MEDICAL POLICY

POLICY TITLE	PROTEOMIC TESTING FOR TARGETED THERAPY IN NON-SMALL-CELL LUNG CANCER
POLICY NUMBER	MP-2.337

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I. POLICY

The use of proteomic testing, including but not limited to the VeriStrat assay, is considered **investigational** for all uses in the management of non-small-cell lung cancer. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference:
MP-2.270 Multimarker Serum Testing Related to Ovarian Cancer

II. PRODUCT VARIATIONS

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

FEP PPO- Refer to FEP Medical Policy Manual MP-2.04.125 Proteomic Testing for Targeted Therapy in non-Small-Cell Lung Cancer. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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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 with another treatment, 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 anaplastic lymphoma kinase (*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 the 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; for that subpopulation, *EGFR* variants have been reported to as high as 30% to 50%. The reported prevalence of *EGFR* variants 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 (*EML4*) gene and the *ALK* 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; variants 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 RAS in RAS-RAF-ERK-MAPK pathway	1%-3% of adenocarcinomas	Heavy smokers
HER	HER (EGFR) family of TK receptors; dimerizes with EGFR family members when activated	1%-2% of NSCLC	Adenocarcinomas Nonsmoking women
PIK3CA	Intracellular signaling pathway	ℜ≈4% of NSCLC	

EGFR: epidermal growth factor receptor; HER: human 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 [Cambridge, United Kingdom]), erlotinib (Tarceva®; OSI Pharmaceuticals [Farmingdale, NY]), and afatinib (Gilotrif™; Boehringer Ingelheim [Ingelheim am Rhein, Germany]). Although the Food and Drug Administration (FDA) 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 T790M–variant-positive NSCLC who have progressed on an EGFR-TKI.

A 2013 meta-analysis of 23 trials assessing the 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.[5] 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.[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*. 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. Despite the rejection, it is worth nothing that in the erlotinib plus docetaxel arm 18 of the 73 patients achieved PFS at 15 weeks; comparatively, in the docetaxel arm, 17 of 74 patients achieved PFS at 15 weeks.

In 2016, Cicenas et al reported results of the IUNO randomized controlled trial, 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 PFS 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.

Proteomic Testing for Systemic Therapy in 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; *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, a 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. The VeriStrat assay has been proposed as a test to predict response to erlotinib in patients with NSCLC following the failure of treatment with first-line therapy. VeriStrat has been proposed as an addition to *EGFR* testing; it has has also been proposed for 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.

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

IV. RATIONALE

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Summary of Evidence

For individuals with newly diagnosed NSCLC and *EGFR*-negative variant status who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes retrospective studies and a prospective nonrandomized study. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. No published studies were identified that assessed the prognostic use of VeriStrat proteomic testing in newly diagnosed stage I or II NSCLC. For individuals with newly diagnosed advanced NSCLC and *EGFR*-negative variant status without prior systemic therapy, 5 studies have assessed the use of VeriStrat as a prognostic test to discriminate between overall survival (primary) and progression-free survival (secondary) outcomes. All studies were retrospective and intended to validate the extent to which the VeriStrat proteomic classification correlated with overall survival or progression-free survival. Only 1 of the 5 studies reported the percentage of participants who were *EGFR*-negative, but it did not report outcomes based on variant status. One observational, nonrandomized study with prospective sample collection for proteomic testing before NSCLC treatment reported the percentage of participants who were *EGFR*-negative, but it did not report outcomes based on variant status. This was also the only study that included a first-line treatment consistent with current guideline-based recommendations—platinum-doublet-based chemotherapy plus cisplatin or carboplatin plus pemetrexed. The VeriStrat classification was not used to direct selection of treatment in any of the clinical trials from which the validation samples were derived. Disposition of populations with variant status are not reported was generally not clear and could not be construed as unknown when wild-type or positive were reported. No studies were identified that used VeriStrat proteomic testing to inform therapeutic options for patients with stage I or II NSCLC if surgery or surgery plus radiotherapy have been completed or who were upstaged as a result of surgical findings. No studies were identified that used VeriStrat proteomic testing to inform therapeutic options for patients with stage I or II NSCLC who were considered medically inoperable. No studies were identified that used VeriStrat proteomic testing to predict response

