: OS for "Good" vs "Poor" Assay	Summary of Outcomes: PFS for "Good" vs "Poor" Assay
VeriStrat-specific studies					
Taguchi et al (2007)[12] (Italian B validation set)	Retrospective	67	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	**Unadjusted** HR of death, 0.50 (95% CI, 0.24 to 0.78; p=0.005) **Adjusted**[a] HR of death, 0.75 (95% CI, 0.55 to 0.99)	**Unadjusted** TTT: HR=0.56 (95% CI, 0.28 to 0.89; p=0.02)
Taguchi et al (2007)[12] (ECOG 3503 validation set)	Retrospective	96	ECOG 3503 trial patients: stage IIIB or IV or recurrent NSCLC treated with first-line erlotinib **ECOG PS:** 30.2% grade 0; 43.8% grade 1; 26.0% grade 2 **Histology:** 64.6% adeno; 11.5% squamous; 1% LCC; 22.9% NOS	**Unadjusted** HR of death, 0.4 (95% CI, 0.24 to 0.70; p<0.001) **Adjusted**[b] HR of death, 0.53 (95% CI, 0.30 to 0.94; p=0.03)	**Unadjusted** TTT : HR=0.53 (95% CI, 0.33 to 0.85; p=0.007)
Amann et al (2010)[21]	Retrospective	88	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	**Unadjusted** HR of death, 0.36 (95% CI, 0.21 to 0.60; p=0.001) **Adjusted (for *EGFR* status)** HR of death, 0.26 (95% CI, 0.06 to 1.16; p=0.08)	**Unadjusted** TTT : HR=0.51 (95% CI, 0.28 to 0.90; p=0.02)
Carbone et al (2010)[15]	Retrospective	35	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	HR of death, 0.14 (61 wk vs 41 wk; 95% CI, 0.03 to 0.58)	PFS: HR=0.045 (36 wk vs 8 wk; 95% CI, 0.008 to 0.237)
Kuiper et al (2012)[17]	Retrospective	50	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	• HR for OS, 0.30 (95% CI, 0.12 to 0.74; p=0.009) • Median OS 13.7 mo for "good" and 5.6 mo for "poor"	• PFS: HR=0.40 (95% CI, 0.17 to 0.94; p=0.035) • Median PFS 5.5 mo for "good" and 2.7 mo for "poor"
Akerley et al (2013)[18]	Retrospective	42	Stage IIIB or 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	Median OS 71.4 for assay "good" and 19.9 wk for assay "poor" (p=0.002)	Median PFS 18.9 wk for "good" and 6.3 wk for "poor" (p=0.004)
Gautschi et al (2013)[19]	Retrospective	117	Pooled analysis of patients from SAKK19/05 and NTR528 trials: untreated, advanced nonsquamous NSCLC, treated with first-line therapy with erlotinib and bevacizumab **ECOG PS:** 52.9% grade 0; 42.5% grade 1; 4.6% grade 2 **Histology:** 89.7% adeno; 10.2% other	• HR=0.48 (95% CI, 0.294 to 0.784; p=0.003) • Median OS was 13.4 mo for assay "good" and 6.2 mo for assay "poor"	• PFS: HR=0.768 (95% CI, 0.482 to 1.22; p=0.253) • Median PFS 4 mo for assay "good" and 3.2 mo for assay "poor"

