



MASSACHUSETTS

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## Medical Policy

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

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## Policy Number: 709

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NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

## Related Policies

- Proteomics-based Testing for the Evaluation of Ovarian Masses, #[249](#)
- Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer, #[563](#)

## Policy

### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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.

### Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

This is not a covered service.

Medical necessity criteria and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the link(s) below.

[Local Coverage Determinations \(LCDs\) for National Government Services, Inc.](#)

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

**Note:** To review the specific LCD, please remember to click “accept” on the CMS licensing agreement at the bottom of the CMS webpage.

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website at <https://www.cms.gov> for information regarding your specific jurisdiction.

## Prior Authorization Information

### Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

### Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is <b>not</b> a covered service.
Commercial PPO and Indemnity	This is <b>not</b> a covered service.
Medicare HMO Blue <sup>SM</sup>	This is <b>not</b> a covered service.
Medicare PPO Blue <sup>SM</sup>	This is <b>not</b> a covered service.

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

### CPT Codes

CPT codes:	Code Description
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival

## Description

### 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.<sup>1</sup> Non-small-cell lung cancer (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.<sup>2</sup> 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.<sup>3</sup> Women had a

higher response rate to platinum-based chemotherapy than men. Additionally, women with adenocarcinoma histology had greater overall survival (OS) than men. A small survival advantage exists for squamous cell carcinoma over non-bronchiolar nonsquamous histology.<sup>4</sup>

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

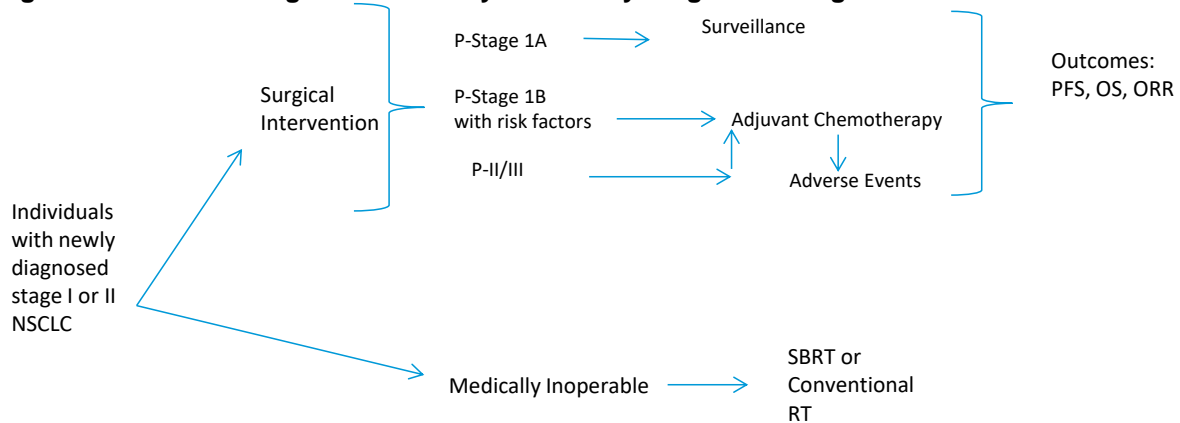
**Treatment**

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). The clinical management pathway for stage I or II NSCLC is shown in Figure 1.<sup>1</sup>

The clinical management pathway for newly diagnosed advanced NSCLC is shown in Figure 2.<sup>1</sup> Treatment recommendations are based on the overall health or performance status of the patient as well as the presence or absence of a treatment-sensitizing genetic variant. The latter is used to select for targeted therapy or platinum-based chemotherapy.

