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

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Molecular Analysis for Targeted Therapy of Non-Small -Cell Lung Cancer is addressed separately in medical policy 00452.

Note: Multimarker Serum Testing Related to Ovarian Cancer is addressed separately in medical policy 00281.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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 U. S., with an estimated 228,150 new cases and142,670 deaths due to the disease in 2019. NSCLC accounts for approximately 85% of lung cancer cases and includes nonsquamous 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 55.6% relative 5-year survival but accounts for only 16% of lung cancer cases at diagnosis. Mortality increases sharply with advancing stage. Metastatic lung cancer has a relative 5-year survival of 4.5%. 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 5 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 nonsquamous 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 (eg, 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. For patients with sensitizing epidermal growth factor receptor (*EGFR)* mutations, recommendations include first-line therapy with EGFR tyrosine kinase inhibitors (TKIs) afatinib, erlotinib, dacomitinib, gefitinib, 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. For patients with progression on TKIs other than osimertinib, testing for T790M is recommended, however, switching to osimertinib can be considered regardless of

mutational status. Osimertinib carries a Category 1 recommendation for T790M+ patients with disease progression on an alternative EGFR TKI. For progression on osimertinib with limited and/or isolated lesions, a continuation of osimertinib and definitive local therapy via surgery, stereotactic ablative radiotherapy, or stereotactic radiosurgery is recommended. 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 tyrosine kinase (TK) receptor, 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 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 U. S. is approximately 15%.

***ALK* Variants**
For 2% to 7% of NSCLC patients in the U. S., 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 is 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
ALK	Encodes a receptor TK in the insulin receptor family	4-5%	• Never smokers • Male • Advanced disease
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

Gene	Gene Function	Estimated Variants Prevalence in NSCLC	Patient and Tumor Characteristics
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	≈4% of NSCLC	

ALK: anaplastic lymphoma kinase; 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 Tyrosine Kinase Inhibitors

Five orally administered EGFR-selective small-molecule TKIs have been approved by the U.S. Food and Drug Administration (FDA) for treating NSCLC: gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib (see Table 2). 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 23 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 has 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 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 18 of the 73 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 21 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.

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 NCCN states that a combination of afatinib and cetuximab may be considered in patients harboring sensitizing *EGFR* mutations with disease progression on EGFR TKI therapy.

Programmed Death-Ligand 1 Inhibitors
Some tumors, including some NSCLCs, express a 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 cancer/T-cell interaction, and thus act as immune checkpoint inhibitors. Pembrolizumab, nivolumab, and atezolizumab, which inhibit the programmed death 1 receptor, and atezolizumab, which inhibits the PD-L1, are used in NSCLC that have a PD-L1 expression on its cells. Durvalumab also targets the PD-L1 protein but is used in unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiotherapy.

Other Targeted Therapies
Crizotinib is a novel MET, ROS1, and ALK TKI, and associated with improved PFS in patients with advanced NSCLC who test positive for *ALK* gene rearrangements. Crizotinib is considered first-line therapy for advanced *ALK*-positive lung adenocarcinoma. Other small-molecule TKIs, designed to selectively bind to and inhibit *ALK* activation, have the FDA approval: ceritinib, alectinib, and brigatinib.

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 for Selecting Targeted Treatment for Non-Small Cell Lung Cancer
The term *proteome* refers to the entire complement of proteins produced by an organism, or cellular system 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 (ie, 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 3 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 2 cohorts of patients (Italian B, Eastern Cooperative Oncology Group 3503) totaling 163 patients have been reported.

This assay uses an 8-peak proteomic signature; 4 of the 8 have been identified as fragments of serum amyloid A protein 1. 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.

Table 2. Targeted Treatment Options Approved by FDA

Drug	Indication	Manufacturer	Approved	NDA/BLA
Gefitinib(Iressa®)	• Monotherapy for locally advanced or metastatic NSCLC after failure of platinum-based and docetaxel chemotherapies • Revised label to limit use to patients currently benefiting or previously benefited from gefitinib • First-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution variants as detected by an FDA-approved test	AstraZeneca	05/03 06/05 08/18	NDA 21-399 (Discontinued) NDA 206995 NDA 206995/S3

Drug	Indication	Manufacturer	Approved	NDA/BLA
Erlotinib (Tarceva®)	• Monotherapy for patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen • Maintenance therapy for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy • First-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution variants as detected by an FDA-approved test • Treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution variants as detected by an FDA-approved test receiving first-line, maintenance, or second- or greater line treatment after progression following at	OSI Pharmaceuticals and Genentech	11/04 04/10 05/13 10/16	NDA 021743 NDA 021743/S16 NDA 021743/S18 NDA 021743/S25

