


<b>MEDICAL POLICY</b>	<b>Non-Small Cell Lung Cancer: Tumor Testing for Targeted Therapy (All Lines of Business except Medicare)</b>
<b>Effective Date: 11/1/2022</b>	Medical Policy Number: 194
 11/1/2022	Technology Assessment Committee Approved Date: 7/16  Medical Policy Committee Approved Date: 12/16; 9/17; 5/18; 3/19; 3/2020; 6/2020; 07/2020; 12/2020; 3/2021; 7/2021; 09/2021; 11/2021; 3/2022; 6/2022; 8/2022
Medical Officer	Date

**See Policy CPT CODE section below for any prior authorization requirements**

**SCOPE:**

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Aycin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

**APPLIES TO:**

All lines of business except Medicare (unless otherwise directed by a Medicare medical policy. Note that investigational services are considered “not medically necessary” for Medicare members.)

**BENEFIT APPLICATION**

Medicaid Members

*Oregon:* Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**DOCUMENTATION REQUIREMENTS**

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making
  - Reason (indication) for performing test, including the suspected condition

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- Existing signs and/or symptoms related to reason for current test request
- Prior test/laboratory results related to reason for current test request
- Family history, if applicable
- How results from current test request will impact clinical decision making
- All relevant CPT/HCPCS codes billed

**POLICY CRITERIA**

**Notes:**

- This policy does not address multi-gene panels for the treatment of non-small cell lung cancer. Please refer to the Medical Policy “Next Generation Sequencing for Somatic Solid Tumors (All Lines of Business Except Medicare)” for additional information. (See [Policy Cross References](#) section below).
  - This policy does not address cell-free DNA tests (also known as circulating tumor DNA tests or liquid biopsies) for non-small cell lung cancer. Please refer to the Medical Policy “[Circulating Tumor Cell and DNA Assays For Cancer Management \(All Lines of Business Except Medicare\)](#) for additional information.
  - Please refer to the Pharmacy Coverage Policies for information regarding targeted therapies associated with genetic testing addressed in this policy. (See [Policy Cross References](#) section below)
- I. Genetic testing of tumor tissue for one or any combination of the following (A.-I.) somatic genetic alterations (see [definition](#)) may be considered **medically necessary** for guidance in selecting FDA-approved targeted therapy in patients with metastatic stage IV non-small cell lung cancer (NSCLC):
    - A. *ALK* gene rearrangements
    - B. *BRAF* V600E mutation
    - C. *EGFR* exon 19 deletion
    - D. *EGFR* T790M and/or L858R point mutations
    - E. *HER2 (ERBB2)* mutations
    - F. *MET* high-level amplification
    - G. *MET* exon 14 skipping mutation
    - H. *RET* gene rearrangements
    - I. *ROS1* gene rearrangements
  - II. Genetic testing for expression of the PD-L1 protein in tumor tissue may be considered **medically necessary** for guidance in selecting FDA-approved targeted therapy in patients with metastatic stage IV NSCLC.

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- III. Genetic testing is considered **not medically necessary not covered** for guidance in selecting targeted therapy in patients with metastatic stage IV NSCLC when the criteria (I. or II) above are not met, including, but not limited to the following (A.-C.):
- A. When genetic alterations other than those identified in criterion I. are requested (e.g., *EGFR* exon 20 insertions, S768I and L861Q mutations, or mutations in the *ALK*, *RET* or *ROS1* genes), unless requested as part of a multi-gene panel that meets criteria per the Medical Policy “Next Generation Sequencing for Cancer (All Lines of Business Except Medicare)”
  - B. When a genetic test is requested for targeted therapy that is not FDA-approved for NSCLC and does not have a National Comprehensive Cancer Network (NCCN) category 1 or 2A recommendation.
  - C. Molecular marker testing for which there is no FDA-approved therapies (e.g., *KRAS* or *PIK3CA* mutations).
- IV. Proteomic testing is considered **not medically necessary and not covered** for screening or guidance in selecting targeted therapy in patients with NSCLC (all stages) (e.g. VeriStrat®).
- V. Proteogenomic testing is considered **not medically necessary and not covered** for screening or guidance in selecting targeted therapy in patients with NSCLC (all stages), including but not limited to, the following tests (A.-C.):
- A. Biodesix Lung Reflex® (e.g. VeriStrat® and GeneStrat®)
  - B. GPS Cancer™ Test
  - C. Molecular Intelligence (MI) Profile™

