Test Specific Guidelines

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 is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure code
VeriStrat	81538

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]

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 patients with NSCLC have activating mutations in the EGFR gene. These patients display improved progression-free survival following treatment with EGFR TKI therapy, such as erlotinib, afatinib, or osimertinib.[4-6]

Another 5-9% of patients with NSCLC have ALK or ROS-1 rearrangements and are treated with inhibitors, including crizotinib (Xalkori).[6,7]

An additional 10% of patients 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 patients 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 patients who fail front-line therapy, EGFR inhibitors can be considered as a potential option.[8,9] This applies in particular to patients whose tumors express an increased number of copies of EGFR (even without EGFR mutations).[9,10]

Test Information

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

The VeriStrat test result is reported as good, poor, or indeterminate.[1] The results are also intended to set patient expectations, facilitate a discussion about prognosis, improve knowledge to potentially reduce anxiety, and improve quality of life.[1]

VSGood results: A good result indicates that a patient is more likely to benefit from standard of care (SOC) treatment and have better overall survival (OS).[1]

VSPoor results: A poor result indicates that a patient will likely have decreased OS and may benefit from alternative treatment strategies such as novel combination of therapies, NGS testing for rare mutations, non-platinum based regimens, 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 (2022) 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 patients with advanced NSCLC who were either EGFR wild type or had an unknown mutation status. For these patients, 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 patients 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 2022 NCCN treatment pathway for patients 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 overall evidence base for predictive use is also characterized by several study design limitations.[12-33] 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 NSCLC patients 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.

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 patients with NSCLC in light of the NCCN guidelines and some of the original design limitations, additional studies supporting its performance are required.

Direct clinical utility studies were not identified in the scientific literature. Examples of these would include prospective studies comparing survival outcomes in patients who had targeted treatment selected either by VeriStrat classification or through other standard variant analysis methods (such as next-generation sequencing).

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 patients 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.

Criteria

Given that 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, the use of VeriStrat is not considered medically necessary.

Veristrat is not considered medically necessary and therefore, not eligible for reimbursement.

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References

Biodesix Laboratories. Veristrat Proteomic Blood Test. Available at: https://www.biodesix.com/products/biodesix-lung-reflex/veristrat-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.

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.

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

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

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

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

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.

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

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

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. V3.2022. Available at http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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

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

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

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

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platinum-based chemotherapy. *Eur J Cancer*. 2019;120:86-96. doi: 10.1016/j.ejca.2019.07.025

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

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

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

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