MEDICAL POLICY

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

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**4/1/2025**

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 general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

If coverage of a test is requested, but is not listed above, please refer to **MP 2.259 - Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies** for additional guidance.

Cross-reference:

MP 2.241 Molecular Analysis for the Targeted Therapy for Non-Small Cell Lung Cancer
MP 2.259 Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies
MP 2.267 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
MP 2.375 Molecular Testing in the Management of Pulmonary Nodules

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

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

Non-small-cell lung cancer

Lung cancer is the leading cause of cancer death in the U. S., with an estimated 228,820 new cases and 135,720 deaths due to the disease in 2020. NSCLC (non-small cell lung cancer) accounts for approximately 85% of lung cancer cases and includes non-squamous carcinoma (adenocarcinoma, large cell carcinoma, other cell types) and squamous cell carcinoma.

Diagnosis

The stage at which lung cancer is diagnosed has the greatest impact on prognosis. Localized disease confined to the primary site has a 59.8 % relative 5-year survival but accounts for only 18 % of lung cancer cases at diagnosis. Mortality increases sharply with advancing stage. Metastatic lung cancer has a relative 5-year survival of 6.3%. Overall, advanced disease, defined as regional involvement and metastatic, accounts for approximately 80% of cases of lung cancer at diagnosis. These statistics are mirrored for the population of NSCLC, with 85% of cases presenting as advanced disease and up to 40% of patients with metastatic disease.

In addition to tumor stage, age, sex, and performance status are independent prognostic factors for survival particularly in early-stage disease. Wheatley-Price et al (2010) reported on a retrospective pooled analysis of 2349 advanced NSCLC patients from five randomized chemotherapy trials. Women had a higher response rate to platinum-based chemotherapy than men. Additionally, women with adenocarcinoma histology had greater overall survival than men. A small survival advantage exists for squamous cell carcinoma over non-bronchiolar non-squamous histology.

The oncology clinical care and research community use standard measures of performance status: Eastern Cooperative Oncology Group scale and Karnofsky Performance Scale.

Treatment

Treatment approaches are multimodal and generally include surgery, radiotherapy, and chemotherapy (either alone or in combination with another treatment, depending on disease stage and tumor characteristics). Per the National Comprehensive Cancer Network (NCCN) guidelines, the clinical management pathway for stage I or II NSCLC is dependent on surgical findings and may involve resection, radiotherapy, chemotherapy, or chemoradiation. First-line chemotherapy regimens for neoadjuvant and adjuvant therapy utilize platinum-based agents (e.g., cisplatin, carboplatin) in combination with other chemotherapeutics and/or radiotherapy. Treatment recommendations are based on the overall health or performance status of the

patient, presence, or absence of metastases, as well as the presence or absence of a treatment-sensitizing genetic variant. These aspects inform the selection of targeted and systemic therapies.

For patients who experience disease progression following initial systemic therapy, subsequent treatment regimens are recommended, mainly featuring novel programmed death-ligand 1 (PD-L1) inhibitors. The NCCN also includes recommendations for targeted therapy or immunotherapy in patients with biomarkers, including sensitizing epidermal growth factor receptor (*EGFR*) mutations. For patients with sensitizing *EGFR* mutations, recommendations include first-line therapy with EGFR tyrosine kinase inhibitors (TKIs) afatinib, erlotinib, dacomitinib, gefitinib, erlotinib plus ramucirumab, erlotinib plus bevacizumab (non-squamous), or osimertinib and subsequent therapy with osimertinib. The NCCN does not make any recommendations for the use of EGFR TKIs in the absence of a confirmed sensitizing *EGFR* mutation. Initial systemic therapy recommendations can be considered for multiple, symptomatic, systemic lesions.

Genomic Alterations
Several common genetic alterations in NSCLC have been targets for drug therapy, the most well-established of which are TKIs targeting the 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 two regions of the *EGFR* gene, including small deletions in exon nineteen and a point mutation 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
There are other genetic variants identified in subsets of patients with NSCLC. The role of testing for these variants is to help select targeted therapies for NSCLC (see policy 2.241 Molecular Analysis for the Targeted Therapy for Non-Small Cell Lung Cancer).

Targeted Treatment Options
EGFR-Selective Small Molecule Tyrosine Kinase Inhibitors
Orally administered EGFR-selective small-molecule TKIs have been approved by the U.S. Food and Drug Administration (FDA) for treating NSCLC include: gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib. Although the FDA approved gefitinib in 2004, a phase 3 trial has suggested gefitinib was not associated with a survival benefit. In 2003, the FDA revised gefitinib labeling, further limiting its use to patients who had previously benefited or were currently benefiting from the drug; no new patients were to be given gefitinib. However, in 2015, the FDA approved gefitinib as a first-line treatment for patients with metastatic, sensitizing *EGFR*-variant positive NSCLC.

In 2015, osimertinib (Tagrisso), an irreversible selective EGFR inhibitor that targets T790M variant-positive NSCLC, received the FDA approval for patients with T790M variant-positive NSCLC who have progressed on an EGFR TKI.