Link to [Policy Summary](#)

## POLICY GUIDELINES

### Definitions

*Somatic mutation*: A mutation that is acquired at some time during a person’s life after conception. Somatic mutations are present only in certain cells, such as cancer cells, and are not found in the germ cells.

### Clinical Utility

Establishing the clinical utility of any test is a key component in determining its ultimate usefulness. Clinical utility may be established when published evidence demonstrates test results can be used to:

1. Guide treatment, management, or preventive decisions; and

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2. Those decisions lead to improved primary health outcomes.

Comprehensive Testing

Numerous comprehensive panel tests are available which test for various combinations of genes and/or proteins in an attempt to guide therapy decisions. These panels may contain various types of tests including protein, transcript, gene, mutation, rearrangement, fusion, deletion, insertion, and amplification testing. Some well-designed tests include only components that have demonstrated clinical utility for metastatic NSCLC therapy. However, other tests include a broader range of components for which the clinical utility of testing is not yet established. It is not recommended that patients undergo panel testing which contains components with unknown clinical significance as test results may lead to unnecessary interventions which is not supported by current evidence or practice standards. Therefore, the clinical utility of each components included in a test must be demonstrated in order to establish the medical necessity of the panel. This principle applies to all types of tests, including but limited to genetic tests, genomics, transcriptomics (assessing RNA) and proteomics.

**CPT CODES**

**Note:** Codes which may be billed for molecular testing addressed in this policy include, but are not limited to, the following:

All Lines of Business except Medicare	
Prior Authorization Required	
81210	<i>BRAF</i> (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81235	<i>EGFR</i> (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81275	<i>KRAS</i> (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	<i>KRAS</i> (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

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81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
<b>Not Covered</b>	
0080U	Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein m130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy
0092U	Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
<b>Unlisted Codes</b>	
All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then <b>prior-authorization is required.</b>	
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

**DESCRIPTION**

**Background**

Lung cancer is the leading cause of death in the United States, with over 234,000 new cases and 154,000 deaths estimated in 2018. Fewer than 18% of patients with lung cancer have an overall survival of greater than five years after diagnosis. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers.<sup>1</sup>

**Targeted Therapy for Non-Small Cell Lung Cancer (NSCLC)**

Treatment of NSCLC has evolved in the past decade, largely due to the advances in understanding of the molecular abnormalities underlying cancer development and progression. For NSCLC, evaluation of specific molecular abnormalities in several genes is now routinely used to guide treatment-making decisions for the selection of first-line and second-line molecule- or mutation-specific targeted therapies. Examples of specific molecular abnormalities identified in NSCLC are described below.

In addition to testing for specific molecular abnormalities through single gene and/or single protein tests and small panel tests, several laboratories have marketed larger, more comprehensive tests, with the

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intention of detecting other somatic mutations. These comprehensive tests typically include large numbers of genes, genetic rearrangements, and/or proteins associated with more than one oncologic indication, thereby increasing the likelihood of detecting abnormalities not specific and of unknown significance. Furthermore, the large majority of the components in these comprehensive tests do not currently have FDA-approved therapies. Examples of comprehensive molecular tests currently being marketed and/or evaluated for NSCLC therapy guidance are described below.

A list of companion diagnostic molecular tests to detect alterations for which there are U.S. Food & Drug Administration (FDA)-approved targeted therapies for NSCLC may be found in the Regulatory Status section below.