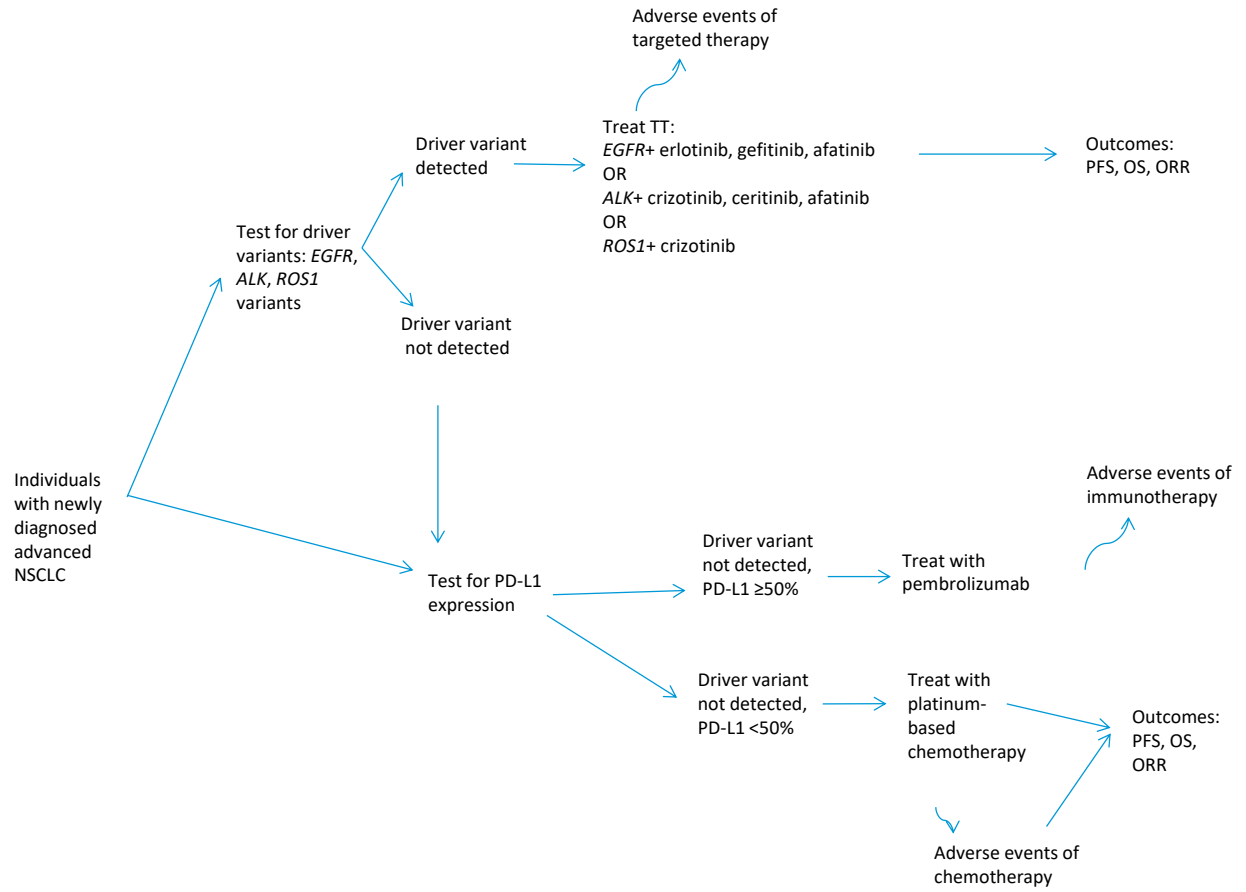
The clinical management pathway for advanced NSCLC after progression on first-line treatment or recurrence is shown in Figure 3. Treatment options are based on objective response to prior therapy, duration of response, as well as the type of and duration of prior therapy (either targeted therapy or chemotherapy).