Keshtgarpour et al (2016)[22]	**Retrospective**	**49**	**Advanced-stage squamous and nonsquamous NSCLC seen at a single clinic. Baseline histology and PS not reported.**	**HR=0.97 (95% CI, 0.48 to 1.97; p=0.94)**	
Grossi et al (2017)[23]	Prospective	76	Stage IIIB NSCLC with supraclavicular lymph node metastases, or stage IV or recurrent NSCLC, chemotherapy-naive. **ECOG PS:** 26% grade 0; 71% grade 1, 3% grade 2	HR=0.26 (95% CI, 0.15 to 0.47; p<0.001)	0.36 (95% CI, 0.22 to 0.61; p<0.001)
Non-VeriStrat proteomic testing algorithms					
Salmon et al (2009)[14] (erlotinib/ bevacizumab generation set)	Retrospective	35	Stage IIIB or IV, recurrent, nonsquamous NSCLC treated with erlotinib and bevacizumab	**Adjusted**[c] HR of death, 1.024 (95% CI, 1.009 to 1.040; p=0.003)	
Salmon et al (2009)[14] (ECOG 3503 validation set)	Retrospective	82	ECOG 3503 trial patients: stage IIIB or IV or recurrent NSCLC treated with first-line erlotinib	**Adjusted**[d] HR of death, 1.012 (95% CI, 1.003 to 1.021; p=0.012)	
Wu et al (2013)[24] (validation set)	Retrospective	44	Stage IIIB or IV NSCLC failed or intolerant to chemotherapy, treated with gefitinib or erlotinib. **Histology:** 79.2% adeno; 20.8% squamous	OS (predicted good vs predicted poor): HR=0.357 (95% CI, 0.186 to 0.688; p=0.002)	PFS (predicted good vs predicted poor): HR=0.06 (95% CI, 0.022 to 0.016; p<0.001).
Yang et al (2015)[25] (validation set)	Retrospective	123	Stage IIIB or IV NSCLC with a known *EGFR* variant status **Variant status:** 42.3% with EGFR-TKI–sensitive variant; 57.7% with *EGFR* WT **Previous EGFR treatment:** 67.5% (30.9% as first-line, 26.8% as second-line, 9.8% as third-line or greater)	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*)	Following EGFR-TKI treatment (81 patients in validation set): PFS=10.0 mo for assay "mutant" and 2.3 mo for assay "wild" (p<0.001)

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.
[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.

Proteomic Testing in NSCLC to Predict Response to Therapy

Based on the association between VeriStrat status and outcomes in patients treated with EGFR-TKIs, it was postulated that VeriStrat testing may predict response to EGFR-TKIs.

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

Outcome	VeriStrat "Good"	VeriStrat "Poor"	VeriStrat "Good" vs "Poor"	p
	Median (95% CI), mo	Median (95% CI), mo	Hazard Ratio (95% CI)	
Gregorc et al (2014)				
OS	11.0 (9.3 to 12.6)	3.7 (2.9 to 5.2)	2. 0 (1.88 to 3.31)	<0.001

PFS	3.4 (2.4 to 4.6)	2.0 (1.6 to 2.4)	1.75 (1.34 to 2.29)	<0.001
Peters et al (2017)				
OS	8.2 (6.7 to 10.6)	5.2 (3.1 to 7.1)	0.49 (0.28 to 0.86)	*NS*
PFS	NR	NR	0.73 (0.44 to 1.22)	*NS*

CI: confidence interval; NR: not reported; 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, the 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. Moreover, 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 RCTs

Classification	N	Chemotherapy	Erlotinib	Hazard Ratio	p
		Median OS (95% CI), mo	Median OS (95% CI), mo	HR (95% CI)	
Gregorc et al (2014)					
VeriStrat "good"	184	10.9 (8.4 to 15.1)	11.0 (9.2 to 12.9)	1.05 (0.77 to 1.46)	0.714
VeriStrat "poor"	79	6.4 (3.0 to 7.4)	3.0 (2.0 to 3.8)	1.72 (1.08 to 2.74)	0.022
Peters et al (2017)					
VeriStrat "good"	58	8.4	7.8	NR	0.88
VeriStrat "poor"	22	5.2	4.4		0.68

CI: confidence interval; HR: hazard ratio; NR: not reported; OS: overall survival.

The authors of the PROSE trial 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 quality of life-adjusted years (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 quality of life adjusted years by 0.05 year per patient.