**Examples of Molecular Markers and Tests Used to Guide Targeted Therapy for NSCLC**

*EGFR* (Epidermal Growth Factor Receptor) Gene Alterations

The *EGFR* gene encodes a tyrosine kinase receptor that is often mutated in a number of malignancies, including NSCLC.<sup>1</sup> The most common genetic alterations in the *EGFR* gene, which are deletions in exon 19 and point mutations in exons 20 and 21 (T790M and L858R, respectively), are associated with responsiveness several FDA-approved *EGFR* tyrosine kinase inhibitors (TKIs). There are several other alterations in the *EGFR* gene, which have been identified, such as insertions in exons 19 and 20, and point mutations (L861Q, G719X, and S68I). However, these alterations are considerably less common and their responsiveness to TKIs has not been well established. Acceptable testing methods to detect *EGFR* genetic alterations, which are approved by the FDA and recommended by the NCCN guidelines, include real-time polymerase chain reaction (RT-PCR), traditional Sanger sequencing and next generation sequencing (NGS). Testing methods NOT recommended include *EGFR* protein expression using immunohistochemistry (IHC) with mutation-specific antibodies, as this approach has not been well validated.

*ALK* (Anaplastic Lymphoma Kinase) Gene Rearrangements

The *ALK* gene encodes a tyrosine kinase receptor that can be rearranged in NSCLC and these rearrangements are associated with responsiveness several FDA-approved *ALK* TKIs.<sup>1</sup> Acceptable testing methods to detect *ALK* rearrangements (FDA-approved and NCCN recommended) include fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), NGS methodologies and RT-PCR.

*ROS-1* (ROS Proto-oncogene 1) Gene Rearrangements

The *ROS1* gene encodes a tyrosine kinase receptor that can be rearranged in NSCLC and these rearrangements lead to fusions with other genes, most commonly CD74, SLC34A2, CCDC6 and FIG.<sup>1</sup> These rearrangements are associated with responsiveness several FDA-approved oral *ROS1* TKIs. Acceptable testing methods to detect *ROS1* rearrangements (FDA-approved and NCCN recommended) include fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), NGS methodologies and RT-PCR.

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### *BRAF* (B-Raf Proto-oncogene) Gene Mutations

The *BRAF* gene encodes a serine/threonine kinase receptor that is often mutated in a number of malignancies, including NSCLC.<sup>1</sup> The presence of a specific mutation in the *BRAF* gene (V600E) is associated with responsiveness to combined therapy with oral inhibitors of the *BRAF* and *MEK* genes that are FDA-approved. There are several other mutations in the *BRAF* gene that have been observed in patients with NSCLC. However, the impact of *BRAF* mutations other than V600E on therapy selection is not well understood at this time. Acceptable testing methods to detect the *BRAF* V600E mutation, which are approved by the FDA and recommended by the NCCN guidelines, include real-time polymerase chain reaction (RT-PCR), traditional Sanger sequencing and next generation sequencing (NGS). Testing methods NOT recommended include *EGFR* protein expression using immunohistochemistry (IHC) with mutation-specific antibodies, as this approach has not been well validated.

### PD-L1 (Programmed Death Ligand 1) Protein Expression

PD-L1 is one of two ligands that can be present on tumor cells that bind to the PD-1 receptor on T-cells. When the PD-L1 ligand is expressed, it binds to the PD-1 receptor, inactivating the T-cell and preventing T-cell mediated cell death.<sup>1,2</sup> NSCLC patients that express PD-L1 on tumor cells may undergo immunotherapies that target either the PD-L1 ligand or the PD-1 receptor. Acceptable testing methods to detect PD-L1 (FDA-approved and NCCN recommended) include IHC.

### *KRAS* (*KRAS* Proto-Oncogene) Gene Mutations

The *KRAS* gene encodes an enzyme called a G protein that activates the MAP/ERK pathway within the cell to transmit signals outside of the cell.<sup>1</sup> Mutations in the *KRAS* gene, most commonly at codon 12, are observed in NSCLC. *KRAS* mutations are thought to impact NSCLC by creating a constitutively active protein that signals through the same pathway as *EGFR*. This oncogenic protein may activate the same pathway independent of *EGFR*, possibly rendering the tumor resistant to TKI therapies. As such, *KRAS* mutations are thought to be prognostic and NOT predictive of TKI therapy. Of note, there are no therapies that target *KRAS* mutations available for any malignancy, including NSCLC.