**Figure 1. Clinical Management Pathways for Newly Diagnosed Stage I or II NSCLC**



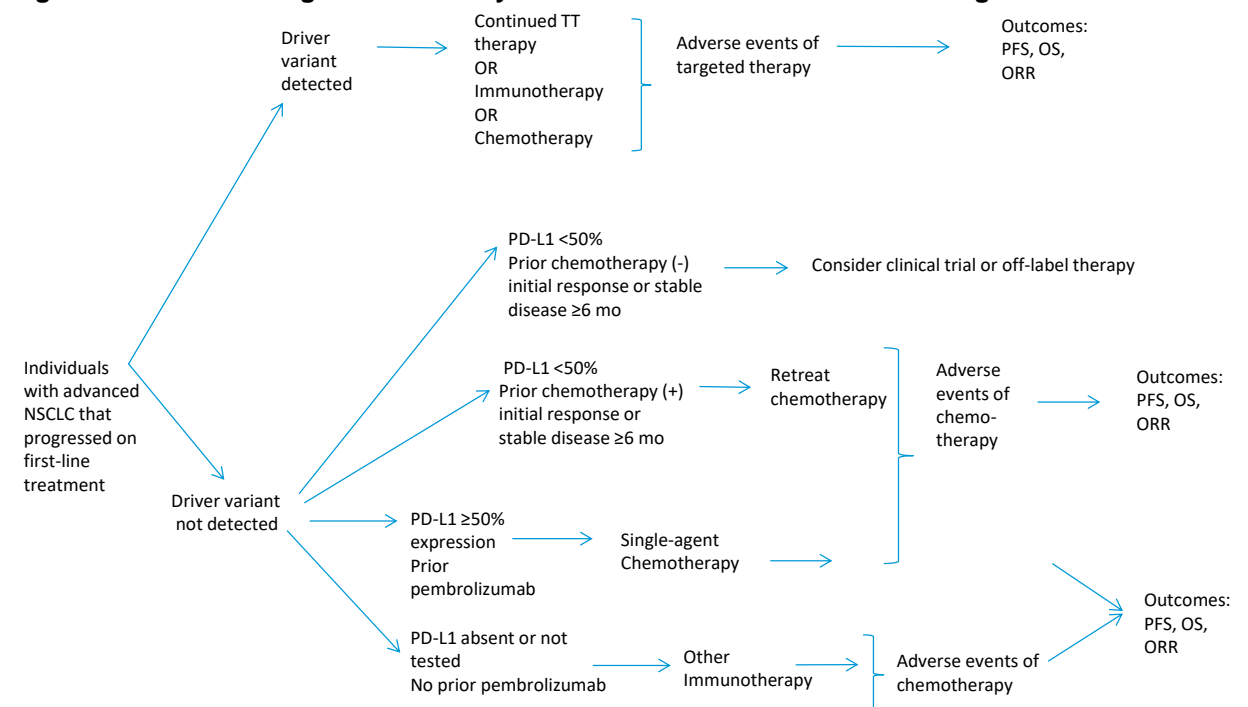
NSCLC: non-small-cell lung cancer; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RT: radiotherapy; SBRT: stereotactic body radiotherapy.

**Figure 2. Clinical Management Pathways for Newly Diagnosed Advanced NSCLC**



NSCLC: non-small-cell lung cancer; ORR: overall response rate; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; TT: targeted treatment.

**Figure 3. Clinical Management Pathways for Advanced NSCLC That Has Progressed**



NSCLC: non-small-cell lung cancer; ORR: overall response rate; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; TT: targeted treatment.

### Genomic 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 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 United States is approximately 15%.<sup>5</sup>

#### ALK Variants

For 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.<sup>6</sup> 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
<i>KRAS</i>	Encodes RAS proteins; variants associated with constitutively activated protein	20%-30%	<ul style="list-style-type: none"> <li>• Adenocarcinomas</li> <li>• Heavy smokers</li> </ul>
<i>ROS1</i>	Encodes a receptor TK in the insulin receptor family	0.9%-3.7%	<ul style="list-style-type: none"> <li>• Adenocarcinoma</li> <li>• Never smokers</li> </ul>
<i>RET</i>	Proto-oncogene that encodes a receptor TK growth factor	0.6%-2%	
<i>MET</i>	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
<i>BRAF</i>	Serine-threonine kinase downstream from RAS in RAS-RAF-ERK-MAPK pathway	1%-3% of adenocarcinomas	Heavy smokers
<i>HER</i>	HER (EGFR) family of TK receptors; dimerizes with EGFR family members when activated	1%-2% of NSCLC	<ul style="list-style-type: none"> <li>• Adenocarcinomas</li> <li>• Nonsmoking women</li> </ul>
<i>PIK3CA</i>	Intracellular signaling pathway	≈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 treating NSCLC: gefitinib (Iressa), erlotinib (Tarceva), and afatinib (Gilotrif) (see Table 2). Although the Food and Drug Administration (FDA) approved gefitinib in 2004, a phase 3 trial has suggested gefitinib was not associated with a survival benefit. In 2003, 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, 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 2015, osimertinib (Tagrisso), 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 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.<sup>7</sup> 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.<sup>5</sup>

