

MEDICAL POLICY

POLICY TITLE	SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN NON-SMALL-CELL LUNG CANCER (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, NTRK) (FORMERLY MOLECULAR ANALYSIS (INCLUDING LIQUID BIOPSY) FOR TARGETED THERAPY OR IMMUNOTHERAPY OF NON-SMALL CELL LUNG CANCER)
POLICY NUMBER	MP 2.241

CLINICAL BENEFIT	<input checked="" type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

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I. POLICY

EGFR Testing

Analysis of tumor tissue for somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (*EGFR*) gene, may be considered **medically necessary** to predict treatment response to a U.S. Food and Drug Administration (FDA) -approved therapy (e.g., erlotinib [Tarceva] alone or in combination with ramucirumab [Cyramza], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], or osimertinib [Tagrisso]) in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous-cell non-small-cell lung cancer (NSCLC), and NSCLC not otherwise specified, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of tumor tissue for somatic variants in exon 20 (e.g., insertion mutations) within the *EGFR* gene, may be considered **medically necessary** to predict treatment response to an FDA-approved therapy (e.g., mobocertinib [Exkivity]) in individuals with NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

At diagnosis, analysis of plasma for somatic variants in exons 19 through 21 (e.g., exon 19 deletions, L858R, T790M) within the *EGFR* gene, using an FDA-approved companion diagnostic plasma test to detect circulating tumor DNA (ctDNA) may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified, if the individual does not

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have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

At progression, analysis of plasma for the EGFR T790M resistance variant for targeted therapy with osimertinib using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified, when tissue biopsy to obtain new tissue is not feasible (e.g., in those who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, or cannot undergo biopsy), and when the individual does not have any FDA-labeled contraindications to osimertinib and it is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of somatic variants in the *EGFR* gene in tissue or plasma, including variants within exons 22 to 24, is considered **investigational** in all other situations.

ALK Testing

Analysis of tumor tissue for somatic rearrangement variants of the anaplastic lymphoma kinase (*ALK*) gene in tissue may be considered **medically necessary** to predict treatment response to an FDA-approved ALK inhibitor therapy (e.g., crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], brigatinib [Alunbrig], or lorlatinib [Lorbrena]) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of plasma for somatic rearrangement variants of the ALK gene using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved ALK inhibitor therapy in individuals with NSCLC (e.g., alectinib [Alecensa]), if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

Analysis of somatic rearrangement variants of the *ALK* gene in tissue or plasma is considered **investigational** in all other situations.

BRAF V600E Testing

Analysis of tumor tissue for the somatic *BRAF*V600E variant may be considered **medically necessary** to predict treatment response to an FDA-approved BRAF and/or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar] and trametinib [Mekinist]), in individuals with advanced lung

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adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of tumor tissue for the somatic *BRAF* V600E variant is considered **investigational** in all other situations.

Analysis of plasma for the somatic *BRAF* V600E variant to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to BRAF and/or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar], trametinib [Mekinist]) in individuals with NSCLC.

ROS1 Testing

Analysis of tumor tissue for somatic rearrangement variants of the *ROS1* gene may be considered **medically necessary** to predict treatment response to an FDA-approved ROS1 inhibitor therapy (e.g., crizotinib [Xalkori]) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of tumor tissue for somatic rearrangement variants of the *ROS1* gene is considered **investigational** in all other situations.

Analysis of plasma for somatic rearrangement variants of the *ROS1* gene to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to ROS1 inhibitor therapy (e.g., crizotinib [Xalkori] or entrectinib) in individuals with NSCLC.

KRAS Testing

Analysis of tumor tissue for somatic variants of the *KRAS* gene (e.g., G12C) may be considered **medically necessary** to predict treatment response to sotorasib (Lumakras) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of plasma for somatic variants of the *KRAS* gene (e.g., G12C) using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to sotorasib (Lumakras) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma

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component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

All other uses of analysis of somatic variants of the *KRAS* gene in tissue or plasma are considered **investigational**.

RET Rearrangement Testing

Analysis of tumor tissue for somatic alterations in the *RET* gene may be considered **medically necessary** to predict treatment response to RET inhibitor therapy (e.g., pralsetinib [Gavreto] or selpercatinib [Retevmo]) in individuals with metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of tumor tissue for somatic alterations in the *RET* gene is considered **investigational** in all other situations.

Analysis of plasma for somatic alterations of the *RET* gene using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to RET inhibitor therapy (e.g., selpercatinib [Retevmo], pralsetinib [Gavreto]) in individuals with NSCLC.

MET Exon 14 Skipping Alteration

Analysis of tumor tissue for somatic alterations in tissue that leads to *MET* exon 14 skipping may be considered **medically necessary** to predict treatment response to capmatinib (Tabrecta) in individuals with metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of plasma for somatic alteration that leads to *MET* exon 14 skipping using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to MET inhibitor therapy (e.g., capmatinib [Tabrecta]) in individuals with NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

All other uses of analysis of somatic variants of the *MET* gene in tissue or plasma are considered **investigational**.