### Other Genetic Alterations in NSCLC

Other driver mutations have been identified in smaller numbers of NSCLC patients, including *RET* gene rearrangements, *MET* gene amplifications and exon skipping point mutations (e.g. *MET*ex14), and *HER2* (also known as *ERBB2*) gene mutations.<sup>1</sup> Although there are therapies that target these genetic alterations that have been FDA-approved for use in other malignancies, they are not currently approved for patients with NSCLC. Despite this, the NCCN recommends testing of the *MET*, *RET* and *HER2* genes for driver mutations, as they believe these targeted therapies are effective in NSCLC patients.

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Proteomic Tests

A proteomic test is one that evaluates the expression of an individual’s entire complement of proteins at any given time, using mass spectrometry or protein microarray methodologies. Proteomic testing has been proposed as a tool to predict response-to and selection-of targeted therapy for patients with survival outcomes NSCLC as well as predict survival outcomes. One example of a currently available proteomic test is described below.

*VeriStrat® (Biodesix, Inc.)*

The VeriStrat® test is a non-invasive blood-based test intended to provide predictive and prognostic proteomic information for patients with NSCLC who test negative for *EGFR* mutations or whose *EGFR* mutation status is unknown.<sup>3</sup> The test “measures a patient’s response to a growing tumor and the chronic activation of complex proteomic pathways known to be associated with aggressive cancer” and classifies a patient’s response as “good” or “poor”. A VeriStrat “Poor” status is said to indicate more aggressive disease; while patients with a VeriStrat “Good” status are thought to have a more favorable prognosis. In addition, the test proposes to identify patients that may benefit from 1st-line platinum doublet therapy or *EGFR* TKI’s.

Of note, Biodesix offers a test called Biodesix Lung Reflex® that combines both VeriStrat® and GeneStrat®. This would be considered a proteogenomic test, described below).

Proteogenomic Tests

Proteogenomic testing is a term describing a new type of molecular testing that simultaneously examines an individual’s genome and proteome. These tests may use either tissue or blood samples and include analysis of DNA, the RNA and proteins. Currently this type of testing is primarily done in research settings. One example of a currently available proteogenomic test is described below.

*GPS Cancer™ Test (NantHealth, Inc.)*

GPS Cancer™ is a molecular test that integrates proteomics detected by mass spectrometry with whole genome (DNA) and whole transcriptome (RNA) sequencing, of both normal and cancer tissue.<sup>4</sup> This test is intended to inform personalized treatment strategies before treatment begins. The test assays protein biomarkers known to induce drug resistance or indicate drug sensitivity for chemotherapy, monoclonal antibody therapy, hormonal therapy, targeted therapy and immunotherapy. In addition, this test “includes whole genome sequencing of over 20,000 genes and 3 billion base pairs, and incorporates whole transcriptome sequencing of over 200,000 RNA transcripts”.



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## REVIEW OF EVIDENCE

The evidence review below will focus on the clinical utility of molecular tests to determine whether testing improves treatment management or overall patient-relevant health outcomes.

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of molecular testing to guide targeted therapy for metastatic stage IV NSCLC. Below is a summary of the available evidence identified through June 2022.

### ALK Gene Testing

The clinical utility of testing for *ALK* gene rearrangements to guide tyrosine kinase inhibitor (TKI) therapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous clinical trials and nonrandomized studies conducted in recent years on the use of genetic testing for *ALK* rearrangements to inform therapy with TKIs in patients with metastatic NSCLC.<sup>3,5-11</sup>

### BRAF V600E Mutation Testing

The clinical utility of testing for mutations in the *BRAF* gene to guide *BRAF*-specific targeted therapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous clinical trials and nonrandomized studies conducted over the past five years on the use of genetic testing for *BRAF* V600E mutations to inform *BRAF*-specific targeted therapy in patients with metastatic NSCLC.<sup>12-14</sup>