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 as reported by Ciuleanu et al (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.<sup>8</sup> 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.<sup>9</sup> 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*.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.

### ***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. Neither drug has an established role in the treatment of NSCLC either as a component of initial therapy or as second-line therapy.

### ***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 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.<sup>13</sup> Crizotinib is considered first-line therapy for advanced *ALK*-positive lung adenocarcinoma.<sup>1</sup> Other small molecule TKIs, designed to selectively bind to and inhibit *ALK* activation, have 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 NSCLC

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.<sup>14</sup> 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.<sup>15</sup> 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 (see Tables 3 and 4).

This assay uses an 8-peak proteomic signature; 4 of the 8 have been identified as fragments of serum amyloid A protein 1.<sup>16</sup> This protein has been found to be elevated in individuals with a variety of conditions associated with acute and chronic inflammation.<sup>17-21</sup> The specificity for malignant biologic processes and conditions has not been determined.<sup>22</sup> 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.<sup>23</sup>

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.<sup>24</sup>

Best practices for peptide measurement and guidelines for publication of peptide and protein identification have been published for the research community.<sup>25</sup>

**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	AstraZeneca	05/03	NDA 21-399
	• Revised label to limit use to patients currently benefiting or previously benefited from gefitinib		06/05	
	• First-line treatment of patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitution variants as detected by an FDA-approved test		06/15	NDA 206995
Erlotinib (Tarceva®)	• Monotherapy for patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen	OSI Pharmaceuticals and Genentech	11/04	NDA 021743
	• Maintenance therapy for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy		04/10	NDA 021743/S16
	• First-line treatment of patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19		05/13	NDA 021743/S18



Drug	Indication	Manufacturer	Approved	NDA/BLA
	<ul style="list-style-type: none"> <li>deletions or exon 21 (L858R) substitution variants as detected by an FDA-approved test</li> <li>Treatment of patients with metastatic NSCLC whose tumors have <i>EGFR</i> 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 least 1 prior chemotherapy regimen</li> </ul>		10/16	NDA 021743/S25
Afatinib (Gilotrif®)	<ul style="list-style-type: none"> <li>First-line treatment of patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitution variants as detected by an FDA-approved test</li> <li>Treatment of patients with metastatic, squamous, NSCLC progressing after platinum-based chemotherapy</li> <li>Treatment of patients with NSCLC whose tumors have nonresistant <i>EGFR</i> variants as detected by an FDA-approved test, which includes variants other than <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitution variants</li> </ul>	Boehringer Ingelheim	07/13	NDA 201292
			04/16	NDA 201292/S7
			01/18	NDA 201292/S14
Necitumumab (Portrazza®)	<ul style="list-style-type: none"> <li><i>EGFR</i> antagonist indicated, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC</li> </ul>	Eli Lilly	11/15	BLA 125547
Osimertinib (Tagrisso®)	<ul style="list-style-type: none"> <li>Treatment of patients with metastatic <i>EGFR</i> T790M variant–positive NSCLC, as detected by an FDA-approved test, who have progressed on or after <i>EGFR</i> TKI therapy</li> <li>First-line treatment of patients with metastatic NSCLC whose tumors have, as detected by an FDA-approved test, <i>EGFR</i> exon 19 deletions or exon 21 L858R variants</li> </ul>	AstraZeneca	11/15	NDA 208065
			04/18	NDA 208065
Crizotinib (Xalkori®)	<ul style="list-style-type: none"> <li>Treatment of patients with locally advanced or metastatic NSCLC that is <i>ALK</i>-positive as detected by an FDA-approved test</li> <li>Treatment of patients with metastatic NSCLC whose tumors are <i>ROS1</i>-positive</li> </ul>	Novartis	08/11	NDA 202570
			03/16	NDA 202570/S16
Ceritinib (Zykadia®)	<ul style="list-style-type: none"> <li>A kinase inhibitor indicated for treatment of patients with <i>ALK</i>-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib</li> </ul>	Novartis	04/14	NDA 205755
Alectinib (Alecensa®)	<ul style="list-style-type: none"> <li>A kinase inhibitor indicated for treatment of patients with <i>ALK</i>-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib</li> <li>A kinase inhibitor indicated for treatment of patients with <i>ALK</i>-positive metastatic NSCLC as detected by an FDA-approved test</li> </ul>	Hoffman-La Roche	12/15	NDA 208434
			11/17	NDA 208434/S3
Brigatinib (Alunbrig®)	<ul style="list-style-type: none"> <li>Treatment of patients with <i>ALK</i>-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib</li> </ul>	ARIAD	04/17	NDA 208772
Pembrolizumab (Keytruda®)	<ul style="list-style-type: none"> <li>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</li> <li>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</li> <li>Expansion of metastatic NSCLC indication to include first-line treatment of patients whose tumors have high PD-L1 expression (TPS ≥ 50%) as determined by an FDA-approved test, with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations</li> <li>Use in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic nonsquamous, NSCLC</li> </ul>	Merck	10/15	BLA 125514/S5
			10/16	BLA 125514/S8
			10/16	BLA 125514/S12
			05/17	BLA 125514/S16

