Introduction

Genes in our DNA tell a cell how to make proteins. The study of proteins in a cell is called “proteomics.” Doing tests on the proteins in a cell (“proteomic testing”) may help to identify which drugs might be helpful in treating non-small cell lung cancer and how aggressive the cancer is. Proteomic testing used for this and all other reasons is unproven (investigational). Medical studies have not determined the types of patients in which proteomic testing could predict the course of the disease. Studies also have not shown that patients whose treatments were chosen based on proteomic testing survived longer than those whose treatments were selected without proteomic testing.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Proteomic testing

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.

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
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<tr>
<td>CPT</td>
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</tr>
<tr>
<td>81538</td>
<td>Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival</td>
</tr>
</tbody>
</table>

*Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).*

**Related Information**

N/A

**Evidence Review**

**Description**

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.
Background

Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in the United States, with an estimated 221,200 new cases and 158,040 deaths due to the disease in 2015. Non-small cell lung cancer (NSCLC) 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 (OS) 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). The clinical management pathway for stage I or II NSCLC is shown in Figure 1.
The clinical management pathway for newly diagnosed advanced NSCLC is shown in Figure 2. 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**

Individuals with newly diagnosed stage I or II NSCLC

Outcomes: PFS, OS, ORR

SBRT or Conventional RT

Adverse Events

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

Variants in 2 regions of the EGFR gene, including small deletions in exon 19 and a point 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 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**

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. The EML4 fusion leads to ligand-independent activation of ALK, which encodes a receptor TK whose precise cellular function is not completely understood. EML4-ALK variants are more common in never-smokers or light smokers, tend to be associated with younger age of NSCLC onset, and typically do not occur in conjunction with EGFR variants.

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

**Other Genetic Variants**

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Function</th>
<th>Estimated Mutation Prevalence in NSCLC</th>
<th>Patient and Tumor Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>Encodes RAS proteins; variants associated with constitutively activated protein</td>
<td>20%-30%</td>
<td>Adenocarcinomas Heavy smokers</td>
</tr>
<tr>
<td>ROS1</td>
<td>Encodes a receptor TK in the insulin receptor family</td>
<td>0.9%-3.7%</td>
<td>Adenocarcinoma Never smokers</td>
</tr>
<tr>
<td>RET</td>
<td>Proto-oncogene that encodes a receptor TK growth factor</td>
<td>0.6%-2%</td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>Oncogene that encodes a receptor TK that is activated in response to binding of hepatocyte growth factor</td>
<td>2-4% of previously untreated NSCLC; 5%-20% of patients with acquired resistance to EGFR TKIs</td>
<td>Patients with acquired resistance to EGFR TKIs</td>
</tr>
<tr>
<td>BRAF</td>
<td>Serine-threonine kinase downstream from RAS in RAS-RAF-ERK-MAPK pathway</td>
<td>1%-3% of adenocarcinomas</td>
<td>Heavy smokers</td>
</tr>
<tr>
<td>HER</td>
<td>HER (EGFR) family of TK receptors; dimerizes with EGFR family members when activated</td>
<td>1%-2% of NSCLC</td>
<td>Adenocarcinomas Nonsmoking women</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Intracellular signaling pathway</td>
<td>≈4% of NSCLC</td>
<td></td>
</tr>
</tbody>
</table>

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 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 benefitted or were currently benefiting from the drug; no new patients were to be given gefitinib. However, in 2015, the 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 the 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-line 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-line and second-line settings. Overall survival (OS) did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any 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 that patients with NSCLC being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for EGFR variants to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.

The primary target population for TKIs in NSCLC is for EGFR variant-positive patients with advanced NSCLC. The use of TKIs in NSCLC in EGFR variant-negative patients is controversial. The TITAN trial 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. 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 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 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 terms of PFS, objective response rate, or disease control rate, maintenance therapy with erlotinib in patients without EGFR variants was not considered efficacious.