to first-line targeted therapies or first-line chemotherapy in patients with newly diagnosed advanced NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with newly diagnosed NSCLC and unknown *EGFR*-variant status who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes 4 retrospective studies and a prospective study. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. All study populations were either unselected for *EGFR*-variant status or status was expressly reported as unknown in conjunction with negative or positive status reports. None of the studies that reported unknown *EGFR*-variant status reported outcomes for the proteomic score based on unknown *EGFR*-variant status. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with NSCLC and *EGFR*-negative variant status and disease progression after first-line systemic therapy who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes an RCT and a retrospective analysis. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. No studies were identified that reported or analyzed outcomes using the proteomic test as a prognostic tool in *EGFR*-negative variant status populations. The evidence includes an RCT (PROSE) using proteomic testing to predict response to erlotinib compared with chemotherapy as second-line treatment for patients with stage IIIB or IV NSCLC, stratified by performancestatus, smoking history, treatment center, and (masked) pretreatment VeriStrat classification. In a multivariate model to predict overall survival, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with overall survival (hazard ratio for VeriStrat are good vs poor, 1.88; 95% confidence interval, 1.25 to 2.84; p=0.003). However, 62% of the combined study population was *EGFR*-negative. A retrospective analysis was also performed on the MARQUEE trial, a phase 3 RCT in patients with stage IIIB or IV nonsquamous NSCLC, comparing the patient response to erlotinib in conjunction with either tivantinib or a placebo; patients were stratified by *EGFR* and *KRAS* variant status, sex, smoking history, and treatment history. Protocol treatments were subsequently discontinued by 93% of patients, and the trial discontinued after prespecified interim futility analysis. In a multivariate model to predict overall survival, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with overall survival (hazard ratio for VeriStrat are good vs poor, 0.52; 95% confidence interval, 0.40 to 0.67; p<0.001). Ninety percent of the combined study population was *EGFR*-negative. An interaction between treatment and VeriStrat status was significant for multivariate analysis including *EGFR* status (p=0.036) but not significant for multivariate analysis including both *EGFR* and *KRAS* variant status (p=0.068). Currently, the use of erlotinib in patients unselected for the presence or absence of an *EGFR*-sensitizing variant is not standard clinical practice. It is recommended that variant status be determined, if not previously

ascertained, before selecting treatment after progression or recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with NSCLC and unknown *EGFR*-variant status with disease progression after first-line systemic therapy who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes 2 RCTs and 3 retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The use of VeriStrat as a prognostic test to discriminate between good and poor survival outcomes was assessed in 3 retrospective studies intended to validate the extent to which VeriStrat proteomic classification correlates with overall survival or progression-free survival. The VeriStrat classification was not used to direct treatment selection in any of the trials from which the validation samples were derived. None of the clinical trials from which the samples for VeriStrat proteomic classification were derived used a therapy consistent with current guidelines-based recommendations. The populations in all 3 studies were unselected for *EGFR*-variant status. In the PROSE RCT, using a multivariate model to predict overall survival, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with overall survival (hazard ratio for VeriStrat are good vs poor, 1.88; 95% CI, 1.25 to 2.84; p=0.003). However, 32.6% of the combined study population had unknown *EGFR* status. In the EMPHASIS RCT, there were no significant differences in progression-free survival or overall survival among patients with VeriStrat are good status receiving erlotinib or chemotherapy or among patients with VeriStrat are poor status receiving erlotinib or chemotherapy. The results of the EMPHASIS RCT were restricted to squamous NSCLC histology. Currently, the use of erlotinib in patients unselected for the presence or absence of an *EGFR*-sensitizing variant is not standard clinical practice. It is recommended that variant status be determined, if not previously ascertained, before selecting treatment after progression or recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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

VII. DISCLAIMER

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

VIII. CODING INFORMATION

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

Investigational: therefore, not covered when used for Proteomic testing:

CPT Codes®								
0080U	81538							

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X. POLICY HISTORY

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MP 2.337	**CAC 3/29/16** New policy adopting BCBSA. Proteomic testing for targeted therapy in non-small-cell lung cancer is investigational. Medicare variation added – coverage is provided for this service. Coding reviewed.
	Admin Update 1/1/2017 Variation reformatting.
	CAC 3/28/17 Consensus Review. No change to policy statements. References and rationale updated. Coding reviewed.
	1/1/18 Admin Update: Medicare variations removed from Commercial Policies.
	2/2/18 Consensus review. No change to the policy statement. Background, rationale, and references updated**.**
	1/1/19 Admin Update: New code 0080U added effective 1/1/19
	4/3/2019 Consensus review. Policy statement unchanged. Condensed rationale. References update.
	07/20/2020- Consensus Review. Reference updates. No changes to policy statement.

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