



MASSACHUSETTS

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Medical Policy

Proteomic Testing for Systemic Therapy in Non-Small-Cell Lung Cancer

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Policy Number: 709

BCBSA Reference Number: 2.04.125 (For Plan internal use only)

Related Policies

- Cerebrospinal Fluid and Urinary Biomarkers of Alzheimer Disease, #[581](#)
- Proteomics-based Testing for the Evaluation of Ovarian Masses, #[249](#)

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is not a covered service.
Commercial PPO and Indemnity	This is not a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival

Description

Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in the U.S., with an estimated 228,820 new cases and 135,720 deaths due to the disease in 2020.¹ NSCLC accounts for approximately 85% of lung cancer cases and includes nonsquamous carcinoma (adenocarcinoma, large cell carcinoma, other cell types) and squamous cell carcinoma.

Diagnosis

The stage at which lung cancer is diagnosed has the greatest impact on prognosis.² Localized disease confined to the primary site has a 59.8 % relative 5-year survival but accounts for only 18 % of lung cancer cases at diagnosis. Mortality increases sharply with advancing stage. Metastatic lung cancer has a relative 5-year survival of 6.3%. Overall, advanced disease, defined as regional involvement and metastatic, accounts for approximately 80% of cases of lung cancer at diagnosis. These statistics are mirrored for the population of NSCLC, with 85% of cases presenting as advanced disease and up to 40% of patients with metastatic disease.

In addition to tumor stage, age, sex, and performance status are independent prognostic factors for survival particularly in early-stage disease. Wheatley-Price et al (2010) reported on a retrospective pooled analysis of 2349 advanced NSCLC patients from 5 randomized chemotherapy trials.³ Women had a higher response rate to platinum-based chemotherapy than men. Additionally, women with adenocarcinoma histology had greater overall survival than men. A small survival advantage exists for squamous cell carcinoma over non-bronchiolar nonsquamous histology.⁴

The oncology clinical care and research community use standard measures of performance status: Eastern Cooperative Oncology Group scale and Karnofsky Performance Scale.

Treatment

Treatment approaches are multimodal and generally include surgery, radiotherapy, and chemotherapy (either alone or in combination with another treatment, depending on disease stage and tumor characteristics). Per the National Comprehensive Cancer Network (NCCN) guidelines, the clinical management pathway for stage I or II NSCLC is dependent on surgical findings and may involve resection, radiotherapy, chemotherapy, or chemoradiation. First-line chemotherapy regimens for neoadjuvant and adjuvant therapy utilize platinum-based agents (eg, cisplatin, carboplatin) in combination with other chemotherapeutics and/or radiotherapy. Treatment recommendations are based on the overall health or performance status of the patient, presence or absence of metastases, as well as the presence or absence of a treatment-sensitizing genetic variant. These aspects inform the selection of targeted and systemic therapies.¹

For patients who experience disease progression following initial systemic therapy, subsequent treatment regimens are recommended, mainly featuring novel programmed death-ligand 1 (PD-L1) inhibitors. The NCCN also includes recommendations for targeted therapy or immunotherapy in patients with biomarkers, including sensitizing epidermal growth factor receptor (*EGFR*) mutations. For patients with sensitizing *EGFR* mutations, recommendations include first-line therapy with EGFR tyrosine kinase inhibitors (TKIs) afatinib, erlotinib, dacomitinib, gefitinib, erlotinib plus ramucirumab, erlotinib plus bevacizumab (nonsquamous), or osimertinib and subsequent therapy with osimertinib. The NCCN does not make any recommendations for the use of EGFR TKIs in the absence of a confirmed sensitizing *EGFR* mutation. Initial systemic therapy recommendations can be considered for multiple, symptomatic, systemic lesions.¹

Genomic Alterations

Several common genetic alterations in NSCLC have been targets for drug therapy, the most well-established of which are TKIs targeting the EGFR and crizotinib targeting the anaplastic lymphoma kinase (*ALK*) gene rearrangement.

***EGFR* Variants**

EGFR, a tyrosine kinase (TK) receptor, is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR-signaling either prevent ligand-binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small molecule TKIs). These targeted therapies dampen signal transduction through pathways downstream to the EGFR, such as the RAS/RAF/MAPK cascade. RAS proteins are G proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and the stimulation of neovascularization.