**Anti-EGFR Monoclonal Antibodies**

For the treatment of KRAS-mutated NSCLC, anti-EGFR monoclonal antibodies have been investigated as possible treatment options. Available anti-EGFR monoclonal antibodies include cetuximab and panitumumab. 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 the 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 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 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 in 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 to genomic alterations. The proteome may be measured by mass spectrometry (MS) or protein microarray. For cancer, proteomic signatures in the tumor or in bodily fluids (ie, pleural fluid or blood) other than the tumor have been investigated as a biomarker for cancer activity.

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.

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>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Manufacturer</th>
<th>Approved</th>
<th>NDA / BLA</th>
</tr>
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<tbody>
<tr>
<td>Gefitinib (Iressa®)</td>
<td>• Monotherapy for locally advanced or metastatic NSCLC after failure of platinum-based and docetaxel chemotherapies</td>
<td>AstraZeneca</td>
<td>05/03</td>
<td>NDA 21-399</td>
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<td></td>
<td>• Revised label to limit use to patients currently benefiting or previously benefited from gefitinib</td>
<td></td>
<td>06/05</td>
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<td>• 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</td>
<td></td>
<td>06/15</td>
<td>NDA 206995</td>
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<td>Erlotinib (Tarceva®)</td>
<td>• Monotherapy for treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen</td>
<td>OSI Pharmaceuticals and Genentech</td>
<td>11/04</td>
<td>NDA 021743</td>
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<td></td>
<td>• Maintenance therapy for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy</td>
<td></td>
<td>04/10</td>
<td>NDA 021743/516</td>
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<td>• 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</td>
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<td>NDA 021743/S18</td>
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<td>• 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 least 1 prior chemotherapy regimen</td>
<td></td>
<td>10/16</td>
<td>NDA 021743/S25</td>
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<td>Afatinib (Gilotrif®)</td>
<td>• 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</td>
<td>Boehringer Ingelheim</td>
<td>07/13</td>
<td>NDA 201292</td>
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<td>• Treatment of patients with metastatic, squamous, NSCLC progressing after platinum-based chemotherapy</td>
<td></td>
<td>04/16</td>
<td>NDA 201292/S7</td>
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<td></td>
<td>• Treatment of patients with NSCLC whose tumors have nonresistant EGFR variants as detected by an FDA-approved test, which</td>
<td></td>
<td>01/18</td>
<td>NDA 201292/S14</td>
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<td>Necitumumab (Portrazza®)</td>
<td>includes additional variants other than EGFR exon 19 deletions or exon 21 (L858R) substitution variants</td>
<td>Eli Lilly</td>
<td>11/15</td>
<td>BLA 125547</td>
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<tr>
<td>Osimertinib (Tagrisso®)</td>
<td>• EGFR antagonist indicated, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC</td>
<td>AstraZeneca</td>
<td>11/15</td>
<td>NDA 208065</td>
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<td>• 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</td>
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<td>Crizotinib (Xalkori®)</td>
<td>• Treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test</td>
<td>Novartis</td>
<td>08/11</td>
<td>NDA 202570</td>
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<td></td>
<td>• Treatment of patients with metastatic NSCLC whose tumors are ROS1-positive</td>
<td></td>
<td>03/16</td>
<td>NDA 202570/ S16</td>
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<td>Ceritinib (Zykadia®)</td>
<td>• A kinase inhibitor indicated for treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib</td>
<td>Novartis</td>
<td>04/14</td>
<td>NDA 205755</td>
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<td>Alectinib (Alecensa®)</td>
<td>• A kinase inhibitor indicated for treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib</td>
<td>Hoffman-La Roche</td>
<td>12/15</td>
<td>NDA 208434</td>
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<td>• A kinase inhibitor indicated for treatment of patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test</td>
<td></td>
<td>11/17</td>
<td>NDA 208434/ S3</td>
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<td>Brigatinib (Alunbrig®)</td>
<td>• Treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib</td>
<td>ARIAD</td>
<td>04/17</td>
<td>NDA 208772</td>
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<tr>
<td>Pembrolizumab (Keytruda®)</td>
<td>• 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</td>
<td>Merck</td>
<td>10/15</td>
<td>BLA 125514/ S5</td>
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<tr>
<td>Nivolumab (Opdivo®)</td>
<td>• Treatment of patients with metastatic NSCLC whose tumors express PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy</td>
<td>Bristol-Myers Squibb</td>
<td>10/16</td>
<td>BLA 125514/ S8</td>
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<td></td>
<td>• 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 EGFR or ALK genomic tumor aberrations</td>
<td></td>
<td>10/16</td>
<td>BLA 125514/ S12</td>
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<td></td>
<td>• Use in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic nonsquamous, NSCLC</td>
<td></td>
<td>05/17</td>
<td>BLA 125514/ S16</td>
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<tr>
<td>Atezolizumab (Tecentriq®)</td>
<td>• Metastatic NSCLC patients who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq</td>
<td>Genentech</td>
<td>4/17</td>
<td>BLA 761034</td>
</tr>
<tr>
<td>Durvalumab (Imfinzi®)</td>
<td>• Treatment of patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiotherapy</td>
<td>AstraZeneca</td>
<td>02/18</td>
<td>BLA 761069/ S-002</td>
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<tr>
<td>Dacomitinib (Vizimpro®)</td>
<td>• 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</td>
<td>Pfizer</td>
<td>09/18</td>
<td>NDA 211288</td>
</tr>
</tbody>
</table>

