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

Effective Date: July 15, 2018

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

Proteomic Testing for Systemic 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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.

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).

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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*-variant status without prior systemic therapy, there were 5 studies that assessed the use of VeriStrat (good or poor) as a prognostic test to discriminate between overall survival (primary outcome) progression-free survival (secondary outcome) 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 did not report outcomes based on variant status. One observational nonrandomized study with prospective sample collection for proteomic testing prior to NSCLC treatment reported the percentage of participants who were *EGFR*-negative but did not report outcomes based on variant status. This was also the only study that included a first-line treatment that is consistent with current guideline-based recommendations: platinum-doublet-based chemotherapy with cisplatin or carboplatin in combination with 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 and radiotherapy have been successfully 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 first-line systemic 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 of 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 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. 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 prognostic 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 multivariable 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. 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 prior, 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 3 retrospective studies and 2 RCTs. 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 correlated 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, a multivariable 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 was 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 guidelines on the management of non-small-cell lung cancer (NSCLC; v.3.2018) 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 unknown patients as well as for patients in either category who have progressed on therapy are provided.

American Society of Clinical Oncology

In 2017, the American Society of Clinical Oncology updated its clinical practice guidelines on systemic therapy for stage IV NSCLC.[44] New or revised recommendations include the following: recommendations for first-line treatment for patients with non-squamous cell carcinoma or squamous cell carcinoma (without positive markers, eg, EGFR/ALK/ROS1), based on programmed death-ligand 1 (PD-L1) expression, second-line treatment in patients who received first-line chemotherapy, without prior immune checkpoint therapy based on PD-L1 expression, as well as recommendations for those patients who cannot receive

immune checkpoint inhibitor. Recommendations are included for patients with a sensitizing EGFR variant, disease progression after first-line epidermal growth factor receptor tyrosine kinase inhibitor therapy based on the results of T790M variant testing and patients with *ROS1* gene rearrangement without prior crizotinib may be offered crizotinib, or if they previously received crizotinib, they may be offered chemotherapy.

In 2018, the Society published an endorsement of other medical associations (College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology) clinical practice guideline for molecular testing for the selection of patient with lung cancer for treatment with targeted tyrosine kinase inhibitors.[45]

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.[46] 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. 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)."[47]

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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.
June 2018	Update Policy	Policy updated with literature review through March 31, 2018; references 2-4, 14, 17-23, 25, 33-34, and 44-45 added. Policy statement unchanged. Policy title changed to reflect expanded scope of PICO table.