Variants in 2 regions of the *EGFR* gene, including small deletions in exon 19 and a point mutation in exon 21 (L858R), appear to predict tumor response to TKIs such as erlotinib. The prevalence of *EGFR* variants in NSCLC varies by population, with the highest prevalence in nonsmoking Asian women with adenocarcinoma; for that subpopulation, *EGFR* variants have been reported to as high as 30% to 50%. The reported prevalence of *EGFR* variants in lung adenocarcinoma patients in the U. S. is approximately 15%.²

***ALK* Variants**

For 2% to 7% of NSCLC patients in the U.S., tumors express a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the *ALK* gene (*EML4-ALK*), which is created by an inversion on chromosome 2p.³ The *EML4* fusion leads to ligand-independent activation of *ALK*, which encodes a receptor TK whose precise cellular function is not completely understood. *EML4-ALK* variants are more common in never smokers or light smokers, tend to be associated with younger age of NSCLC onset, and typically do not occur in conjunction with *EGFR* variants.

Testing for the *EML4-ALK* fusion gene in patients with adenocarcinoma-type NSCLC is used to predict response to the small molecule TKI crizotinib.

Other Genetic Variants

There are other genetic variants identified in subsets of patients with NSCLC. The role of testing for these variants is to help select targeted therapies for NSCLC (see policy 2.04.45-Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer).

Targeted Treatment Options

EGFR-Selective Small Molecule Tyrosine Kinase Inhibitors

Orally administered EGFR-selective small-molecule TKIs approved by the U.S. Food and Drug Administration (FDA) for treating NSCLC include: gefitinib, erlotinib, afatinib, dacomitinib, mobocertinib,

and osimertinib. Although the FDA approved gefitinib in 2004, a phase 3 trial has suggested gefitinib was not associated with a survival benefit. In 2003, the FDA revised gefitinib labeling, further limiting its use to patients who had previously benefited or were currently benefiting from the drug; no new patients were to be given gefitinib. However, in 2015, the FDA approved gefitinib as a first-line treatment for patients with metastatic, sensitizing *EGFR*-variant positive NSCLC.

In 2015, osimertinib (Tagrisso), an irreversible selective *EGFR* inhibitor that targets T790M variant-positive NSCLC, received the FDA approval for patients with T790M variant-positive NSCLC who have progressed on an *EGFR* TKI.

A meta-analysis by Lee et al (2013) assessing 23 trials on the use of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC reported improved progression-free survival (PFS) in *EGFR* variant-positive patients treated with *EGFR* TKIs in the first- and second-line settings and as maintenance therapy.⁷ Comparators were chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings. Among *EGFR* variant-negative patients, PFS was improved with *EGFR* TKIs compared with placebo for maintenance therapy but not in the first- and second-line settings. OS did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcomes. Reviewers concluded that *EGFR*-variant testing is indicated to guide treatment selection in NSCLC patients.

On the basis of the results of 5, phase 3 randomized controlled trials, the American Society of Clinical Oncology recommended in 2011 that patients with NSCLC being considered for first-line therapy with an *EGFR* TKI (patients who have not previously received chemotherapy or an *EGFR* TKI) should have their tumor tested for *EGFR* variants to determine whether an *EGFR* TKI or chemotherapy is the appropriate first-line therapy.⁸

The primary target population for TKIs in NSCLC is for *EGFR* variant-positive patients with advanced NSCLC. The use of TKIs in NSCLC for patients with non-sensitizing, wild-type *EGFR*-variant status is controversial. The TITAN trial as reported by Ciuleanu et al (2012) demonstrated no significant differences in OS between erlotinib and chemotherapy as a second-line treatment for patients unselected on the basis of *EGFR*-variant status, with fewer serious adverse events in erlotinib-treated patients.⁹ Karampeazis et al (2013) reported similar efficacy between erlotinib and standard chemotherapy (pemetrexed) for second-line therapy in patients unselected on the basis of *EGFR*-variant status.⁹ By contrast, in the TAILOR trial, as reported by Garassino et al (2013), standard chemotherapy was associated with longer OS than erlotinib for second-line therapy in patients with wild-type *EGFR*.¹⁰ Auliac et al (2014) compared sequential erlotinib plus docetaxel with docetaxel alone as second-line therapy among patients with advanced NSCLC and *EGFR* wild-type or unknown status.¹¹ Based on Simon's optimal 2-stage design, the erlotinib plus docetaxel strategy was rejected. Despite the rejection, it is worth noting that in the erlotinib plus docetaxel arm 18 of the 73 patients achieved PFS at 15 weeks; comparatively, in the docetaxel arm, 17 of 74 patients achieved PFS at 15 weeks.