Another RCT evaluating the VeriStrat test as a predictor of therapy response (the EMPHASIS trial) was published by Peters et al (2017). The study compared second-line treatment with erlotinib or chemotherapy with docetaxel in patients with stage IIIB or IV squamous cell NSCLC who failed first-line platinum-based doublet chemotherapy. Group assignment was stratified by VeriStrat status ("good" vs "poor") and ECOG performance status (0-1 vs 2). Recruitment for the trial ended early due to low enrollment and the release of results from other trials (eg, PROSE). The investigators performed an analysis of the findings from EMPHASIS and an exploratory analysis combining results with those from the squamous cell NSCLC cohort in the PROSE trial. Eighty patients were randomized, of whom 58 (72.5%) were categorized as VeriStrat "good". The primary end point was PFS and was analyzed on an intention-to-treat basis. After a median follow-up of 20.5 months, 73 patients had experienced disease progression; median PFS was 2.7 months. Median PFS was 1.6 months in the erlotinib group and 3.0 months in the docetaxel group; the difference between groups was not statistically significant (p=0.37). PFS did not differ significantly by VeriStrat status (see Table 3), and there was no significant interaction between treatment and VeriStrat status (p=0.80).

A secondary outcome, OS was 7.1 months for both the erlotinib and the docetaxel groups (p=0.91). Moreover, OS did not differ by VeriStrat status (see Table 4). Among patients classified as VeriStrat "good", median OS was 8.4 months in the erlotinib group and 7.8 months in the docetaxel group (p=0.88). Among patients classified as VeriStrat "poor", median OS was 5.2 months in the erlotinib group and 4.4 months in the docetaxel group (p=0.68). However, patients classified as VeriStrat "good" had a longer OS than those classified as VeriStrat "poor". The VeriStrat "good" group had a median OS of 8.2 months compared with 5.2 months in the VeriStrat "poor" group (p=0.012).

In the exploratory analysis combining findings from EMPHASIS with those of the squamous cell cohort in PROSE (n=127), there was no significant difference in OS between the treatment arms (median OS, 7 months with erlotinib vs 7.8 months with chemotherapy; p=0.13). Further, there were no significant differences for the VeriStrat "good" group receiving erlotinib vs chemotherapy (p=0.52), or for the VeriStrat "poor" group receiving erlotinib vs chemotherapy (p=0.097). In the combined population, OS was higher overall in the VeriStrat "good" group (median, 9 months) than in the VeriStrat "poor" group (median, 4.6 months; p<0.001).

Several retrospective analyses of data from RCTs evaluating the efficacy of TKIs have examined VeriStrat as a prognostic and/or predictive test. 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 vs 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 variant 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 vs 6.6 months for those on placebo (HR=0.63; 95% CI, 0.47 to 0.85; p=0.002), while in VeriStrat "poor" patients, the median survival for erlotinib was 3.98 months and 3.09 months for placebo (HR=0.77; 95% CI, 0.55 to 1.06; p=0.11). For 252 erlotinib-treated patients with data available to evaluate for objective response, VeriStrat "good" patients (n=157 [62%]) had a significantly higher response rate (11.5%) than VeriStrat "poor" patients (1.1%; p=0.002). In a Cox multivariable regression model to predict OS, the interaction term between VeriStrat status and treatment type was not statistically significant, indicating that both "good" and "poor" cohorts derived similar survival benefit from erlotinib. The authors concluded that VeriStrat status predicted response to erlotinib but did not predict differential benefit from erlotinib for OS or PFS.

In 2013, Stinchcombe et al retrospectively analyzed the role of VeriStrat in predicting treatment outcomes in patients enrolled in a multicenter RCT comparing gemcitabine, erlotinib, or a combination as first-line therapy for NSCLC. Enrolled patients were 70 years and older with a histologic or cellular diagnosis of NSCLC, and no requirement for *EGFR* status. In the overall trial results, neither erlotinib nor the combination therapy demonstrated efficacy.