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 of Evidence

For individuals with newly diagnosed NSCLC and EGFR-negative variant status who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes retrospective studies and a prospective nonrandomized study. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. No published studies were identified that assessed the prognostic use of VeriStrat proteomic testing in newly diagnosed stage I or II NSCLC. For individuals with newly diagnosed advanced NSCLC and EGFR-negative variant status without prior systemic therapy, 5 studies have assessed the use of VeriStrat (“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 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 IIIIB 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 IIIIB 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 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% CI, 1.25 to 2.84; p=0.003). However, 32.6% of the combined study population had unknown EGFR status. In the EMPHASIS RCT, there were no significant differences in progression-free survival or overall survival among patients with VeriStrat “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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03289780a</td>
<td>Clinical Effectiveness Assessment of VeriStrat® Testing and Validation of Immunotherapy Tests in NSCLC Subjects (INSIGHT)</td>
<td>1000</td>
<td>Dec 2020</td>
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</tbody>
</table>

NCT: national clinical trial

a Denotes industry sponsorship or cosponsorship
Clinical Input Received 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 is adequate evidence that the use of VeriStrat to guide treatment selection will 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 (v.1.2019) guidelines on the management of non-small cell lung cancer (NSCLC) recommend routine testing for epidermal growth factor receptor (EGFR) variants in patients with 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).1 Recommendations for first-line treatment for EGFR-positive patients with advanced or metastatic NSCLC, and EGFR-negative or EGFR-unknown patients as well as for patients in either category who have progressed on therapy are provided.

American Society of Clinical Oncology

The American Society of Clinical Oncology (2017) updated its clinical practice guidelines on systemic therapy for stage IV NSCLC.47 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 rearrangement without prior crizotinib may be offered crizotinib, or if they previously received crizotinib, they may be offered chemotherapy.

The Society (2018) endorsed clinical 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 patient with lung cancer for treatment with targeted tyrosine kinase inhibitors.48

American College of Chest Physicians

The American College of Chest Physicians (2013) updated its evidence-based clinical practice guidelines on the treatment of stage IV NSCLC.49 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.”

Medicare National Coverage

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

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 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 test.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/13/15</td>
<td>New Policy. Policy created with literature review through September 6, 2014. Proteomic testing considered investigational for all indications in the management of non-small-cell lung cancer.</td>
</tr>
<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81538, effective 1/1/16, added to policy.</td>
</tr>
<tr>
<td>05/01/17</td>
<td>Annual Review, approved April 11, 2017. Policy updated with results of clinical input; reference 10 added. Policy statement unchanged. The term mutations replaced with the term variants.</td>
</tr>
<tr>
<td>10/24/17</td>
<td>Policy moved to new format; no change to policy statements.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
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