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Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Testing

Analysis of tumor tissue for *NTRK* gene fusions may be considered **medically necessary** to predict treatment response to TRK inhibitor therapy (e.g., larotrectinib [Vitrakvi] or entrectinib [Rozlytrek]) in individuals with metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

Analysis of plasma for *NTRK* gene fusions using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to TRK inhibitor therapy (e.g., larotrectinib [Vitrakvi] or entrectinib [Rozlytrek]) in individuals with metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

All other uses of analysis of *NTRK* fusions in tissue or plasma are considered **investigational**.

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 individuals meeting the following criteria:

- Individual does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; AND
- Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing.

Testing for other variants may become available between policy updates.

Policy Guidelines

This policy does not address germline testing for inherited risk of developing cancer.

This policy does not address monoclonal antibody therapies such as amivantamab-vmjw (Rybrevant).

For expanded panel testing, see **MP 2.259**.

This policy does not address HER2 testing. Agents targeted against HER2 in non-small-cell lung cancer (NSCLC) with approved companion diagnostic tests include the antibody-drug conjugate fam-trastuzumab deruxtecan-nxki (Enhertu), which is not a true targeted therapy.

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Testing for individual genes (not gene panels) associated with U.S. Food and Drug Administration (FDA) -approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (<https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms. The most recent guidelines (v.10.2024) recommend that *EGFR* variants (category 1), *ALK* rearrangements (category 1), and PD-L1 testing (category 1) as well as *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET* exon 14 skipping alteration, *RET*, and *HER2* testing (all category 2A) be performed in the workup of NSCLC in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and NSCLC 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.

PD-L1 testing is addressed separately in **MP 2.388**.

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.”

Repeat Genomic Testing

There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with NSCLC, as tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making. For example, repeat testing (tissue or liquid based) of *EGFR* for T790M at progression on or after *EGFR* tyrosine kinase inhibitor therapy may be considered to

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select patients for treatment with osimertinib. T790M is an acquired resistance mutation that is rarely seen at initial diagnosis. The American Society of Clinical Oncology (ASCO) currently suggests repeat genomic testing for individuals on targeted therapy with suspected acquired resistance, especially if choice of next-line therapy would be guided. The ASCO guidance is not tumor specific, and it cautions to consider clinical utility (Chakravarty et al, 2022; PMID 35175857).

Concurrent Somatic Liquid-Based and Tissue-Based Genomic Testing

Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time to monitor for resistance variant T790M, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that mutations that are going to be followed longitudinally can be detected by the liquid biopsy. Current NCCN guidelines for NSCLC (v.10.2024) state the following: "Studies have demonstrated ctDNA and tissue testing to have very high specificity. Both ctDNA and tissue testing have appreciable false-negative rates, supporting the complementarity of these approaches, and data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection."

Recommended Testing Strategies

Individuals who meet criteria for genetic testing as outlined in the policy statements above should be tested for the variants specified.

- When tumor tissue is available, use of tissue for testing of any/all variants and biomarkers outlined in this policy is recommended but is not required in all situations. In certain situations, circulating tumor DNA testing (liquid biopsy) may be an option.

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

<i>Histologic Subtype for NSCLC</i>
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 and subject to benefit variations as discussed in Section VI. Please see additional information below.

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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 are 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.

Somatic variants in the TK domain of the *EGFR* gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R, indicating substitution of leucine by arginine at codon position 858) are the most commonly found *EGFR* variants associated with sensitivity to *EGFR* TKIs (afatinib, erlotinib, gefitinib). These variants are referred to as sensitizing variants. Almost all patients who initially respond to an *EGFR* TKI experience disease progression. The most common of these secondary variants, called resistance variants, involves the substitution of methionine for threonine at position 790 (T790M) on exon 20.

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Fang et al (2013) reported *EGFR* variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage squamous cell carcinoma (SCC). In a separate cohort of 63 Chinese patients with SCC who received erlotinib or gefitinib as second- or third-line treatment (63% never-smokers, 21% women), *EGFR* variant prevalence (all exon 19 deletion or L858R) was 23.8%.

In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al (2006) reported *EGFR* variants in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies. Eberhard et al (2005) observed *EGFR* variants in 6.4% of patients with SCC and Rosell et al (2009) observed *EGFR* variants in 11.5% of patients with large cell carcinomas. Both studies had small sample sizes.

In 2 other studies, the acquired *EGFR* T790M variant has been estimated to be present in 50% to 60% of TKI-resistant cases in approximately 200 patients.

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

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technologies, or NGS. *EGFR*, *ALK*, *ROS1*, and *KRAS* driver mutations are considered to be mutually exclusive.

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

NTRK Gene Fusions

The presence of *NTRK* gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry.¹¹ Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *NTRK* gene fusions as well as other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

Circulating Tumor DNA (Liquid Biopsy)

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

Targeted Treatment, Immunotherapy, and Companion Diagnostic Testing

U.S. Food and Drug Administration (FDA) -approved targeted treatments for the variants described above are summarized in Table 1. (Note this information is current as of October 8, 2024. FDA maintains a list of oncology drug approval notifications at <https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications>.) This review does not evaluate any FDA-approved monoclonal antibody therapies, and they are not included in the table below.