Cicenas et al (2016) reported on results of the IUNO randomized controlled trial, which compared maintenance therapy using erlotinib followed by second-line chemotherapy if progression occurred with placebo followed by erlotinib if progression occurred in 643 patients who had advanced NSCLC and no known *EGFR* variant.¹² Because there were no significant differences between groups in PFS, objective response rate, or disease control rate, maintenance therapy with erlotinib in patients without *EGFR* variants was not considered efficacious.

Exon 19 deletions and p.L858R point mutations in exon 21 are the most commonly described sensitizing *EGFR* mutations, or mutations in *EGFR* that are associated with responsiveness to *EGFR* TKI therapy. According to the NCCN, most recent data indicate that NSCLC tumors that do not harbor a sensitizing *EGFR* mutation should not be treated with an *EGFR* TKI in any line of therapy.¹³

Proteomics Testing for Selecting Targeted Treatment for Non-Small Cell Lung Cancer

The term *proteome* refers to the entire complement of proteins produced by an organism, or cellular system and *proteomics* refers to the large-scale comprehensive study of a specific proteome. The proteome may differ from cell to cell and may vary over time and in response to selected stressors.

A cancer cell's proteome is related to its genome and genomic alterations. The proteome may be measured by mass spectrometry (MS) or protein microarray. For cancer, proteomic signatures in the tumor or bodily fluids (ie, pleural fluid or blood) other than the tumor have been investigated as a biomarker for cancer activity.

A commercially available serum-based test (VeriStrat) has been developed and proposed to be used as a prognostic tool to predict expected survival for standard therapies used in the treatment of NSCLC. The test is also proposed to have predictive value for response to EGFR TKIs.¹³ The test uses matrix-assisted laser desorption ionization MS analysis, and a classification algorithm was developed on a training set of pretreatment sera from 3 cohorts (Italian A, Japan A, Japan B) totaling 139 patients with advanced NSCLC who were treated with second-line gefitinib.¹⁴ The classification result is either "good" or "poor". Two validation studies using pretreatment sera from 2 cohorts of patients (Italian B, Eastern Cooperative Oncology Group 3503) totaling 163 patients have been reported.

This assay uses an 8-peak proteomic signature; 4 of the 8 have been identified as fragments of serum amyloid A protein 1.¹⁵ This protein has been found to be elevated in individuals with a variety of conditions associated with acute and chronic inflammation.^{16,17,18,19,20} The specificity for malignant biologic processes and conditions has not been determined.²¹ With industry support, Fidler et al (2018) used convenience biorepository samples to investigate 102 analytes for potential correlations between the specific peptide and protein biomarkers and VeriStrat classification.²² The VeriStrat test is currently marketed as a tool to measure a patient's "immune response to lung cancer." Biodesix indicates that a VeriStrat "Good" result indicates "a disease state that is more likely to respond to standard of care treatment," whereas a VeriStrat "Poor" rating indicates a chronic inflammatory disease state associated with aggressive cancer and patients that "may benefit from an alternative treatment strategy." The Biodesix website does not indicate whether the VeriStrat test should be reserved for use in patients with advanced lung cancer.¹³

Although the VeriStrat matrix-assisted laser desorption ionization MS-based predictive algorithm has the largest body of literature associated with it, other investigators have used alternative MS methods, such as surface-enhanced laser desorption ionization/time-of-flight MS, and alternative predictive algorithms, to assess proteomic predictors of lung cancer risk.²³

Best practices for peptide measurement and guidelines for publication of peptide and protein identification have been published for the research community.²⁴

Summary

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.

