MEDICAL POLICY

POLICY TITLE	**MOLECULAR ANALYSIS (INCLUDING LIQUID BIOPSY) FOR TARGETED THERAPY OR IMMUNOTHERAPY OF NON-SMALL CELL LUNG CANCER**
POLICY NUMBER	**MP- 2.241**

Effective Date:	**1/1/2024**

I. POLICY

In the absence of FDA-labeled contraindications to requested therapies, molecular analyses will be approved as follows:

EGFR Testing

Analysis of somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (*EGFR*), may be considered **medically necessary** to predict treatment response to an FDA- approved therapy in individuals with advanced and metastatic non-small cell lung cancer (NSCLC).

Analysis of tumor tissue for somatic variants in exon 20 (eg, insertion mutations) within the *EGFR* gene, may be considered **medically necessary** to predict treatment response to an FDA-approved therapy in individuals with NSCLC.

Analysis of other *EGFR* variants within exons 22 to 24, or other applications related to NSCLC is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

EGFR Testing – Liquid biopsy/Plasma

At diagnosis: only analysis of somatic variants in exons 19 through 21 (eg, exon 19 deletions, L858R, T790M) within the *EGFR* gene, using plasma specimens to detect circulating tumor (ctDNA) with one of the following

- the cobas EGFR Mutation Test v2,
- Guardant360 CDx test,
- FoundationOne Liquid CDx
- OncoBEAM test, or
- InVisionFirst-Lung test

may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an EGFR tyrosine kinase inhibitor therapy in individuals with advanced or metastatic NSCLC.

Analysis using Agilent Resolution ctDx FIRST or LiquidHALLMARK is considered **investigational**, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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At progression: analysis of the EGFR T790M resistance variant for targeted therapy with osimertinib using plasma specimens to detect ctDNA with one the following:

- the cobas EGFR Mutation Test v2,
- Guardant360 CDx test,
- OncoBEAM test, or
- InVisionFirst-Lung test

may be considered **medically necessary** in patients with advanced or metastatic NSCLC when tissue biopsy to obtain new tissue is not feasible.

Analysis of plasma for somatic variants in exon 20 (eg, insertion mutations) within the *EGFR* gene using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary**.

Plasma Testing When Tissue is Insufficient

Plasma tests for oncogenic driver variants deemed medically necessary on tissue biopsy may be considered **medically necessary** to predict treatment response to targeted therapy for patients meeting the following criteria:

- Patient does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; **OR**
- The patient is considered medically unfit for invasive tissue sampling **AND**
- An FDA-approved test is available

* Follow-up tissue-based analysis is recommended should no driver variant be identified via plasma testing

Analysis of Somatic Rearrangement Variants

Analysis of somatic rearrangement variants using tumor tissue, or plasma testing when tissue is insufficient (as above), to predict treatment response is **medically necessary** in individuals with advanced or metastatic non-small cell lung cancer as follows:

- ALK Testing
- ROS1 Testing
- KRAS Testing
- HER2 Testing
- MET Exon 14 Skipping Alteration Testing

Analysis of somatic rearrangement variants using tumor tissue to predict treatment response is **medically necessary** in individuals with advanced or metastatic non-small cell lung cancer as follows:

- BRAF V600E Testing
- RET Rearrangement Testing

Analysis of somatic rearrangement variants of the above listed genes is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

NTRK Gene Fusion Testing

Analysis of somatic NTRK gene fusions may be considered **medically necessary** to predict treatment response in patients with advanced and metastatic NSCLC.

Analysis of somatic NTRK gene fusions is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

PD-L1 Testing

PD-L1 testing may be considered **medically necessary** to predict treatment response in patients with advanced and metastatic NSCLC.

PD-L1 testing is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

Tumor Mutational Burden

Analysis of tumor mutational burden for targeted therapy in patients with NSCLC is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

*If coverage of a test is requested, but is not listed above, please refer to **MP 2.259** - Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies for additional guidance.*

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

Policy Guidelines

These gene tests, including the ctDNA tests, are intended for use in patients with advanced (stage III or IV) non-small-cell lung cancer.

