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.

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

Definition

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]

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- 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]
    - **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 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).

References

1. Biodesix Laboratories. Veristrat Proteomic Blood Test. Available at: https://www.biodesix.com/our-tests/iq-lung

2. Chae YK, Kim WB, Davis AA, et al. Mass spectrometry-based serum proteomic signature as a potential biomarker for survival in patients with non-small cell lung cancer receiving immunotherapy. *Transl Lung Cancer Res*. 2020;9(4):1015-1028.

3. National Cancer Institute. Non-Small Cell Lung Cancer Treatment (PDQ) - Health Professional Version. Available at: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq.

4. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361(10):947-57. Available at http://www.nejm.org/doi/full/10.1056/NEJMoa0810699#t=article

5. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA.* 2004;101(36):13306-11. Available at: http://www.pnas.org/content/101/36/13306.full

6. Vu P, Patel SP. Non-small cell lung cancer targetable mutations: present and future. *Precision Cancer Medicine* [Online], 3 (2020): Web. 23 Nov. 2020.

7. Crizotinib prescribing information. Pfizer Inc., New York, NY, USA. Available at: http://labeling.pfizer.com/showlabeling.aspx?id=676

8. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo controlled phase 3 study. *Lancet Oncol.* 2010;11(6):521-9.

9. Wang C, Xu F, Shen J, et al. Successful treatment of lung adenocarcinoma with gefitinib based on EGFR gene amplification. *J Thorac Dis*. 2018;10(11):E779-E783. doi: 10.21037/jtd.2018.10.55

10. Tsao M, Sakurada A, Cutz J, et al. Erlotinib in lung cancer- molecular and clinical predictors of outcome. *N Engl J Med.* 2005;353(2):133-44. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa050736#t=article

11. Riely G, Wood D, Ettinger D, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 5.2024 – April 23, 2024. Non-Small Cell Lung Cancer, available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V5.2024 – April 23, 2024. ©2024 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN

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12. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomized phase 3 Trial. *Lancet Oncol.* 2014;15(7):713-21.

13. Akerley WL, Nelson RE, Cowie RH, et al. The impact of a serum based proteomic mass spectrometry test on treatment recommendation in advanced non-small-cell lung cancer. *Curr Med Res Opin.* 2013;29(5):517-25.

14. Gadgeel S, Goss G, Soria JC, et al. Evaluation of the VeriStrat((R)) serum protein test in patients with advanced squamous cell carcinoma of the lung treated with second-line afatinib or erlotinib in the phase III LUX-Lung 8 study. *Lung Cancer*. 2017;109:101-108.

15. Peters S, Stahel RA, Dafni U, et al. Randomized phase III trial of erlotinib versus docetaxel in patients with advanced squamous cell non-small cell lung cancer failing first-line platinum-based doublet chemotherapy stratified by VeriStrat Good versus VeriStrat Poor. The European Thoracic Oncology Platform (ETOP) EMPHASIS-lung Trial. *J Thorac Oncol*. 2017;12(4):752-762.

16. Grossi F, Genova C, Rijavec E, et al. Prognostic role of the VeriStrat test in first line patients with non-small cell lung cancer treated with platinum-based chemotherapy. *Lung Cancer*. 2018;117:64-69.

17. Taguchi F, Solomon B, Gregorc V, et al. Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: a multicohort cross-institutional study. *J Natl Cancer Inst*. 2007;99(11):838-846.

18. Spigel DR, Burris HA, 3rd, Greco FA, et al. Erlotinib plus either pazopanib or placebo in patients with previously treated advanced non-small cell lung cancer: A randomized, placebo-controlled phase 2 trial with correlated serum proteomic signatures. *Cancer*. 2018;124(11):2355-2364.

19. Keshtgarpour M, Tan WS, Zwanziger J, et al. Prognostic value of serum proteomic test and comorbidity index in diversified population with lung cancer. *Anticancer Res*. 2016;36(4):1759-1765.

20. Carbone DP, Salmon JS, Billheimer D, et al. VeriStrat classifier for survival and time to progression in non-small cell lung cancer (NSCLC) patients treated with erlotinib and bevacizumab. *Lung Cancer*. 2010;69(3):337-340.