Summary of Evidence

For individuals with newly diagnosed NSCLC and wild-type *EGFR*-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 (OS), 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*-negative variant status without prior systemic therapy, 5 studies have assessed the use of VeriStrat ("good" or "poor") as a

prognostic test to discriminate between OS (primary) and progression-free survival (PFS) (secondary) outcomes. All studies were retrospective and intended to validate the extent to which the VeriStrat proteomic classification correlated with OS or PFS. Only 1 of the 5 studies reported the percentage of participants who were *EGFR*-negative, but it did not report outcomes based on variant status. One observational, nonrandomized study with prospective sample collection for proteomic testing before NSCLC treatment reported the percentage of participants who were *EGFR*-negative, but it did not report outcomes based on variant status. This was also the only study that included a first-line treatment consistent with current guideline-based recommendations³⁴platinum-doublet-based chemotherapy plus cisplatin or carboplatin plus pemetrexed. The VeriStrat classification was not used to direct the 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 plus radiotherapy have been 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 that the technology results in an improvement in the net health outcome.

For individuals with newly diagnosed NSCLC and unknown *EGFR*-variant status who receive management with a serum proteomic test to predict survival and select treatment, the evidence includes a randomized controlled trial (RCT), 4 retrospective studies, and a prospective study. Relevant outcomes are OS, 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 for the proteomic score based on unknown *EGFR*-variant status. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with NSCLC and wild-type *EGFR*-variant status 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 RCT and a retrospective analysis. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. No studies were identified that reported or analyzed outcomes using the proteomic test as a prognostic tool in *EGFR*-negative variant status populations. The evidence includes an RCT (PROSE) using proteomic testing to predict response to erlotinib compared with chemotherapy as a 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 multivariate model to predict OS, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with OS (hazard ratio for VeriStrat “good” vs “poor,” 1.88; 95% confidence interval, 1.25 to 2.84; $p=.003$). However, 62% of the combined study population was *EGFR*-negative. A retrospective analysis was also performed on the MARQUEE trial, a phase 3 RCT in patients with stage IIIB or IV nonsquamous NSCLC, comparing the patient response to erlotinib in conjunction with either tivantinib or a placebo; patients were stratified by *EGFR* and *KRAS* variant status, sex, smoking history, and treatment history. Protocol treatments were subsequently discontinued by 93% of patients, and the trial discontinued after prespecified interim futility analysis. In a multivariate model to predict OS, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with OS (hazard ratio for VeriStrat “good” vs “poor,” 0.52; 95% confidence interval, 0.40 to 0.67; $p<.001$). Ninety percent of the combined study population was *EGFR*-negative. An interaction between treatment and VeriStrat status was significant for multivariate analysis including *EGFR* status ($p=.036$) but not significant for multivariate analysis including both *EGFR* and *KRAS* variant status ($p=.068$). 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 that the technology results in an improvement in the net health outcome.

For individuals with NSCLC and unknown *EGFR*-variant status 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 2 RCTs and 3 retrospective studies. Relevant outcomes are OS, 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 correlates with OS or PFS. 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, using a multivariate model to predict OS, which included clinical characteristics and *EGFR*-variant status, VeriStrat classification was significantly associated with OS (hazard ratio for VeriStrat “good” vs “poor,” 1.88; 95% confidence interval, 1.25 to 2.84; p=.003). However, 32.6% of the combined study population had unknown *EGFR* status. In the EMPHASIS RCT, there were no significant differences in PFS or OS 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 that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
2/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.
12/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
09/2018	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2018	Annual policy review. Policy title changed.
8/2017	Annual policy review. In the Background, in the discussion of osimertinib, NSCLC variant T890M changed to T790M. 8/1/2017.
5/2017	Annual policy review. Background section clarified programmed death ligand 1 inhibitors are not only used for cancers expressing PD-L1. 5/1/2017
3/2017	Annual policy review. New references added.
1/2016	Annual policy review. New references added.
1/2016	Clarified coding information.
3/2015	New medical policy describing investigational indications. Effective 3/1/2015.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

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[Managed Care Guidelines](#)