Guidelines from the National Comprehensive Cancer Network on non-small-cell lung cancer provide recommendations for biomarker testing. Guidelines are updated frequently; refer to the source document for current recommendations. The most recent guidelines recommend that EGFR variants and ALK rearrangement testing and PD-L1 testing (category 1) as well as KRAS, ROS1, BRAF and NTRK1/2/3, MET Exon 14 skipping alteration, RET testing, and HER2 testing (category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell

carcinoma, and non-small-cell lung cancer not otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling, defined as a single assay or a combination of a limited number of assays and that it is acceptable to have a tiered approach based on low-prevalence, co-occurring biomarkers. The guidelines additionally recommend identifying the emerging biomarker, high-level MET amplification, while noting that the definition of this biomarker is evolving and may differ according to the assay used.

The 2018 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology have recommended the following:

> "One set of genes must be offered by all laboratories that test lung cancers, as an absolute minimum: EGFR, ALK, and ROS1. A second group of genes should be included in any expanded panel that is offered for lung cancer patients: BRAF, MET, RET, ERBB2 (HER2), and KRAS, if adequate material is available. KRAS testing may also be offered as a single-gene test to exclude patients from expanded panel testing. All other genes are considered investigational at the time of publication."

Histologic Subtype for Non-Small Cell Lung Cancer (NSCLC) per the NCCN

Histologic Subtype for NSCLC
Adenocarcinoma
Large cell carcinoma
NSCLC not other specified
Squamous cell carcinoma

https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

III. DESCRIPTION/BACKGROUND

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NON-SMALL-CELL LUNG CANCER

Treatment options for non-small-cell lung cancer (NSCLC) depend on disease stage and include various combinations of surgery, radiotherapy, systemic therapy, and best supportive care. Unfortunately, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with

advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30% to 45%. The identification of specific, targetable oncogenic "driver mutations" in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology. Testing for epidermal growth factor receptor (*EGFR*) variants and anaplastic lymphoma kinase (*ALK*) rearrangements is routine in clinical decision making for the treatment of NSCLC. The use of testing for other variants to direct targeted therapy continues to evolve.

EGFR Gene

EGFR, a receptor tyrosine kinase (TK), 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 tyrosine kinase inhibitors [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 stimulation of neovascularization.

Variants in 2 regions of the *EGFR* gene (exons 18-24)—small deletions in exon 19 and a point variant in exon 21 (L858R)—appear to predict tumor response to TKIs such as erlotinib. Likewise, tumors with an acquired exon 20 (T790M) substitution variant appear to respond to osimertinib following the failure of TKI therapy.

The prevalence of *EGFR* variants in NSCLC varies by population, with the highest prevalence in nonsmoking Asian women with adenocarcinoma, in whom *EGFR* variants have been reported to be up to 30% to 50%. The reported prevalence in the white population is approximately 10%.

ALK Gene

ALK is a TK that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement that leads to a fusion gene and expression of a protein with constitutive TK activity that has been demonstrated to play a role in controlling cell proliferation. The *EML4-ALK* fusion gene results from an inversion within the short arm of chromosome 2.

The *EML4-ALK* rearrangement ("*ALK*-positive") is detected in 3% to 6% of NSCLC patients, with the highest prevalence in never-smokers or light ex-smokers who have adenocarcinoma.

BRAF Gene

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the *BRAF* gene is the most frequently mutated in NSCLC, in 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. Most *BRAF* variants occur more frequently in smokers.

ROS1 Gene

ROS1 codes for a receptor TK of the insulin receptor family, and chromosomal rearrangements result in fusion genes. The prevalence of *ROS1* fusions in NSCLC varies from 0.9% to 3.7%. Patients with *ROS1* fusions are typically never-smokers with adenocarcinoma.

KRAS Gene

The *KRAS* gene (which encodes RAS proteins) can harbor oncogenic variants that result in a constitutively activated protein, independent of signaling from the EGFR, possibly rendering a tumor resistant to therapies that target the EGFR. Variants in the *KRAS* gene, mainly codons 12 and 13, have been reported in 20% to 30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers. KRAS variants can be detected by direct sequencing, PCR technologies, or NGS. *EGFR*, *ALK*, *ROS1*, and *KRAS* driver mutations are considered to be mutually exclusive.