A meta-analysis by Lee et al (2013) assessing twenty-three trials on 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. 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. OS did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcomes. 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 in 2011 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 for patients with non-sensitizing, wild-type EGFR-variant status is controversial. The TITAN trial as reported by Ciuleanu et al (2012) demonstrated no significant differences in OS between erlotinib and chemotherapy as a 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, as reported by Garassino et al (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 Simon's optimal 2-stage design, the erlotinib plus docetaxel strategy was rejected. Despite the rejection, it is worth noting that in the erlotinib plus docetaxel arm eighteen of the seventy-three patients achieved PFS at 15 weeks; comparatively, in the docetaxel arm, 17 of 74 patients achieved PFS at 15 weeks.

Cicenas et al (2016) reported on results of the IUNO randomized controlled trial, which compared maintenance therapy using erlotinib followed by second-line chemotherapy if progression occurred with placebo followed by erlotinib if progression occurred in 643 patients who had advanced NSCLC and no known *EGFR* variant. Because there were no significant differences between groups in PFS, objective response rate, or disease control rate, maintenance therapy with erlotinib in patients without *EGFR* variants was not considered efficacious.

Exon 19 deletions and p.L858R point mutations in exon twenty-one are the most commonly described sensitizing *EGFR* mutations, or mutations in *EGFR* that are associated with responsiveness to EGFR TKI therapy. According to the NCCN, most recent data indicate that NSCLC tumors that do not harbor a sensitizing *EGFR* mutation should not be treated with an EGFR TKI in any line of therapy.

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 and *proteomics* refers to the large-scale comprehensive study of a specific proteome. The proteome may differ from cell to cell and may vary over time and in response to selected stressors.

A cancer cell's proteome is related to its genome and genomic alterations. The proteome may be measured by mass spectrometry (MS) or protein microarray. For cancer, proteomic signatures in the tumor or bodily fluids (i.e., pleural fluid or blood) other than the tumor have been investigated as a biomarker for cancer activity.

A commercially available serum-based test (VeriStrat) has been developed and proposed to be used as a prognostic tool to predict expected survival for standard therapies used in the

treatment of NSCLC. The test is also proposed to have predictive value for response to EGFR TKIs. The test uses matrix-assisted laser desorption ionization MS analysis, and a classification algorithm was developed on a training set of pretreatment sera from three cohorts (Italian A, Japan A, Japan B) totaling 139 patients with advanced NSCLC who were treated with second line gefitinib. The classification result is either “good” or “poor". Two validation studies using pretreatment sera from two cohorts of patients (Italian B, Eastern Cooperative Oncology Group 3503) totaling 163 patients have been reported.

This assay uses an 8-peak proteomic signature; four of the eight have been identified as fragments of serum amyloid A protein one. This protein has been found to be elevated in individuals with a variety of conditions associated with acute and chronic inflammation. The specificity for malignant biologic processes and conditions has not been determined. With industry support, Fidler et al (2018) used convenience biorepository samples to investigate 102 analytes for potential correlations between the specific peptide and protein biomarkers and VeriStrat classification. The VeriStrat test is currently marketed as a tool to measure a patient's "immune response to lung cancer." Biodesix indicates that a VeriStrat "Good" result indicates "a disease state that is more likely to respond to standard of care treatment," whereas a VeriStrat "Poor" rating indicates a chronic inflammatory disease state associated with aggressive cancer and patients that "may benefit from an alternative treatment strategy." The Biodesix website does not indicate whether the VeriStrat test should be reserved for use in patients with advanced lung cancer.

Although the VeriStrat matrix-assisted laser desorption ionization 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.
Best practices for peptide measurement and guidelines for publication of peptide and protein identification have been published for the research community.

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, five 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 one of the five 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 "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 that the technology results in an improvement in the net 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 a randomized controlled trial (RCT), four 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 that the technology results in an improvement in the net health outcome.

For individuals with NSCLC and wild-type *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 performance status, 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 non-squamous 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 that the technology results in an improvement in the net health outcome.

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 three 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 three 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 three 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% confidence interval, 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 “good” status receiving erlotinib or chemotherapy or among patients with VeriStrat “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 that the technology results in an improvement in the net health outcome.

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 health benefit plan. Benefit determinations are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies 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 Blue Cross' Provider Services or Member Services. Capital Blue Cross 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:

Procedure Codes								
81538								

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TOP

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X. POLICY HISTORY

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MP 2.337	**07/20/2020 Consensus Review.** Reference updates. No changes to policy statement.
	04/07/2021 Consensus Review. Description/Background updated. References updated. No change to policy statement.
	10/04/2022 Consensus Review. No change to policy statement. NCCN language added. Cross referenced policies updated. FEP language revised. Background, Rationale and References updated.
	09/27/2023 Consensus Review. Coding table and references updated. Removed 0080U from policy as it does not apply to cancer management. Added policy guidelines.
	09/23/2024 Consensus Review. No change to policy statement. References reviewed and updated. No coding changes.

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