BlueCross BlueShield Federal Employee Program.

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

Effective Date: April 15, 2018

Related Policies:
2.04.62 Proteomics-Based Testing Related to Ovarian Cancer

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 (TKIs).

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 of 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.

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

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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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).

RATIONALE

Summary of Evidence

For individuals with *EGFR*-negative or *EGFR*-status unknown NSCLC with disease progression after first-line treatment who receive management with a serum proteomic test to select targeted therapy, the evidence includes RCTs and observational studies. Relevant outcomes are overall survival and disease-specific survival. A limited body of evidence exists for the analytic validity of proteomic testing to predict response to EGFR TKIs for NSCLC in general. At least 1 study has reported good test reproducibility for the widely studied proteomic test, the VeriStrat assay. The literature related to the clinical validity of proteomic testing in patients with advanced NSCLC consists of 2 RCTs in patients who failed first-line chemotherapy and several retrospective analyses of clinical trials of EGFR TKIs, with or without other therapies. The evidence is limited by heterogeneity in the treatment regimens used and patient population characteristics. Most studies, including the 2 RCTs (PROSE and EMPHASIS), found that classification based on proteomic testing (ie, VeriStrat "good" vs "poor") is associated with survival Within the VeriStrat "poor" group, one of the trials—but not the other—found a significantly longer overall survival with erlotinib than with chemotherapy. However, it is not clear that identifying VeriStrat status is useful for selecting second-line therapy. In both RCTs, there was no significant benefit using erlotinib compared with chemotherapy on progression-free survival or overall survival, making the utility of VeriStrat in this population uncertain. No direct evidence for a serum proteomic test for the selection of a NSCLC treatment strategy was identified. Absent direct evidence, a chain of evidence could be used to support the use of the VeriStrat assay to select patients for 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 the third-line setting, proteomic testing could be used to select patients who are least likely to benefit. However, given the evidence from the available trials and the lack of support from guidelines (eg, National Comprehensive Cancer Network) for EGFR TKIs in this setting, EGFR-TKI therapy is no longer standard therapy for any *EGFR*-negative or -unknown patients in the second-line setting. 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 guidelines on the management of non-small-cell lung cancer (NSCLC; v.8.2017) 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]

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EGFR-Positive Populations

Erlotinib, afatinib, or gefitinib are recommended as first-line therapy for patients with advanced or metastatic NSCLC with *EGFR*-sensitizing variants (category 1 recommendation). If the variant is discovered during first-line chemotherapy, the National Comprehensive Cancer Network recommends completing planned chemotherapy, including maintenance therapy, or interrupting followed by erlotinib, afatinib, or gefitinib.

For *EGFR*-positive patients who have progression on a tyrosine kinase inhibitor (TKI), T790M testing is recommended. Treatment options following progression include local therapy, osimertinib (if T790M-positive; category 1 recommendation), or continuation of erlotinib, afatinib, or gefitinib, depending on the level and location of symptoms.

EGFR-Negative or -Unknown Populations

For patients with adenocarcinoma, large cell, NSCLC not otherwise specified of ECOG Performance Status score of 0, 1, or 2 who are programmed death ligand 1– and *ROS1*-negative or -unknown, and without *ALK* (anaplastic lymphoma kinase) rearrangements or *EGFR*-sensitizing variants, systemic chemotherapy is recommended. For patients who have progression on first-line systemic chemotherapy, with good performance status, treatment options include the following:

- Systemic immune checkpoint inhibitors (preferred):
  - Nivolumab (category 1 recommendation); OR
  - Pembrolizumab (category 1 recommendation); OR
  - Atezolizumab (category 1 recommendation); OR
- Other systemic therapy:
  - Docetaxel; OR
  - Pemetrexed; OR
  - Gemcitabine; OR
  - Ramucirumab and Docetaxel

American Society of Clinical Oncology

In 2011, the American Society of Clinical Oncology issued a provisional clinical opinion on *EGFR* variant testing for patients with advanced NSCLC considering first-line EGFR-TKI therapy.[3] The opinion concluded that such patients who have not previously received chemotherapy or an EGFR-TKI should undergo *EGFR* variant testing to determine whether chemotherapy or an EGFR-TKI is appropriate first-line treatment.

In 2015, the Society also updated its clinical practice guidelines on systemic therapy for stage IV NSCLC.[33] The guidelines included a recommendation on first-line treatment of patients without an *EGFR*-sensitizing variant, but did not include specific recommendations on second- or third-line treatment of patients without an *EGFR*-sensitizing variant.

College of American Pathologists et al

In 2013, the College of American Pathologists and two other medical associations published joint evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR-TKI therapy.[34] Based on excellent quality evidence (category A), the guidelines recommended *EGFR* variant testing in patients with lung adenocarcinoma regardless of clinical characteristics (eg, smoking history).

American College of Chest Physicians

The American College of Chest Physicians updated its evidence-based clinical practice guidelines on the treatment of stage IV NSCLC in 2013.[35] 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

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compared with first-line platinum-based therapy in patients with *EGFR* variants, especially exon 19 deletion and L858R. Moreover, the College recommended "testing patients with NSCLC for *EGFR* mutations at the time of diagnosis whenever feasible, and treating with first-line EGFR-TKIs if mutation-positive."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Novitas Solutions established a local Medicare coverage determination for the VeriStrat test in June 2013, which serves as a national coverage determination because the test is only offered at a single lab within the local carrier's coverage region. The coverage determination document noted: "The VeriStrat® assay (NOC 84999*)* is a mass spectrophotometric, serum-based predictive proteomics assay for NSCLC patients, where 'first-line' *EGFR* mutation testing is either wild-type or not able to be tested (e.g., if tissue might not be available)."[36]

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POLICY HISTORY

Date	Action	Description
December 2014	New Policy	Policy created with literature review. Proteomic testing considered investigational for all indications in the management of non-small cell lung cancer.
March 2016	Update Policy	Policy updated with literature review through September 1, 2016. References 6-9, 10, 23, and 29-30 added.
March 2018	Update Policy	Policy updated with literature review through September 11, 2017; reference 10, 23, 26, 29, and 31 added. Policy statement unchanged.

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