HER2 Gene

Human epidermal growth factor receptor 2 (*HER2*) is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. *HER2* is expressed in approximately 25% of NSCLC. *HER2* variants are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.

RET Gene

RET (rearranged during transfection) is a proto-oncogene that encodes a receptor TK growth factor. Translocations that result in fusion genes with several partners have been reported. *RET* fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.

MET Gene

MET amplification is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs.

NTRK Gene Fusions

NTRK gene fusions encode tropomyosin receptor kinase fusion proteins that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma. It is estimated that NTRK gene fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers.

PD-1/PD-L1

Programmed cell ligand-1 (PD-L1) is a transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. Blocking the PD-L1 protein may prevent cancer cells from inactivating T cells.

Tumor Mutational Burden

Tumor mutational burden, a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types, including lung cancer.

Targeted Treatment, Immunotherapy, and Companion Diagnostic Testing

Targeted treatments, immunotherapy, and FDA-approved companion diagnostic tests are available on the FDA site https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

IV. RATIONALE

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Summary of Evidence

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for *EGFR* variants and *ALK* rearrangements, the evidence includes phase 3 studies comparing tyrosine kinase inhibitors (TKIs) (e.g., afatinib, erlotinib, gefitinib, osimertinib, et al) with chemotherapy. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, quality of life (QOL), and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and progression-free survival (PFS), with a reduction in toxicity and improvement in QOL. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for *BRAF* variants and *ROS1* rearrangements, the evidence includes nonrandomized trials and observational studies of BRAF and MEK inhibitors and crizotinib or ceritinib, respectively. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown that combination therapy with dabrafenib and trametinib for *BRAF* V600E- variant NSCLC and crizotinib for NSCLC with *ROS1* rearrangements result in response rates of 60% and 70%, respectively, with acceptable toxicity profiles. In an analysis of 53 patients with *ROS-1* fusion-positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib, the objective response rate was 77%, with a median duration of response of 24.6 months and acceptable toxicity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for *RET* or *MET* gene testing, the evidence includes nonrandomized trials of kinase inhibitors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown efficacy in PFS and duration of response for selpercatinib and pralsetinib in patients with RET-fusion positive NSCLC, and for capmatinib in patients with *MET* Exon 14 skipping alterations, with acceptable toxicity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for KRAS as a technique to predict treatment nonresponse to anti-EGFR therapy with TKIs or testing for HER2 variants to select the use of the anti-EGFR monoclonal antibody cetuximab (Erbitux), the evidence includes post hoc analysis of trials, observational studies, and meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analysis of trials, observational studies, and meta-analyses. Although studies have shown that *KRAS* variants in patients with NSCLC confer a high level of resistance to TKIs, data are insufficient to assess any additional benefit to *KRAS* testing beyond *EGFR* testing. In 2 randomized trials with post hoc analyses of *KRAS* variant status and use of the anti-EGFR monoclonal antibody cetuximab with chemotherapy, *KRAS* variants did not identify patients who would benefit from anti-EGFR antibodies, because outcomes with cetuximab were similar regardless of *KRAS* variant status, Studies for *HER2* variant testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for KRAS to select targeted treatment, the evidence includes a phase 2, open-label trial of sotorasib in patients with KRAS variant NSCLC. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Presence of the KRAS alteration in tissue was confirmed on central laboratory testing with the use of the therascreen KRAS RGQ PCR Kit. Among 124 patients evaluated for the primary outcome, 4 (3.2%) had a complete response and 42 (33.9%) had a partial response, with an acceptable safety profile. Median duration of response was 11.1 months (95% confidence interval [CI]: 6.9 to not evaluable). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive NTRK gene fusion testing, the evidence includes nonrandomized trials of larotrectinib and entrectinib in patients with solid tumors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In 55 patients with consecutively and prospectively identified tropomyosin receptor kinase fusion-positive solid tumors who received larotrectinib, including 4 patients with lung tumors, the overall response rate was 80% (95% CI, 67 to 90). The median PFS had not been reached after a median follow-up duration of 9.9 months (range, 0.7 to 25.9). Responses were observed regardless of tumor type or age of the patient. In an integrated analysis of 3 phase 1-2 trials in patients with NTRK solid tumors who received entrectinib, 10 of whom had NSCLC, response was 57% (95% CI 43.2% to 70.8%) with an acceptable safety profile. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy with fam-trastuzumab deruxtecan-nxki who receive somatic testing for *HER2* variants, the evidence includes a multicenter, blinded, and randomized dose-optimization trial. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity.

