FEP 2.04.125 Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer

Effective Date: April 1, 2019

Related Policies:
2.04.62 Multimarker Serum Testing Related to Ovarian Cancer
2.04.45 Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer
2.04.143 Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

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

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.

OBJECTIVE
The objective of this evidence review is to determine whether the use of proteomic testing to select therapy improves the net health outcome in patients with non-small-cell lung cancer.

POLICY STATEMENT
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.

POLICY GUIDELINES
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.\textsuperscript{14}

Table 1. Targeted Treatment Options Approved by FDA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Manufacturer</th>
<th>Approved</th>
<th>NDA/BLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>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.</td>
<td>AstraZeneca</td>
<td>05/03, 06/05, 06/15</td>
<td>NDA 21-399NDA 206995</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>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 third-line treatment</td>
<td>OSI Pharmaceuticals and Genentech</td>
<td>11/04, 04/10, 05/13, 10/16</td>
<td>NDA 021743ND A 021743/S1 6NDA 021743/S1 8NDA 021743/S2 5</td>
</tr>
<tr>
<td><strong>Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer</strong></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>Agent</strong></th>
<th><strong>Description</strong></th>
<th><strong>Company</strong></th>
<th><strong>Approval Dates</strong></th>
<th><strong>NDA Numbers</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Afatinib (Gilotrif®)</strong></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. 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</td>
<td>Boehringer Ingelheim</td>
<td>07/13 04/16 01/18</td>
<td>NDA 201292 NDA 201292/S7 NDA 201292/S14</td>
</tr>
<tr>
<td><strong>Necitumumab (Portrazza®)</strong></td>
<td>EGFR antagonist indicated, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC</td>
<td>Eli Lilly</td>
<td>11/15</td>
<td>BLA 125547</td>
</tr>
<tr>
<td><strong>Osimertinib (Tagrisso®)</strong></td>
<td>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</td>
<td>AstraZeneca</td>
<td>11/15 04/18</td>
<td>NDA 208065ND A 208065</td>
</tr>
<tr>
<td><strong>Crizotinib (Xalkori®)</strong></td>
<td>Treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test. Treatment of patients with metastatic NSCLC whose tumors are ROS1-positive</td>
<td>Novartis</td>
<td>08/11 03/16</td>
<td>NDA 202570ND A 202570/S16</td>
</tr>
<tr>
<td><strong>Ceritinib (Zykadia®)</strong></td>
<td>A kinase inhibitor indicated for treatment of patients with ALK-positive metastatic</td>
<td>Novartis</td>
<td>04/14</td>
<td>NDA 205755</td>
</tr>
</tbody>
</table>

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**FEP 2.04.125 Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usage &amp; Indications</th>
<th>Company</th>
<th>Approval Dates</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<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. A kinase inhibitor indicated for treatment of patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test</td>
<td>Hoffman-La Roche</td>
<td>12/15 11/17</td>
<td>NDA 208434ND A 208434/S3</td>
</tr>
<tr>
<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>
</tr>
<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. Treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS &gt;= 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Expansion of metastatic NSCLC indication to include first-line treatment of patients whose tumors have high PD-L1 expression (TPS &gt;=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</td>
<td>Merck</td>
<td>10/15 10/16 10/16 05/17</td>
<td>BLA 125514/S5 BLA 125514/S8 BLA 125514/S1 2BLA 125514/S1 6</td>
</tr>
<tr>
<td>Nivolumab (Opdivo®)</td>
<td>Treatment of patients with metastatic NSCLC with progression on or after</td>
<td>Bristol-Myers Squibb</td>
<td>10/15</td>
<td>BLA 125554/S0 05</td>
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<table>
<thead>
<tr>
<th>Procedure</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Atezolizumab (Tecentriq®)</td>
<td>Metastatic NSCLC patients who have disease progression on platinum-based chemotherapy. Patients with EGFR or ALK gene tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving drug.</td>
</tr>
<tr>
<td></td>
<td>Genentech 4/17 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>
</tr>
<tr>
<td></td>
<td>AstraZeneca 02/18 BLA 761069/S-002</td>
</tr>
<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>
</tr>
<tr>
<td></td>
<td>Pfizer 09/18 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.

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA 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.

**RATIONALE**

**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 newly diagnosed advanced NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For individuals with NSCLC and EGFR-negative variant status and disease progression after first-line systemic therapy who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes an RCT and a retrospective analysis. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. No studies were identified that reported or analyzed outcomes using the proteomic test as a prognostic tool in EGFR-
negative variant status populations. The evidence includes an RCT (PROSE) using proteomic testing to predict response to erlotinib compared with chemotherapy as second-line treatment for patients with stage IIIB or IV NSCLC, stratified by 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% 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.
SUPPLEMENTAL INFORMATION

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). 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.

American Society of Clinical Oncology
The American Society of Clinical Oncology (2017) 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
The American College of Chest Physicians (2013) 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
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. Novitas Solutions established a local coverage determination for the VeriStrat test in June 2013 in the local coverage determination Biomarkers for Oncology (L35396).

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REFERENCES


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FEP 2.04.125 Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer


POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>December 2014</td>
<td>New Policy</td>
<td>Policy created with literature review. Proteomic testing considered investigational for all indications in the management of non-small cell lung cancer.</td>
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<tr>
<td>March 2016</td>
<td>Update Policy</td>
<td>Policy updated with literature review through September 1, 2016. References 6-9, 10, 23, and 29-30 added.</td>
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| March 2019 | Update Policy | Policy updated with literature review through August 4, 2018; references 33 and 43-44 added. Policy statement unchanged. |