Drug	Indication	Manufacturer	Approved	NDA/BLA
Nivolumab (Opdivo®)	<ul style="list-style-type: none"> <li>Treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving drug</li> </ul>	Bristol-Myers Squibb	10/15	BLA 125554/S005
Atezolizumab (Tecentriq®)	<ul style="list-style-type: none"> <li>Metastatic NSCLC patients who have disease progression during or following platinum-containing chemotherapy. Patients with <i>EGFR</i> or <i>ALK</i> gene tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq.</li> </ul>	Genentech	4/17	BLA 761034
Durvalumab (Imfinzi®)	<ul style="list-style-type: none"> <li>Treatment of patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiotherapy</li> </ul>	AstraZeneca	02/18	BLA 761069/S-002
Dacomitinib (Vizimpro®)	<ul style="list-style-type: none"> <li>First-line treatment of patients with metastatic NSCLC with <i>EGFR</i> exon 19 deletion or exon 21 L858R substitution variants, as detected by an FDA-approved test</li> </ul>	Pfizer	09/18	NDA 211288

*ALK*: anaplastic lymphoma kinase; *BLA*: biologics license application; *EGFR*: epidermal growth factor receptor; *FDA*: 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.

## Summary

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 *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 (“good” or “poor”) 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 “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 a randomized controlled trial (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 “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 “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 “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 the effects of the technology on health outcomes.

## Policy History

Date	Action
1/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
09/2018	BCBSA National medical policy review. Description, summary and references updated. Policy statement unchanged. 9/1/2018
6/2018	BCBSA National medical policy review. Policy title changed.
8/2017	BCBSA National medical policy review. In the Background, in the discussion of osimertinib, NSCLC variant T890M changed to T790M. 8/1/2017.
5/2017	BCBSA National medical policy review. Background section clarified programmed death ligand 1 inhibitors are not only used for cancers expressing PD-L1. 5/1/2017
3/2017	New references added from BCBSA National medical policy.
2/2017	Non-coverage for Medicare Advantage members clarified based on Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000). 2/2017
1/2016	New references added from BCBSA National medical policy.
1/2016	Clarified coding information.
12/2015	Policy updated to include Medicare LCD L35396. Effective 12/1/2015.
3/2015	New medical policy describing investigational indications. Effective 3/1/2015.

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