In the DESTINY-Lung02 trial, patients with activating *HER2* mutations who have received prior systemic therapy demonstrated an objective response rate (ORR) of 58% (95% CI, 43% to 71%) and median duration of response of 8.7 months (95% CI, 7.1 months to not estimable) when treated with the novel antibody-drug conjugate trastuzumab deruxtecan. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive PD-L1 testing, the evidence includes RCTs comparing immunotherapy to chemotherapy. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In RCTs, patients with high PD-L1 expression had longer PFS and fewer adverse events when treated with anti-PD-L1 monoclonal antibodies than with platinum chemotherapy. In the KEYNOTE trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive tumor mutational burden (TMB) testing, the evidence includes a RCT and retrospective observational studies. In a subgroup analysis of the KEYNOTE trial, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high TMB ($\geq$10 mutations per megabase). In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies. Additionally, there is no consensus on how to measure TMB. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers of EGFR TKIs sensitivity using ctDNA with the cobas EGFR Mutation Test v2, Guardant360 CDx, FoundationOne Liquid CDx, OncoBEAM, or InVision tests(liquid biopsy), the evidence includes numerous studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are OS, disease-specific survival, and test validity. Current evidence does not permit determining whether cobas or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of cobas. The cobas EGFR Mutation Test has adequate evidence of clinical validity for the EGFR TKI-sensitizing variants. The cobas, Guardant360 CDx, and FoundationOne Liquid CDx tests have received FDA-approval as companion diagnostics for EGFR-sensitizing variants and are therefore not subject to extensive evidence review. The OncoBEAM and InVision tests have adequate evidence of clinical validity for the EGFR TKI-sensitizing variants. The U.S. Food and Drug Administration has suggested that a strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the cobas test would result in an overall diagnostic performance equivalent to tissue biopsy. Several additional studies of the clinical validity of cobas have shown it to be moderately sensitive and highly specific compared with a reference standard of tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the cobas test should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients

with EGFR TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. The cobas test can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who progressed on *EGFR* TKIs who receive testing for biomarkers of *EGFR* TKI resistance using ctDNA (liquid biopsy) with tests other than the cobas EGFR Mutation Test v2, Guardant360 CDx, OncoBEAM, or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the other commercially available tests have multiple studies of adequate quality to estimate the performance characteristics for detection of the *EGFR* T790M variant with sufficient precision. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of these methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers of EGFR TKI sensitivity using ctDNA with tests other than the cobas EGFR Mutation Test v2, Guardant360 CDx, OncoBEAM, or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with tissue reference standard. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests other than the cobas, Guardant360 CDx, OncoBEAM, and InVision tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of these methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced-stage NSCLC who are being considered for targeted therapy who undergo testing for ALK rearrangements using FoundationOne Liquid CDx, the evidence includes an exploratory retrospective analysis of data from a RCT comparing crizotinib to alectinib, and 1 clinical bridging study that compared FoundationOne Liquid to another liquid biopsy test. Relevant outcomes are OS, disease-specific survival, and test validity. There are no studies directly comparing FoundationOne liquid to tissue biopsy. Clinical validity has not been demonstrated in multiple well-designed and conducted studies; therefore, a chain of indirect evidence to show clinical utility cannot be established. One nonrandomized trial directly assessed the clinical utility of FoundationOne Liquid to select patients for treatment with alectinib, but this study was limited by its lack of a control group and no comparison to tissue

biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced-stage NSCLC who are being considered for targeted therapy who undergo testing for MET exon 14 skipping alterations using FoundationOne Liquid CDx, the evidence includes a clinical bridging study that compared FoundationOne Liquid to tissue testing using data from a nonrandomized, open-label phase 2 study of capmatinib therapy. Relevant outcomes are OS, disease-specific survival, and test validity. There is no direct evidence of the clinical utility of FoundationOne Liquid to select patients for targeted therapy for capmatinib. Clinical validity has not been demonstrated in multiple well-designed and conducted studies, and therefore a chain of indirect evidence to show clinical utility cannot be established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers other than EGFR using a liquid biopsy to select a targeted therapy, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with the tissue biopsy reference standard. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision for variants other than EGFR. BCBSA found no RCTs providing evidence of the clinical utility of those methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who progressed on EGFR TKIs who receive testing for biomarkers of EGFR TKI resistance using liquid biopsy, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are OS, disease-specific survival, and test validity. For variants that indicate EGFR TKI resistance and suitability for alternative treatments with osimertinib, liquid biopsy is moderately sensitive and moderately specific compared with a reference standard of tissue biopsy. Given the moderate clinical sensitivity and specificity of liquid biopsy, using liquid biopsy alone or in combination with tissue biopsy might result in the selection of different patients testing positive for EGFR TKI resistance. It cannot be determined whether patient outcomes are improved. However, although there is higher discordance in the liquid versus tissue results for the resistance variant, retrospective analyses have suggested that patients positive for T790M in liquid biopsy have outcomes with osimertinib that appear to be similar overall to patients positive by a tissue-based assay. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.. Although the evidence is limited, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published joint guidelines endorsed by American Society of Clinical Oncology with an expert consensus opinion that physicians may use liquid biopsy (cell-free DNA) to identify EGFR T790M variants in patients with progression or resistance to EGFR-targeted TKIs

and that testing of the tumor sample is recommended if the liquid biopsy result is negative. Similarly, the National Comprehensive Cancer Network guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when testing for the T790M resistance variant, liquid biopsy should be considered and when a liquid biopsy is negative tissue-based testing is strongly recommended.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational therefore not covered when used to test for genetic alterations in the geneTMB for targeted therapy in patients with NSCLC:

Procedures codes								
81404	81405	81479						

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Investigational therefore not covered for cell-free DNA testing

Procedure Codes								
0179U	0436U	81479						

Covered when medically necessary (tissue testing):

Procedure Codes								
81191	81192	81193	81194	81210	81235	81275	81276	81401
81457	81458	81459	81404	81405	81445	81450	81455	81479
88342	88363	88365	0022U	0037U	0334U			

Covered when medically necessary for plasma/cell-free DNA testing with cobas EGFR Mutation testv2, Guardant 360 test, OncoBEAM test, FoundationOne Liquid CDx, or InVisionFirst-Lung test OR for plasma testing when tissue is insufficient:

Procedure Codes								
0239U	0242U	0326U	81235	81277	81445	81450	81455	81462
81463	81464	81479	86152	86153				

ICD-10-CM Diagnosis Codes	Description
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
D38.1	Neoplasm of uncertain behavior of trachea, bronchus and lung

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.241	**CAC 4/26/11 New Policy.** Adopted BCBSA (medically necessary).
	CAC 6/26/12 Consensus review. No changes, references updated. FEP variation added.
	12/20/2013 Administrative update. 2013 Codes added
	05/20/13 Administrative update. Code review completed.
	8/1/13 Administrative update. Add Medicare variation referencing LCD L33142.
	CAC 11/26/13 Consensus review. No change to policy statements. Added rationale section. References updated**.**
	7/24/14 Administrative update. For the Medicare variation - For Novitas MAC jurisdictions, the LCD has been assigned a new number. Biomarkers for Oncology LCD changed from L33124 to L34796
	CAC 1/27/15 Minor revision. ▪ Policy title revised to "Molecular Analysis for Targeted Therapy for Non-Small Cell Lung Cancer" for this review. ▪ First policy statement revised to state analysis of two types of somatic mutation within the epidermal growth factor receptor (EGFR) gene -- small deletions in exon 19 and a point mutation in exon 21 (L858R) – may be considered medically necessary to predict treatment response to erlotinib or afatinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. Previously, afatinib was not included and the medically necessary indication as for non-small cell lung cancer.