Of 146 patients enrolled in the trial, 98 had available plasma samples for analysis. In the gemcitabine arm, VeriStrat "good" patients (n=20) had similar PFS and OS rates to VeriStrat "poor" patients. In the erlotinib arm, median PFS was 89 days in 26 VeriStrat "good" patients compared with 22 days in 12 VeriStrat "poor" patients (HR=0.33; 95% CI, 0.16 to 0.70; p=0.002). Similarly, in the erlotinib arm, median OS was 255 days in VeriStrat "good" patients compared with 51 days in VeriStrat "poor" patients (HR=0.40; 95% CI, 0.19 to 0.85; p=0.014). PFS and OS rates between erlotinib-only and gemcitabine-only groups did not differ significantly for either VeriStrat "good" or "poor" patients, although the point estimate for the hazard ratio favored erlotinib in the "good" group and favored gemcitabine in the "poor" group. In a multivariable model, the treatment arm (erlotinib vs gemcitabine) and the VeriStrat-treatment arm interaction term was significantly associated with PFS (adjusted HR=0.20; 95% CI, 0.09 to 0.45; p<0.001). In a similar model to predict OS, the VeriStrat-treatment arm interaction term was significantly associated with OS (adjusted HR=0.49; 95% CI, 0.27 to 0.88; p=0.017), although the treatment arm was not associated with OS.

In 2017, Gadgeel et al conducted a retrospective analysis of data from the LUX-Lung 8 trial, which compared second-line treatment with 1 of 2 TKIs: erlotinib or afatinib in patients with advanced stage IIIB or IV squamous NSCLC. *EGFR* variant status was not considered in study eligibility. Blood samples for VeriStrat analysis were available for 691 (87%) of 795 randomized patients; of these, 12 were indeterminate results and four could not be analyzed. The primary objective of the analysis was to evaluate whether VeriStrat status pretreatment was associated with OS and in the afatinib vs erlotinib groups. In the cohort with VeriStrat results (n=675), OR was significantly higher in the afatinib group (median, 7.8 months) than in the erlotinib group (median, 6.9 months; p=0.03). When stratified by VeriStrat status, OS was significantly

higher with afatinib than with erlotinib in the VeriStrat "good" group (median, 11.5 vs 8.9 months; HR=0.79; 95% CI, 0.63 to 0.98) but not the VeriStrat "poor" group (median, 4.7 vs 4.8 months; HR=0.90; 95% CI, 0.70 to 1.16). In the VeriStrat stratified analysis, findings were similar for PFS. The study lacked a group receiving chemotherapy with which to compare the efficacy of TKIs.

Section Summary: Clinical Validity
The literature related to the predictive value of proteomic testing in patients with advanced NSCLC consists of 2 RCTs in patients who failed first-line chemotherapy and several retrospective analyses of clinical trials of EGFR-TKIs, with or without other therapies. Most studies, including the 2 RCTs, demonstrated that classification based on proteomic testing (ie, VeriStrat "good" vs "poor") is associated with survival outcomes. The evidence is limited by heterogeneity in the treatment regimens used and patient population characteristics. In the PROSE RCT, for patients classified as VeriStrat "good"; there was no significant difference in OS in the erlotinib and chemotherapy groups; however, for patients classified as VeriStrat "poor", there was a significantly higher median OS in patients in the erlotinib group. In the EMPHASIS trial, there were no significant differences in PFS or OS among patients with VeriStrat "good" status receiving erlotinib or chemotherapy or among patients with VeriStrat "poor" status receiving erlotinib or chemotherapy. Moreover, in both the PROSE and EMPHASIS RCTs, there was no significant benefit on PFS or OS of erlotinib treatment compared with chemotherapy overall, making the utility of VeriStrat in this population uncertain.

Clinical Utility
The proposed clinical utility of VeriStrat is for selecting patients who are unlikely to benefit from EGFR-TKIs in the second-line setting. Direct evidence from studies that demonstrate improved outcomes for patients managed with a strategy that includes proteomic testing compared with a strategy that does not include proteomic testing would be helpful in demonstrating the clinical utility of proteomic testing to select targeted therapy for NSCLC.