Drug	Indication	Manufacturer	Approved	NDA/BLA
	least 1 prior chemotherapy regimen			
Afatinib (Gilotrif®)	• First-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution variants as detected by an FDA-approved test • Treatment of patients with metastatic, squamous, NSCLC progressing after platinum-based chemotherapy • Treatment of patients with NSCLC whose tumors have nonresistant *EGFR* variants as detected by an FDA-approved test, which includes variants other than *EGFR* exon 19 deletions or exon 21 (L858R) substitution variants	Boehringer Ingelheim	07/13 04/16 01/18	NDA 201292 NDA 201292/S7 NDA 201292/S14
Necitumumab (Portrazza®)	• *EGFR* antagonist indicated, in	Eli Lilly	11/15	BLA 125547

Drug	Indication	Manufacturer	Approved	NDA/BLA
	combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC			
Osimertinib (Tagrisso®)	• Treatment of patients with metastatic *EGFR* T790M variant-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy • First-line treatment of patients with metastatic NSCLC whose tumors have, as detected by an FDA-approved test, EGFR exon 19 deletions or exon 21 L858R variants	AstraZeneca	11/15 08/18	NDA 208065 NDA 208065/S11
Crizotinib (Xalkori®)	• Treatment of patients with locally advanced or metastatic NSCLC that is *ALK*-positive as detected by an FDA-approved test	Novartis	08/11 03/16 06/19	NDA 202570 NDA 202570/S16 NDA 202570/S28

Drug	Indication	Manufacturer	Approved	NDA/BLA
	• Treatment of patients with metastatic NSCLC whose tumors are *ROS1*-positive • Treatment of patients with metastatic NSCLC whose tumors are *ROS1*- or *ALK*-positive			
Ceritinib (Zykadia®)	• A kinase inhibitor indicated for treatment of patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib • A kinase inhibitor indicated for treatment of patients with *ALK*-positive metastatic NSCLC	Novartis	04/14 03/19	NDA 205755 (Discontinued) NDA 211225
Alectinib (Alecensa®)	• A kinase inhibitor indicated for treatment of patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib • A kinase inhibitor indicated for treatment	Hoffman-La Roche	12/15 06/18	NDA 208434 NDA 208434/S4

Drug	Indication	Manufacturer	Approved	NDA/BLA
	of patients with *ALK*-positive metastatic NSCLC as detected by an FDA-approved test			
Brigatinib (Alunbrig®)	• Treatment of patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib	ARIAD	04/17	NDA 208772
Pembrolizumab (Keytruda®)	• Treatment of patients with metastatic, PD-L1-positive NSCLC, as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy • Treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy • Expansion of metastatic NSCLC indication to	Merck	10/15 10/16 10/16 05/17	BLA 125514/S5 BLA 125514/S8 BLA 125514/S12 BLA 125514/S16

Drug	Indication	Manufacturer	Approved	NDA/BLA
	include first-line treatment of patients whose tumors have high PD-L1 expression (TPS ≥50%) as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations • Use in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic nonsquamous, NSCLC			
Nivolumab (Opdivo®)	• Treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving drug	Bristol-Myers Squibb	10/15	BLA 125554/S005
Atezolizumab (Tecentriq®)	• Metastatic NSCLC patients who have	Genentech	4/17	BLA 761034

Drug	Indication	Manufacturer	Approved	NDA/BLA
	disease progression during or following platinum-containing chemotherapy. Patients with *EGFR* or *ALK* gene tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq.			
Durvalumab (Imfinzi®)	• Treatment of patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiotherapy	AstraZeneca	02/18	BLA 761069/S-002
Dacomitinib (Vizimpro®)	• First-line treatment of patients with metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R substitution variants, as detected by an FDA-approved test	Pfizer	09/18	NDA 211288

Drug	Indication	Manufacturer	Approved	NDA/BLA
Larotrectinib (Vitrakvi®)	• A kinase inhibitor indicated for the treatment of patients with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment	Bayer	11/18	NDA 210861
Lorlatinib (Lorbrena®)	• A kinase inhibitor indicated for the treatment of patients with *ALK*-positive metastatic NSCLC whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease, or alectinib as the first ALK inhibitor for metastatic disease, or ceritinib as the first ALK	Pfizer	11/18	NDA 210868

Drug	Indication	Manufacturer	Approved	NDA/BLA
	inhibitor for metastatic disease			
Dabrafenib (Tafinlar®)	• A kinase inhibitor indicated for the treatment of patients with metastatic NSCLC with BRAF V600E mutation as detected by an FDA-approved test	Novartis	07/19	NDA 202806/S13
Trametinib (Mekinist®)	• A kinase inhibitor indicated for the treatment of patients with metastatic NSCLC with BRAF V600E mutation as detected by an FDA-approved test	Novartis	07/19	NDA 204114/S13
Entrectinib (Rozlytrek®)	• A kinase inhibitor for the treatment of patients with metastatic *ROS1*-positive NSCLC	Genentech	08/19	NDA 212726

ALK: anaplastic lymphoma kinase; BLA: biologics license application; *EGFR*: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; NDA: new drug application; NSCLC: non-small-cell lung cancer; PD-L1: programmed death-ligand 1; TKI: tyrosine kinase inhibitor; TPS: Tumor Proportion Score.