	▪ A new statement was added that testing for ROS, RET, MET, BRAF and HER2 mutations is considered investigational. ▪ Policy MP-2.240 KRAS Mutation Analysis in Non-Small Cell Lung Cancer (NSCLC) merged with this policy. Background, rationale, references, and guidelines updated. FEP variation updated to reflect combining two policies. (MP 2.240 Info added into this policy). Cellular and histologic classification of NSCLC added to policy guidelines. No coding changes.
	11/2/15 Administrative update. LCD number changed from L34796 to L35396 due to Novitas update to ICD-10.
	CAC 3/29/16 Minor revision. Policy updated only to address *ALK* rearrangement testing. Policy statement added that analysis of somatic rearrangement mutations of the *ALK* gene is considered medically necessary to predict treatment response to crizotinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. Policy statement added that testing for *ALK* gene rearrangements is investigational for all other clinical situations. Reference and rationale update. Coding reviewed.
	1/1/17 Administrative update. Product variation section reformatted.
	CAC 3/28/17 Minor revision. Added testing for T790M mutation in patients who have progressed on or after EGFR-TKI therapy to the EGFR Gene medically necessary statement. The medically necessary statement language for the EGFR and ALK Genes were revised to reference the gene inhibitor therapy with examples of therapy types/drugs. FEP variation updated. Policy Guidelines, Description/Background, Rationale and Reference sections updated. Appendix added. Coding Reviewed
	1/1/18 Administrative update. Medicare variations removed from Commercial Policies.
	1/25/18 Minor revision. Policy section updates: • Genetics nomenclature update 'mutation' to 'variant'; • 'Point mutation' replaced with 'single-nucleotide variant' within the EGFR Gene policy statement; • *ROS1* and *BRAF* testing added as medically necessary when criteria are met; and • Genes within the 'Other Genes' statement updated. FEP variation removed as policy was archived December 2015. Policy Guidelines, Description/Background, Rationale and Reference sections updated. Coding revised to mirror policy statements.
	12/14/18 Minor review. The policy section on *EGFR* Testing was changed. Testing for additional variants in the *EGFR* gene was added as medically necessary. Policy statements on other variants unchanged. Description/Background and Reference sections updated. Rationale condensed. Coding reviewed.

	11/7/19 Minor review. New indications for NTRK testing and tumor mutational burden (TMB) testing added. Medically necessary statement for NTRK testing and investigational statement for TMB testing. Literature reviewed and references and coding updated. Effective 5/1/2020.
	9/10/20 Consensus review. No changes made to the policy statement. Policy guidelines, product variation, description, rationale, benefit variation, disclaimer, and references updated. Coding reviewed.
	9/22/20 Administrative update. New codes 81191, 81192, 81193, 81194 added. Effective 1/1/2021.
	5/24/21 Minor review. RET and MET testing are MN and KRAS and HER2 remain INV. Added PD-L1 criteria. Updated tables, background, references and rationale. Coding updated for criteria changes.
	2/2/22 Major review. MP 2.283 was retired (Circulating Tumor DNA management of NSCLC) and merged with this policy. Criteria from MP 2.283 (related to ctDNA) was copied and revised as follows: EGFR testing (at diagnosis) was changed from: exons 18 through 21 to: exons 19 through 21; acomitinib was added to list of EGFR TKIs; HER2, RET rearrangement testing, and MET exon 14 skipping remain INV, denial statement expanded from one collective to three separate. KRAS testing (in tissue) was revised from INV to medically necessary. Analysis of tumor mutational burden statement revised; INV status unchanged. Plasma testing when tissue is insufficient was added as MN with criteria. Literature, references and coding updated.
	6/10/2022 Admin update. Added new code 0326U as MN effective 7/1/22
	9/12/2022 Administrative update. Added code 0334U effective 10/1/22
	7/31/2023 Minor review. Added MN statement regarding testing for Exon 20. Added FoundationOne as MN for liquid biopsy testing. Added Agilent ResolutionFirst and LiquidHALLMARK as INV. Added MN statement for liquid biopsy testing for ALK, ROS1, KRAS, HER2, and MET; condensed for readability. Reformatted sections on plasma testing for readability. Added statement to reference MP 2.259. Removed tables from background. Updated policy guidelines, background, rationale, references. Place 0326U in coding table.
	12/12/2023 Administrative update. Added code 0436U as INV. Added codes 81457, 81458, 81459, 81462, 81463, and 81464 as MN. Eff 1/1/2024.

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