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21. Grossi F, Rijavec E, Genova C, et al. Serum proteomic test in advanced non-squamous non-small cell lung cancer treated in first line with standard chemotherapy. *B J Cancer*. 2017;116(1):36-43.

22. Stinchcombe TE, Roder J, Peterman AH, et al. A retrospective analysis of VeriStrat status on outcome of a randomized phase II trial of first-line therapy with gemcitabine, erlotinib, or the combination in elderly patients (age 70 years or older) with stage IIIB/IV non-small-cell lung cancer. *J Thorac Oncol*. 2013;8(4):443-451.

23. Kuiper JL, Lind JS, Groen HJ, et al. VeriStrat((R)) has prognostic value in advanced stage NSCLC patients treated with erlotinib and sorafenib. *Br J Cancer*. 2012;107(11):1820-1825.

24. Gautschi O, Dingemans AM, Crowe S, et al. VeriStrat(R) has a prognostic value for patients with advanced non-small cell lung cancer treated with erlotinib and bevacizumab in the first line: pooled analysis of SAKK19/05 and NTR528. *Lung Cancer*. 2013;79(1):59-64.

25. Amann JM, Lee JW, Roder H, et al. Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 3503. *J Thorac Oncol*. 2010;5(2):169-178.

26. Sun W, Yuan X, Tian Y, et al. Non-invasive approaches to monitor EGFR-TKI treatment in non-small-cell lung cancer. *J Hematol Oncol*. 2015;8:95. doi: 10.1186/s13045-015-0193-6

27. Lu S. Development of treatment options for Chinese patients with advanced squamous cell lung cancer: focus on afatinib. *Onco Targets Ther*. 2019;12:1521-1538. doi: 10.2147/OTT.S188296

28. Leal TA, Argento AC, Bhadra K, et al. Prognostic performance of proteomic testing in advanced non-small cell lung cancer: a systematic literature review and meta-analysis. *Curr Med Res Opin*. 2020;36(9):1497-1505. doi: 10.1080/03007995.2020.1790346

29. Muller M, Hummelink K, Hurkmans DP, et al. A Serum Protein Classifier Identifying Patients with Advanced Non–Small Cell Lung Cancer Who Derive Clinical Benefit from Treatment with Immune Checkpoint Inhibitors. *Clin Cancer Res*. 2020;26(19):5188-5197. doi: 10.1158/1078-0432.CCR-20-0538

30. Lee SM, Upadhyay S, Lewanski C, et al.The clinical role of VeriStrat testing in patients with advanced non–small cell lung cancer considered unfit for first-line platinum-based chemotherapy. *Eur J Cancer*. 2019;120:86-96. doi: 10.1016/j.ejca.2019.07.025

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31. Buttigliero C, Shepherd FA, Barlesi F, et al. Retrospective Assessment of a Serum Proteomic Test in a Phase III Study Comparing Erlotinib plus Placebo with Erlotinib plus Tivantinib (MARQUEE) in Previously Treated Patients with Advanced Non-Small Cell Lung Cancer. *The Oncol*. 2020;24(6): e251-e259. doi: 10.1634/theoncologist.2018-0089

32. Jia B, Dong Z, Wu D, et al. Prediction of the VeriStrat test in first-line therapy of pemetrexed-based regimens for advanced lung adenocarcinoma patients. *Cancer Cell Int*. 2020;20(1):590. doi: 10.1186/s12935-020-01662-5

33. Rich P, Mitchell RB, Schaefer E, et al. Real-world performance of blood-based proteomic profiling in first-line immunotherapy treatment in advanced stage non-small cell lung cancer. *J Immunother Cancer*. 2021;9(10):e002989. doi: 10.1136/jitc-2021-002989

34. Koc MA, Wiles TA, Weinhold DC, et al. Molecular and translational biology of the blood-based VeriStrat(R) proteomic test used in cancer immunotherapy treatment guidance. *J Mass Spectrom Adv Clin Lab*. 2023;30:51-60. doi: 10.1016/j.jmsacl.2023.11.001

35. Korenstein D, Chimonas S, Barrow B, et al. Development of a conceptual map of negative consequences for patients of overuse of medical tests and treatments. *JAMA Inter Med*. 2018;178(10):1401-1407.

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