VeriStrat Testing for NSCLC TKI Response

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Introduction

VeriStrat testing for NSCLC TKI response is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
VeriStrat	81538

Criteria

VeriStrat testing is not currently supported in clinical practice guidelines for the treatment of advanced NSCLC and the published evidence does not independently meet the criteria for coverage for this indication.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

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What is VeriStrat testing for non-small cell lung cancer?

The aim of the VeriStrat® test is to assess overall prognosis in advanced NSCLC and to predict treatment response to TKIs, single agent chemotherapy, and/or PDL1 inhibitors.[1,2]

- NSCLC is any type of cancer of the lung epithelial cells that is not classified as small-cell lung cancer.[3]
- Although associated with cigarette use and smoke exposure, NSCLC can be diagnosed in individuals who have never smoked.[3]
- Treatment selection in NSCLC may be guided by molecular genetic testing:
  - Approximately 15-25% of individuals with NSCLC have activating mutations in the EGFR gene. These individuals display improved progression-free survival following treatment with EGFR TKI therapy, such as erlotinib, afatinib, or osimertinib.[4-6]
  - Another 5-9% of individuals with NSCLC have ALK or ROS-1 rearrangements and are treated with inhibitors, including crizotinib (Xalkori).[6,7]
  - An additional 10% of individuals with NSCLC harbor alterations that are also amenable to FDA approved inhibitors including: activating BRAF or ERBB2 (HER2) mutations, MET amplification or exon 14 skipping mutations, or fusions involving RET, NTRK1, NTRK2, or NTRK3.[6]
- For the remaining approximately 50% of individuals who are negative for these targetable alterations, other therapies are used as first-line treatment (including chemotherapy and/or PDL1 inhibitors).[2,6] However, for individuals who fail front-line therapy, EGFR inhibitors can be considered as a potential option.[8,9] This applies in particular to individuals whose tumors express an increased number of copies of EGFR (even without EGFR mutations).[9,10]

Test information

Introduction

VeriStrat is a proprietary, serum-based proteomic test designed to be an adjunct to a conventional clinical workup and combined with the individual's clinical history, other diagnostic tests, and clinicopathologic factors.[1]

- The test has been developed to measure an individual's immune response to NSCLC and help determine if an individual may have a more aggressive cancer. VeriStrat is currently marketed as part of the IQLung treatment guidance.[1]
- The VeriStrat test result is reported as good, poor, or indeterminate.[1] The results are also intended to provide "a broader view of each patient's disease state to empower teams with a testing strategy for any stage of NSCLC to help expedite personalized treatment decisions."[1]

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  - **VSGood results:** A good result indicates that an individual is more likely to benefit from standard of care (SOC) treatment, including immunotherapy regimens, and have better overall survival (OS).[1]
  - **VSPoor results:** A poor result indicates that an individual wil be less likely to benefit from SOC treatment and will likely have decreased OS. These individuals may benefit from expedited treatment initiation or alternative treatment strategies such as novel combination of therapies, clinical trials, and/or palliative care.[1]
  - **Indeterminate results:** In rare instances (< 2%), a test result of indeterminate is reported, indicating that a VSGood or VSPoor classification could not be confirmed.
- VeriStrat is not a replacement for assays designed to detect targetable oncogenic drivers (including EGFR, BRAF, ALK, ROS, MET, RET, or NTRK1/2/3).

Guidelines and evidence

National Comprehensive Cancer Network

Previous National Comprehensive Cancer Network (NCCN) guidelines for the treatment of NSCLC supported the use of proteomic tests to evaluate potential therapies in advanced NSCLC. However, likely due to technical advances, availability of next generation sequencing testing for solid tumors, and treatment options, available current NCCN (2024) guidelines no longer incorporate these proteomic tests into their NSCLC evaluation algorithms.[11]

- Previous EviCore criteria (VeriStrat Testing for NSCLC TKI Response) were largely based on the 2015 NCCN Guidelines. These recommended proteomic testing for individuals with advanced NSCLC who were either EGFR wild type or had an unknown mutation status. For these individuals, the NCCN stated that those with a “Poor” result should not be offered second-line erlotinib therapy.
- In contrast, current NCCN guidelines for NSCLC no longer include specific recommendations for proteomic testing; there is no mention of proteomic testing or the use of VeriStrat for NSCLC.

Selected Relevant Publications

The available peer-reviewed clinical validity studies assessed the predictive performance of VeriStrat-directed erlotinib therapy compared with chemotherapy in individuals who were either EGFR wild type or had an unknown EGFR mutation status and had progressed after first-line treatment. These studies do not align with the NCCN treatment pathway for individuals with EGFR wild-type or unknown EGFR status with NSCLC and progression after first-line treatment. The NCCN treatment pathways do not include erlotinib as a recommended agent in either case. For lung cancers with

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unknown mutational status, NCCN stated that these should be treated as though they do not harbor driver oncogenes.[11] Therefore, to definitively establish clinical validity and predictive power, studies are needed that evaluate VeriStrat in the context of randomized controlled trials evaluating guideline-recommended therapies for NSCLC.

The evidence base for VeriStrat is large and of low quality.[12-34] The overall evidence base for predictive use is also characterized by several study design limitations. For example, VeriStrat was not used to determine treatment in the available studies and the majority of the study authors reported that treatment selection was based on standard of care. In addition, a “VSGood” result claims to identify individuals with NSCLC who are EGFR wild-type but still likely to benefit from EGFR-TKI therapy. Yet the clinical validity studies did not consistently test for EGFR variants and, consequently, the true relationship between VeriStrat results, EGFR status, and survival cannot be definitively understood. There was a lack of direct clinical utility studies identified in the scientific literature that compared survival outcomes of patients where treatment selection was guided by VeriStrat classification to those treated with SOC.

Similar flaws to those observed in the publications assessing response to EGFR inhibitors were also observed in publications addressing more recently approved targeted therapies, including PDL1 inhibitors.

For VeriStrat to demonstrate clinical validity in individuals with NSCLC in light of the NCCN guidelines and some of the original design limitations, additional studies supporting its performance are required.

Regarding the prognostic ability of VeriStrat, the majority of the available evidence predicting disease outcomes included retrospective clinical validity studies which evaluated the test in individuals with advanced NSCLC who were treatment-naïve or had either failed first-line treatment or had a recurrence. To infer how well VeriStrat performed as a prognostic test, these studies examined the degree of association between VSGood or VSPoor scores and survival outcomes. Overall, this evidence base demonstrating the performance of VeriStrat as a prognostic test is of low quality.

A number of individual study limitations were observed that weakened the strength of the evidence base. This includes the VeriStrat score not being used to determine treatment and the variability in testing for activating variants. Also, the adjustments for variant status in survival analyses were inconsistently reported and the relationship between VeriStrat scores and overall survival (OS) as well as progression-free survival (PFS) in study populations with unknown mutational status was not clear.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for VeriStrat Testing for NSCLC TKI Response will ensure that members will not receive testing for which there is not a body of evidence

demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[35] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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