### Epidermal Growth Factor Receptor (EGFR) Gene Testing

The clinical utility of testing for small deletions in exon 19 and point mutations T790M and L858R in the *EGFR* gene to guide tyrosine kinase inhibitor (TKI) therapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous systematic reviews conducted over the past five years on the use of genetic testing of the *EGFR* gene to inform therapy with TKIs in patients with metastatic NSCLC.<sup>15-25</sup>

### PD-L1 Protein Testing

The clinical utility of testing for PD-L1 protein expression to PD-1 pathway-specific immunotherapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous clinical trials and nonrandomized studies conducted in recent years on the use of testing for PD-L1 protein expression PD-1 pathway-specific immunotherapy in patients with metastatic NSCLC.<sup>26-32</sup>

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### ROS1 Gene Testing

The clinical utility of testing for *ROS1* gene rearrangements to guide tyrosine kinase inhibitor (TKI) therapy in patients with metastatic NSCLC has been definitively demonstrated. This evidence has been published as numerous clinical trials and nonrandomized studies conducted recent years on the use of genetic testing for *ROS1* rearrangements to inform therapy with TKIs in patients with metastatic NSCLC.<sup>33-35</sup>

### Additional Actionable Genetic Targets for NSCLC

There is sufficient evidence of clinical utility for the following genetic alterations and their ability to guide targeted treatments for patients with metastatic NSCLC:

- *RET* gene rearrangements<sup>36-39</sup>
- *MET* gene amplifications and exon skipping point mutations (e.g. METex14)<sup>40-46</sup>
- *HER2* (also known as *ERBB2*) mutations<sup>47-49</sup>

This evidence has been published as clinical trials and nonrandomized studies conducted in recent years on NSCLC patients and are supported by strong NCCN recommendations despite not being FDA-approved for NSCLC at this time.

### Other Genetic Alterations in NSCLC

The following tests or test components lack demonstrated clinical utility in patients with NSCLC:

- Uncommon alterations in *EGFR*, including insertions in exon 20 and point mutations: G719X, L861Q, and S768I<sup>2,50-55</sup>
- *KRAS* mutations<sup>4,56-62</sup>
- *PIK3CA* mutations<sup>60</sup>

Evidence regarding these molecular markers is limited by one or more of the following:

- Poor study design including:
  - small sample sizes of primary studies
  - heterogeneity in patient cohorts within and between studies, including heterogeneity in clinical variables including age, ethnicity, smoking status, staging, histological types
  - heterogeneity between trials in terms of treatment regimens administered based on molecular marker status
- Inconsistent or lack of association between positive marker status and prediction of drug efficacy, reported as disease control rate, progression free survival or overall survival.
- Inconsistent or lack of association between positive marker status and prognosis of survival, independent of therapy.

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Therefore, the benefit of utilizing these molecular markers in patients with metastatic NSCLC remains unclear or unknown.

Proteomic Tests

Evidence regarding proteomic testing to guide treatment decisions and provide management-altering prognostic information for NSCLC has been focused primarily on the VeriStrat® assay. Studies reporting on the clinical utility of VeriStrat and other tests such as Nodify XL2, BDX-XL2, and Reveal Lung Nodules test are limited by one or more of the following:

- Body of evidence consists largely of retrospective analyses of clinical trials or physician treatment decisions.<sup>63-66</sup>
- Trials have been heterogeneous in terms of:
  - Evaluating the test for first-line, second-line or third line therapy guidance
  - Treatment regimens used
  - Patient population characteristics
- Trials have reported inconsistent associations of VeriStrat status with survival outcomes.<sup>48,67,68</sup>