References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 7.2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed November 9, 2021.
2. Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Lung and Bronchus Cancer. n.d.; <https://seer.cancer.gov/statfacts/html/lungb.html>. Accessed November 9, 2021.
3. Wheatley-Price P, Blackhall F, Lee SM, et al. The influence of sex and histology on outcomes in non-small-cell lung cancer: a pooled analysis of five randomized trials. *Ann Oncol*. Oct 2010; 21(10): 2023-2028. PMID 20332134
4. Chansky K, Sculier JP, Crowley JJ, et al. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathologic TNM stage in surgically managed non-small cell lung cancer. *J Thorac Oncol*. Jul 2009; 4(7): 792-801. PMID 19458556
5. Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. *J Clin Oncol*. May 20 2011; 29(15): 2121-7. PMID 21482992
6. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol*. Jul 2013; 8(7): 823-59. PMID 23552377
7. Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst*. May 01 2013; 105(9): 595-605. PMID 23594426
8. Ciuleanu T, Stelmakh L, Cicenias S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol*. Mar 2012; 13(3): 300-8. PMID 22277837
9. Karampeazis A, Voutsina A, Souglakos J, et al. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study. *Cancer*. Aug 01 2013; 119(15): 2754-64. PMID 23661337
10. Garassino MC, Martelli O, Brogini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol*. Sep 2013; 14(10): 981-8. PMID 23883922
11. Auliac JB, Chouaid C, Greillier L, et al. Randomized open-label non-comparative multicenter phase II trial of sequential erlotinib and docetaxel versus docetaxel alone in patients with non-small-cell lung cancer after failure of first-line chemotherapy: GFPC 10.02 study. *Lung Cancer*. Sep 2014; 85(3): 415-9. PMID 25082565
12. Cicenias S, Geater SL, Petrov P, et al. Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based chemotherapy (IUNO study). *Lung Cancer*. Dec 2016; 102: 30-37. PMID 27987585
13. Biodesix. VeriStrat proteomic test. 2019; <https://www.biodesix.com/products/lung-cancer/veristrat>. Accessed November 9, 2021.
14. 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*. Jun 06 2007; 99(11): 838-46. PMID 17551144
15. 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*. Apr 2016; 36(4): 1759-65. PMID 27069156

16. Wang DX, Liu H, Yan LR, et al. The relationship between serum amyloid A and apolipoprotein A-I in high-density lipoprotein isolated from patients with coronary heart disease. *Chin Med J (Engl)*. 2013; 126(19): 3656-61. PMID 24112159
17. Santoso A, Kaniawati M, Bakri S, et al. Secretory Phospholipase A2 Is Associated with the Odds of Acute Coronary Syndromes through Elevation of Serum Amyloid-A Protein. *Int J Angiol*. Mar 2013; 22(1): 49-54. PMID 24436584
18. Kotani K, Koibuchi H, Yamada T, et al. The effects of lifestyle modification on a new oxidized low-density lipoprotein marker, serum amyloid A-LDL, in subjects with primary lipid disorder. *Clin Chim Acta*. Nov 2009; 409(1-2): 67-9. PMID 19723514
19. Bozinovski S, Uddin M, Vlahos R, et al. Serum amyloid A opposes lipoxin A to mediate glucocorticoid refractory lung inflammation in chronic obstructive pulmonary disease. *Proc Natl Acad Sci U S A*. Jan 17 2012; 109(3): 935-40. PMID 22215599
20. Filippin-Monteiro FB, de Oliveira EM, Sandri S, et al. Serum amyloid A is a growth factor for 3T3-L1 adipocytes, inhibits differentiation and promotes insulin resistance. *Int J Obes (Lond)*. Aug 2012; 36(8): 1032-9. PMID 21986708
21. Diamandis EP. Analysis of serum proteomic patterns for early cancer diagnosis: drawing attention to potential problems. *J Natl Cancer Inst*. Mar 03 2004; 96(5): 353-6. PMID 14996856
22. Fidler MJ, Fhied CL, Roder J, et al. The serum-based VeriStrat(R) test is associated with proinflammatory reactants and clinical outcome in non-small cell lung cancer patients. *BMC Cancer*. Mar 20 2018; 18(1): 310. PMID 29558888
23. Jacot W, Lhermitte L, Dossat N, et al. Serum proteomic profiling of lung cancer in high-risk groups and determination of clinical outcomes. *J Thorac Oncol*. Aug 2008; 3(8): 840-50. PMID 18670301
24. Abbatiello S, Ackermann BL, Borchers C, et al. New Guidelines for Publication of Manuscripts Describing Development and Application of Targeted Mass Spectrometry Measurements of Peptides and Proteins. *Mol Cell Proteomics*. Mar 2017; 16(3): 327-328. PMID 28183812
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*. Feb 2010; 5(2): 169-78. PMID 20035238
26. 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*. Nov 20 2012; 107(11): 1820-5. PMID 23079575
27. Akerley W, Boucher K, Rich N, et al. A phase II study of bevacizumab and erlotinib as initial treatment for metastatic non-squamous, non-small cell lung cancer with serum proteomic evaluation. *Lung Cancer*. Mar 2013; 79(3): 307-11. PMID 23273522
28. 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*. Jan 2013; 79(1): 59-64. PMID 23122759
29. 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*. Apr 2013; 8(4): 443-51. PMID 23370367
30. 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. *Br J Cancer*. Jan 03 2017; 116(1): 36-43. PMID 27898657
31. Spigel DR, Burris HA, 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*. Jun 01 2018; 124(11): 2355-2364. PMID 29645086
32. Hanna N, Johnson D, Temin S, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. Oct 20 2017; 35(30): 3484-3515. PMID 28806116
33. 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*. Sep 2010; 69(3): 337-40. PMID 20036440