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, the IUNO trial did not find that erlotinib was efficacious in patients with NSCLC with no known *EGFR* variant, and the PROSE and EMPHASIS trials found that OS did not differ significantly for patients with advanced NSCLC treated with second-line erlotinib or chemotherapy. There were mixed findings on PFS in the PROSE and EMPHASIS trials. Due to study findings and the lack of support from guidelines (eg the National Comprehensive Cancer Network) 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.

Akerley et al published 2 studies evaluating the impact of VeriStrat testing on physician treatment recommendations. In a 2013 study of 226 physicians who provided pre- and posttest treatment plan information for 403 VeriStrat tests, in 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%. In a larger 2017 study, Akerley et al reported on 2411 physicians reporting on 14,327 VeriStrat tests. The investigators only included test that were ordered for NSCLC, were ordered as the sole test, were not indeterminate, and were not ordered in patients with known *EGFR* variant status. VeriStrat findings were a classification of "good" for 1950 (78.2%) patients and "poor" in 544 patients (21.8%). After receiving the test results, physicians changed their treatment recommendations in 28.2% of the cases; within this group, 13.2% were classified as VeriStrat "good" and 81.6% as VeriStrat "poor". Physicians initially considered treatment with an EGFR-TKI in 484 (89.0%) of 544 classified as VeriStrat "poor"; after receiving test results only 49 (10%) were actually recommended EGFR-TKI treatment. The studies did not evaluate patient outcomes, and did not evaluate the impact of *EGFR* testing on treatment recommendations (the number of patients who had previously received *EGFR* tests was not reported).

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 available trials and the lack of support from guidelines for EGFRTKIs in this setting, EGFR-TKI therapy is no longer standard therapy for any *EGFR*-negative or -unknown patient in the second-line setting. Two studies by the same research group evaluated changes in treatment recommendations before and after receiving VeriStrat test results; patient outcomes were not reported.

SUMMARY OF EVIDENCE
For individuals with *EGFR*-negative or *EGFR*-status unknown NSCLC with disease progression after first-line treatment who receive management with a serum proteomic test to select targeted therapy, the evidence includes RCTs and observational studies. Relevant outcomes are overall survival and disease-specific survival. 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 widely studied proteomic test, the VeriStrat assay. The literature related to the clinical validity of proteomic testing in patients with advanced NSCLC consists of 2 RCTs in patients who failed first-line chemotherapy and several retrospective analyses of clinical trials of EGFR TKIs, with or without other therapies. The evidence is limited by heterogeneity in the treatment regimens used and patient population characteristics. Most studies, including the 2 RCTs (PROSE and EMPHASIS), found that classification based on proteomic testing (ie, VeriStrat "good" vs "poor") is associated with survival Within the VeriStrat "poor" group, one of the trials—but not the other—found a significantly longer overall survival with erlotinib than with chemotherapy. However, it is not clear that identifying VeriStrat status is useful for selecting second-line therapy. In both RCTs, there was no significant benefit using erlotinib compared with chemotherapy on progression-free survival or overall survival, making the utility of VeriStrat in this population uncertain. 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 the VeriStrat assay 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 the third-line setting, proteomic testing could be used to select patients who are least likely to benefit. However, given the evidence from the available trials and the lack of support from guidelines (eg, National Comprehensive Cancer Network) for EGFR TKIs in this setting, EGFR-TKI therapy is no longer standard therapy for any *EGFR*-negative or -unknown patients in the second-line setting. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 05/20/2015
Current Effective Date: 03/21/2018

05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. New policy.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. Coverage changed to investigational.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 03/2019

Coding

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

Policy # 00446
Original Effective Date: 05/20/2015
Current Effective Date: 03/21/2018

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479, 81538, 81599, 84999
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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