In 2021, Hayes published a review of the VeriStrat® test for prognostic use in patients with advanced NSCLC.<sup>69</sup> The review included 2 studies that assessed analytical validity, 6 studies that assesses clinical validity, and 2 studies that assessed clinical utility. No studies reported on the current commercially available VeriStrat test’s analytical validity, but the 2 included studies reported on aspects of the test, showing the test to be reproducible. Among the 6 studies assessing clinical validity, some evidence has shown that the VeriStrat test has prognostic and predictive value. Patients with a VS Good test results had significantly improved progression-free and overall survival compared to patients with a VS Poor test result, irrespective of administered treatment. Evidence also suggests that patients with VS Good test results had better survival outcomes when treated with EDGR TKI therapy rather than placebo or chemotherapy, while there was no difference in outcomes among patient with VS Poor test results. Hayes notes that these clinical validity studies had a number of limitations, including retrospective study design in 5 of 6 studies, lack of placebo control, not powered for the analyses conducted, and unrepresentative patient selections. The 2 studies evaluated for clinical utility through the test’s impact on physician treatment recommendations. Both studies showed that test results influenced physician decisions, yet they did not directly evaluate patient health outcomes and studies were industry funded, offering very-low-quality evidence for the clinical utility of the test.

Hayes rated VeriStrat® test as a “C” for use of the VeriStrat test, stating, “Although there is some published evidence regarding the analytical validity of the test and clinical validity of the test’s classifications to be associated with patients’ overall survival and progression-free survival, the impact on health outcomes has not been demonstrated.”<sup>69</sup>

Therefore, the benefit of utilizing proteomic tests in patients with metastatic NSCLC remains unclear.

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Proteogenomic Tests

Evidence regarding proteogenomic testing to guide treatment decisions and provide management-altering prognostic information for oncologic indications has been focused primarily on the GPS Cancer™ test. Very few studies have reported on the use of proteogenomic tests for diagnosis or prognosis. Studies are needed to standardize and validate proteogenomic testing methods, and once this has been established, the clinical validity and utility of proteogenomic testing can be adequately evaluated. To date, there are no studies reporting on the clinical validity or clinical utility of the GPS Cancer™ test for NSCLC or any other indication. Therefore, the benefit of utilizing proteogenomic tests in patients with metastatic NSCLC is unknown.

**CLINICAL PRACTICE GUIDELINES**

National Comprehensive Cancer Network (NCCN)

The NCCN non-small cell lung cancer (NSCLC) clinical practice guidelines (v3.2022) recommend the following for evaluation of metastatic NSCLC:<sup>1</sup>

- “...(T)he following biomarkers should be tested including *EGFR* mutations, *BRAF* mutations, *ALK* fusions, *ROS1* fusions, *METex14* skipping mutations, *RET* rearrangements, and PD-L1 expression levels.”
- To minimize wasting of tissue, NCCN recommends broad molecular profiling be done as part of biomarker testing using validated panel tests, which assess a minimum of the following potential genetic variants: *EGFR* mutations, *BRAF* mutations, *ALK* fusions and *ROS1* fusions simultaneously, be performed.
- Patients may have rare driver mutations such as *HER2 (ERBB2)* mutations, *RET* gene rearrangements, *MET* gene amplifications, or *MET* mutations; for which these are targeted that are NOT FDA-approved for NSCLC.
  - NCCN recommends these tests to guide targeted therapy in these situations, indicating that there is sufficient evidence that these therapies are effective for patients with metastatic NSCLC.
  - Although NCCN considered these tests to guide “emerging” therapies, they provided a category 2A recommendation for these genetic alterations and specific therapies.
- NCCN acknowledges that in many patients only small biopsy samples may be acquired (typically using minimally invasive methods), and therefore judicious use of tests such as immunohistochemistry for protein analysis and/or diagnosis is recommended in order to conserve tissue for molecular studies.
  - Based on limited tissue samples, NCCN indicates the use of broader molecular profiling tests using a number of appropriate methods (next generation sequencing, multiplex mutation screening, and fluorescent in situ hybridization [FISH]) for markers that have FDA-approved therapies.

