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

Description of Procedure or Service

Proteomic testing has been proposed as a way to predict outcomes and 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 EGFR tyrosine kinase inhibitors (TKIs).

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. NSCLC, which includes nonsquamous carcinoma (adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell carcinoma, causes about 85% of lung cancer cases. Treatment approaches generally include surgery, radiotherapy, and chemotherapy, either alone or in combination, depending on the disease stage and tumor characteristics.

However, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication, and up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have brief responses, with a median time to progression of 3 to 5 months. Second-line chemotherapy after platinum-based chemotherapy is associated with small improvements in time to progression. However, genetic abnormalities in NSCLC and the development of therapies targeted to those abnormalities have prompted interest in tests to predict response to targeted therapies.

Genetic Alterations in NSCLC

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 EGFR and crizotinib targeting the ALK gene rearrangement.

EGFR Mutations in NSCLC

The EGFR, a 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 EGF receptor, 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.

Mutations 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 mutations in NSCLC varies by population, with the highest prevalence in nonsmoking, Asian women, with adenocarcinoma, in whom EGFR mutations have been reported to be up to 30% to 50%. The
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reported prevalence of EGFR mutations in lung adenocarcinoma patients in the United States is approximately 15%.

ALK Mutations in NSCLC
In about 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 gene and the anaplastic lymphoma kinase 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 mutations are more common in never-smokers or light smokers and tend to be associated with younger age of NSCLC onset, and typically do not occur in conjunction with EGFR mutations.

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

Current Targeted Treatment Options for NSCLC

EGFR-Selective Small Molecule TKIs
Three orally administered EGFR-selective small molecule TKIs have been identified for use in treating NSCLC: gefitinib (Iressa®, AstraZeneca), erlotinib (Tarceva®, OSI Pharmaceuticals), and afatinib (Gilotrif™, Boehringer Ingelheim). Although originally the U.S. Food and Drug Administration (FDA) approved gefitinib, in 2004 a phase 3 trial suggested that gefitinib was not associated with a survival benefit. In May 2005, 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 July 2015, the FDA approved gefitinib for the first-line treatment of patients with metastatic NSCLC for patients with EGFR-mutated tumors. Erlotinib and afatinib also have approval by the FDA.

A 2013 meta-analysis of 23 trials of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC reported improved progression-free survival (PFS) in EGFR mutation-positive patients treated with EGFR TKIs in the first- and second-line settings and for maintenance therapy. Comparisons were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively. Among EGFR mutation-negative patients, PFS was improved with EGFR TKIs compared with placebo for maintenance therapy but not in the first- and second-line settings. Overall survival (OS) did not differ between treatment groups in either mutation-positive or mutation-negative patients. Statistical heterogeneity was not reported for any outcome. The authors concluded that EGFR mutation 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 recommends that patients with NSCLC who are 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 mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.

The primary role for TKIs in NSCLC is for EGFR mutation-positive patients with advanced NSCLC. The use of TKIs in NSCLC in EGFR mutation-negative patients is controversial. The TITAN trial demonstrated no significant differences in OS between erlotinib and chemotherapy as second-line treatment for patients unselected on the basis of EGFR mutation status, with fewer serious adverse events in erlotinib-treated patients. Karampeazis et al reported similar efficacy between erlotinib and standard chemotherapy (pemetrexed) for second-line therapy in patients unselected on the basis of EGFR mutation status. In contrast, in the TAILOR trial, standard chemotherapy was associated with longer OS than erlotinib for second-line therapy in patients with wild-type EGFR. Aulicic et al 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 a Simon’s optimal
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2-stage design, the erlotinib plus docetaxel strategy was rejected, with 18 of 73 patients in the erlotinib plus docetaxel arm achieving PFS at 15 weeks compared with 17 of 74 patients in the docetaxel arm.

In 2016, Cicenas et al reported results of the IUNO RCT, which compared maintenance therapy with erlotinib followed by second line chemotherapy if progression occurred to placebo followed by erlotinib if progression occurred in 643 patients with advanced NSCLC with 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. Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. The benefits of cetuximab in NSCLC have been questioned by the National Comprehensive Cancer Network. Panitumumab is not generally used in NSCLC.