34. 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*. Mar 2018; 117: 64-69. PMID 29395121
35. Herbst RS, Johnson DH, Mininberg E, et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. *J Clin Oncol*. Apr 10 2005; 23(11): 2544-55. PMID 15753462
36. Salmon S, Chen H, Chen S, et al. Classification by mass spectrometry can accurately and reliably predict outcome in patients with non-small cell lung cancer treated with erlotinib-containing regimen. *J Thorac Oncol*. Jun 2009; 4(6): 689-96. PMID 19404214
37. Wu X, Liang W, Hou X, et al. Serum proteomic study on EGFR-TKIs target treatment for patients with NSCLC. *Onco Targets Ther*. 2013; 6: 1481-91. PMID 24204163
38. Yang L, Tang C, Xu B, et al. Classification of Epidermal Growth Factor Receptor Gene Mutation Status Using Serum Proteomic Profiling Predicts Tumor Response in Patients with Stage IIIB or IV Non-Small-Cell Lung Cancer. *PLoS One*. 2015; 10(6): e0128970. PMID 26047516
39. 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, randomised phase 3 trial. *Lancet Oncol*. Jun 2014; 15(7): 713-21. PMID 24831979
40. 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*. Apr 2017; 12(4): 752-762. PMID 28017787
41. Carbone DP, Ding K, Roder H, et al. Prognostic and predictive role of the VeriStrat plasma test in patients with advanced non-small-cell lung cancer treated with erlotinib or placebo in the NCIC Clinical Trials Group BR.21 trial. *J Thorac Oncol*. Nov 2012; 7(11): 1653-60. PMID 23059783
42. 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*. Jul 2017; 109: 101-108. PMID 28577938
43. 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. *Oncologist*. Jun 2019; 24(6): e251-e259. PMID 30139835
44. Scagliotti G, von Pawel J, Novello S, et al. Phase III Multinational, Randomized, Double-Blind, Placebo-Controlled Study of Tivantinib (ARQ 197) Plus Erlotinib Versus Erlotinib Alone in Previously Treated Patients With Locally Advanced or Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol*. Aug 20 2015; 33(24): 2667-74. PMID 26169611
45. 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*. Oct 2019; 120: 86-96. PMID 31499384
46. Akerley WL, Nelson RE, Cowie RH, et al. The impact of a serum based proteomic mass spectrometry test on treatment recommendations in advanced non-small-cell lung cancer. *Curr Med Res Opin*. May 2013; 29(5): 517-25. PMID 23452275
47. Akerley WL, Arnaud AM, Reddy B, et al. Impact of a multivariate serum-based proteomic test on physician treatment recommendations for advanced non-small-cell lung cancer. *Curr Med Res Opin*. Jun 2017; 33(6): 1091-1097. PMID 28277859
48. Hanna NH, Robinson AG, Temin S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. *J Clin Oncol*. Mar 20 2021; 39(9): 1040-1091. PMID 33591844
49. Hanna NH, Schneider BJ, Temin S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. *J Clin Oncol*. May 10 2020; 38(14): 1608-1632. PMID 31990617
50. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society

of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. *J Clin Oncol*. Mar 20 2018; 36(9): 911-919. PMID 29401004

51. Socinski MA, Evans T, Gettinger S, et al. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. May 2013; 143(5 Suppl): e341S-e368S. PMID 23649446