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- NCCN recommends broader molecular profiling of genes other than *EGFR*, *BRAF*, *ALK* and *ROS1* may be performed for use in context of clinical trials, but does not address any specific tests by name.
- NCCN states that testing for the *EGFR* mutation in patients who have progressed on first line therapies may be done using a plasma biopsy (also known as cell-free DNA testing or liquid biopsy) if there is insufficient tumor sample left for testing. However, if the plasma biopsy is negative then re-biopsying tumor tissue is recommended if feasible. This statement was based on two small trials (n=58 and 60) which used plasma samples to detect *EGFR* mutations, and one plasma genotyping validation study (n=180 patients). Although the positive predictive value was 79% (one study) and the sensitivity of plasma assays for the T790M mutation ranged from 70-77% (two studies), the test was also reported to have a 30% false negative rate, indicating that tumor biopsy tissue is needed for T790M genotyping.
- NCCN states that circulating tumor DNA (from blood, also known as liquid biopsy or cell-free DNA) can be considered in specific clinical circumstances, most notably:
  - If a patient is medically unfit for invasive tissue sampling; **or**
  - In the initial diagnostic setting, following pathologic confirmation of a NSCLC diagnosis, there is insufficient material for molecular analysis and follow-up tissue-based analysis is planned for patient in which an oncogenic driver is not identified; **or**
  - In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available.

#### American Society of Clinical Oncology (ASCO)

In 2018, ASCO endorsed recommendations published by the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) regarding molecular testing for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors.<sup>70</sup> After making a few small modifications to the 2018 CAP/IASLS/AMP guidelines, ASCO recommended the following:<sup>71</sup>

- The following testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics:
  - *EGFR* mutation testing (neither IHC for expression nor fluorescent or chemiluminescent in situ hybridization for copy number should be used)
  - *ROS1* rearrangement testing (IHC may be used, but a positive IHC result must be confirmed by a molecular or cytogenetic method)
  - *BRAF* mutation testing
  - *ALK* rearrangement testing (IHC or FISH may be used)
- The following tests are not recommended as routine stand-alone assays outside of the context of a clinical trial: *RET*, *HER2 (ERBB2)*, and *MET* testing.

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- There is insufficient evidence to support the use of circulating tumor cell molecular analysis (also known as cell-free [CF] DNA, plasma genotyping or liquid biopsy) to identify *EGFR* mutations for targeted therapy use.

**POLICY SUMMARY**

There is sufficient evidence that genetic testing of certain genetic alterations in the *ALK, EGFR, BRAF, ROS1, RET, MET and/or HER2* genes and/or testing for PD-L1 protein expression provides guidance for targeted therapies for metastatic non-small cell lung cancer (NSCLC) that lead to improvements in progression free and overall survival. In addition, current U.S.-based clinical guidelines recommend the testing of these molecular targets in this patient population. However, there is insufficient evidence of clinical utility and a lack of support by clinical practice guidelines for the testing of additional mutations in the genes noted above, for other genes including *KRAS* or *PIK3CA*.

**INSTRUCTIONS FOR USE**

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

**REGULATORY STATUS**

U.S. Food & Drug Administration (FDA)

According to the FDA, “a companion diagnostic device can be in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.”<sup>3</sup>

Of note, companion diagnostic tests are approved by the FDA based on sufficient clinical validity, as reported as adequate test performance measures like sensitivity, specificity, positive predictive values and/or negative predictive values. FDA-approval does not require evidence of clinical utility.

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### Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

## **POLICY CROSS REFERENCES**

### Health Plans Medical Policies

- Next Generation Sequencing for Somatic Solid Tumors (All Lines of Business Except Medicare)
- [Circulating Tumor Cell and DNA Assays For Cancer Management \(All Lines of Business Except Medicare\)](#)
- [Genetic Counseling \(All Lines of Business Except Medicare\)](#)
- [Genetic Testing: Non-Covered Genetic Panel Tests \(All Lines of Business Except Medicare\)](#)

### Health Plans Pharmacy Policies

- [Injectable Anti-Cancer Medications. Antineoplastics, ORPTCONC102](#)
- Oral Anti-Cancer Medications. Antineoplastics, ORPTCONC103

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