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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The commercially available proteomic test (VeriStrat®; Biodesix)‡ is available under 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. FDA has chosen not to require any regulatory review of these tests.

Rationale/Source

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.

For individuals with newly diagnosed NSCLC and wild-type *EGFR*-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 (OS), 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 ("good" or "poor") as a prognostic test to discriminate between OS(primary) and progression-free survival (PFS) (secondary) outcomes. All studies were retrospective and intended to validate the extent to which the VeriStrat proteomic classification correlated with OS or PFS. 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 the 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 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 a randomized controlled trial (RCT), 4 retrospective studies, and a prospective study. Relevant outcomes are OS, 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 wild-type *EGFR*-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 a RCT and a retrospective analysis. Relevant outcomes are OS, 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 a 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 OS, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with OS(hazard ratio for VeriStrat "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 OS, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with OS (hazard ratio for VeriStrat "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 OS, 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 OS or PFS. 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 OS, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with OS(hazard ratio for VeriStrat "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 PFS or OS 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 the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

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

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (v8.2020)[i,ii] guidelines on the management of non-small cell lung cancer (NSCLC) recommend routine testing for *EGFR* variants in patients with advanced or metastatic nonsquamous NSCLC (category 1 recommendation) and consideration for *EGFR*-variant testing in patients with metastatic squamous NSCLC who were never smokers or with small biopsy specimens or mixed histology (category 2A recommendation). Recommendations for first-line treatment for *EGFR*-positive patients with advanced or metastatic NSCLC, and *EGFR*-negative or -unknown patients as well as for patients in either category who have progressed on therapy are provided. See the Background section for additional information.

[i] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)‡ for *Non-Small Cell Lung Cancer* V.8.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. To view the most recent and complete version of the

guideline, go online to NCCN.org.
[ii] NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

American Society of Clinical Oncology
In 2017, the American Society of Clinical Oncology updated its clinical practice guidelines on systemic therapy for stage IV NSCLC. New or revised recommendations included the following recommendations: first-line treatment for patients with nonsquamous cell carcinoma or squamous cell carcinoma (without positive markers, eg, *EGFR*, *ALK*, *ROS1*), based on programmed death-ligand 1 expression; second-line treatment in patients who received first-line chemotherapy, without prior immune checkpoint therapy based on programmed death-ligand 1 expression; as well as recommendations for those patients who cannot receive immune checkpoint inhibitor. Recommendations are included for patients with a sensitizing *EGFR* variant, for patients with disease progression after first-line EGFR tyrosine kinase inhibitor therapy based on the results of T790M variant testing, and for patients with *ROS1* gene rearrangements without prior crizotinib may be offered crizotinib, or if they previously received crizotinib, they may be offered chemotherapy.

The Society (2018) endorsed practice guidelines from other medical associations (College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology) addressing molecular testing for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors.

American College of Chest Physicians
In 2013, the American College of Chest Physicians updated its evidence-based clinical practice guidelines on the treatment of stage IV NSCLC. Based on a review of the literature, the College reported improved response rates, progression-free survival, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with *EGFR* variants, especially exon 19 deletion and L858R variant. Moreover, the College recommended, "testing patients with NSCLC for *EGFR* mutations at the time of diagnosis whenever feasible, and treating with first-line EGFR-TKIs if mutation-positive."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Novitas Solutions established a local coverage determination for the VeriStrat test in June 2013 in the local coverage determination Biomarkers for Oncology (L35396).

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02271581	INSYNC: Leo Jenkins Cancer Center (LJCC) - Symptom Management Service (SMS) Protocol - Phase II Trial Regarding The Effect Of Comprehensive Symptom Management On Inflammation And Survival In Metastatic Lung Cancer	100	Jul 2020 (recruiting)*
NCT03289780[a]	An Observational Study Assessing the Clinical Effectiveness of VeriStrat and Validating Immunotherapy Tests in Subjects With Non-Small Cell Lung Cancer	1,000	Dec 2020 (recruiting)

NCT: national clinical trial.
[a] Denotes industry sponsorship or co-sponsorship.
* No results reported

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Policy History

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

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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.
03/07/2019 Medical Policy Committee review
03/20/2019 Medical Policy Implementation Committee approval. No change to coverage.
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03/11/2020 Medical Policy Implementation Committee approval. No change to coverage.
03/04/2021 Medical Policy Committee review
03/10/2021 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 03/2022

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Code Type	Code
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ICD-10 Diagnosis	All related diagnoses

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    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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