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 and nivolumab, 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.

Other Targeted Therapies
Crizotinib is a novel MET-, ROS-1-, and ALK-TKI, which is associated with improved PFS in patients with advanced NSCLC that is ALK gene rearrangement-positive. Crizotinib is considered first-line therapy for advanced ALK-positive lung adenocarcinoma.

Two other small molecule TKIs designed to selectively bind to and inhibit ALK which have FDA approval include ceritinib and alectinib.

Proposed targeted therapies for other genetic alterations in NSCLC are trastuzumab for HER2 mutations, crizotinib for MET amplification and ROS-1 rearrangement, vemurafenib and dabrafenib for BRAF mutations 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, which may vary over time and in response to selected stressors, and proteomics refers to the large-scale comprehensive study of a specific proteome. A cancer cell’s proteome is related to its genome and to genomic alterations, but may not be static over time. The proteome may be measured with mass spectrometry 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.

For NSCLC, 1 commercially available serum-based test, VeriStrat® (Biodesix Inc., Boulder, CO) has been developed that is proposed to predict response to TKIs. The test relies on a predictive algorithm based on matrix-assisted laser desorption ionization (MALDI) mass spectrometry (MS) analysis of pretreatment serum to generate a “good” or “poor” assessment for response to TKIs. VeriStrat has been proposed as a method to predict response to erlotinib in patients with NSCLC after failure of treatment with first-line therapy. Proposed uses have been in addition to EGFR testing, or in patients who do not have tumor samples available for EGFR testing.
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Although the VeriStrat MALDI-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 (SELDI/TOF) mass spectrometry, and alternative predictive algorithms, in the assessment of proteomic predictors of lung cancer risk.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Proteomic testing for targeted therapy in non-small cell lung cancer is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

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

Not applicable.

When Proteomic Testing for Targeted Therapy in Non-Small Cell Lung Cancer is not covered

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. BCBSNC does not provide coverage for investigational services or procedures.

Policy Guidelines

For individuals with EGFR negative or EGFR status unknown non-small-cell lung cancer with disease progression after first-line treatment who receive management with a serum proteomic test to select targeted therapy, the evidence includes 1 prospective study evaluating the test’s use in predicting response to EGFR TKI therapy and retrospective studies evaluating the prognostic ability of this testing. Relevant outcomes are overall survival and disease-specific survival.

Although a limited body of literature exists for analytic validity of proteomic testing to predict response to epidermal growth factor receptor (EGFR) TKIs for NSCLC in general, at least 1 study reports good test reproducibility for the most widely studied proteomic test, the VeriStrat assay. The evidence from retrospective studies supports the clinical validity of proteomic testing in determining the prognosis of patients with advanced NSCLC who are treated with EGFR TKIs, but due to heterogeneity in the treatment regiments used, it is difficult to determine specific populations for whom proteomic testing is prognostic. Evidence from 1 prospective study suggests that VeriStrat discriminates between patients.
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who are likely to respond to EGFR TKI therapy. If EGFR-TKI therapy were used as a standard of care in patients who are EGFR-unknown or -negative in the second- or third-line setting, proteomic testing could be used to select patients who are least likely to benefit, and those patients could be offered chemotherapy as an alternative. RCT evidence has suggested that erlotinib is not beneficial for EGFR-unknown or -negative patients in the second-line setting, and clinical guidelines do not support its use. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81538*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


Senior Medical Director Review 10/2014


**Policy Implementation/Update Information**

11/25/14 New policy developed. 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. Senior medical director review. Reference added. (lpr)

5/26/15 Specialty Matched Consultant Advisory Panel review 4/29/2015. No change to policy. (lpr)

11/24/15 Updated the description and policy guidelines sections. Removed the regulatory status section. Added CPT code 81538 to the Billing/Coding section for effective date 1/1/2016.
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No change to policy statement. (lpr)

(lpr)

4/28/17  Updated Description and Policy Guidelines sections. Reference added. Specialty 
Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. 
(lpr)

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