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Table 1. Targeted Treatments for Non-Small-Cell Lung Cancer

Target	FDA-Approved Targeted Therapies
<i>EGFR</i>	<ul style="list-style-type: none"> • Gefitinib (Iressa), • Erlotinib (Tarceva) alone or in combination with ramucirumab (Cyramza) • Afatinib (Gilotrif) • Osimertinib (Tagrisso) • Dacomitinib (Vizimpro) • Mobocertinib (Exkivity)
<i>ALK</i>	<ul style="list-style-type: none"> • Crizotinib (Xalkori) • Ceritinib (Zykadia) • Alectinib (Alecensa) • Brigatinib (Alunbrig) • Lorlatinib (Lorbrena)
<i>BRAF</i>	<ul style="list-style-type: none"> • Dabrafenib (Tafinlar) alone or in combination with trametinib (Mekinist) • Encorafenib (Braftovi) in combination with binimetinib (Mektovi)
<i>ROS1</i>	<ul style="list-style-type: none"> • Crizotinib (Xalkori)
<i>KRAS</i>	<ul style="list-style-type: none"> • Sotorasib (Lumakras) • Adagrasib (Krazati)
<i>RET</i>	<ul style="list-style-type: none"> • Selpercatinib (Retevmo) • Pralsetinib (Gavreto)
<i>MET</i>	<ul style="list-style-type: none"> • Capmatinib (Tabrecta) • Tepotinib (Tepmetko)
<i>NTRK</i>	<ul style="list-style-type: none"> • Larotrectinib (Vitrakvi) • Entrectinib (Rozlytrek)

Table 2 summarizes the FDA-approved targeted treatments for individuals with NSCLC along with the concurrently approved companion diagnostic tests. The information in Table 2 is current as of October 18, 2023. An up-to-date list of FDA cleared or approved companion diagnostics is available at: <https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>.)

Table 2. Targeted Treatments for Advanced Non-Small-Cell Lung Cancer and FDA Approved Companion Diagnostic Tests

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Treatment	FDA-Approved Companion Diagnostic Tests	Biomarkers	NCCN Recommendation Level/Guideline
Adagrasib (Krazati)	<ul style="list-style-type: none"> Agilent Resolution ctDx FIRST assay therascreen KRAS RGQ PCR Kit 	KRAS	2A or higher/ NSCLC Treatment (v.4.2023)
Afatinib (Gilotrif)	<ul style="list-style-type: none"> 2013: theascreen EGFR RGQ PCR kit (Qiagen) 2016: <i>therascreen</i> EGFR RGQ PCR Kit (Qiagen) 2017: FoundationOne CDx™ (Foundation Medicine) 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) 	EGFR	Same as above
Alectinib (Alecensa)	<ul style="list-style-type: none"> 2017: FoundationOne CDx™ (Foundation Medicine) 2017: Ventana ALK (D5F3) CDx Assay 2020: FoundationOne Liquid CDx 	ALK	Same as above
Brigatinib (Alunbrig)	<ul style="list-style-type: none"> 2020: Vysis ALK Break Apart FISH Probe Kit 	ALK gene rearrangements	Same as above
Capmatinib (Tabrecta)	<ul style="list-style-type: none"> 2020: FoundationOne CDx™ 2021: FoundationOne Liquid CDx™ 	<i>MET</i> single nucleotide variants and indels that lead to <i>MET</i> exon 14 skipping	Same as above
Ceritinib (Zykadia)	<ul style="list-style-type: none"> 2017: FoundationOne CDx™ (Foundation Medicine) 2017: VENTANA ALK (D5F3) CDx Assay 	<ul style="list-style-type: none"> ALK rearrangements, ALK protein expression 	Same as above
Crizotinib (Xalkori)	ALK tests:	ALK	Same as above

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	<ul style="list-style-type: none"> • 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine) <p>ROS tests:</p> <ul style="list-style-type: none"> • 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific) 		
Dacomitinib (Vizimpro)	<ul style="list-style-type: none"> • 2018: theascreen EGFR RGQ PCR Kit • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) 	EGFR	Same as above
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	<ul style="list-style-type: none"> • 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine) 	BRAF V600E	Same as above
Erlotinib (Generic)	<ul style="list-style-type: none"> • 2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2016: cobas® EGFR Mutation Test v2 (tissue or blood test) (Roche Diagnostics) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) 	EGFR	Same as above

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Gefitinib (Iressa)	<ul style="list-style-type: none"> 2015: theascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit 2017: Oncomine™ Dx Target Test 2017: FoundationOne CDx™ (Foundation Medicine) 2018: cobas® EGFR Mutation Test v2 (tissue or plasma test) (Roche Diagnostics) 2020: cobas® EGFR Mutation Test v2 (tissue or plasma) (Roche Diagnostics) 2020: FoundationOne® Liquid CDx 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) 	Exon 19 deletion or exon 21 L858R substitution mutation	Same as above
Lorlatinib (Lorbrena)	<ul style="list-style-type: none"> 2021: Ventana ALK (D5F3) CDx Assay 	ALK	Same as above
Mobocertinib (Exkivity)	<ul style="list-style-type: none"> 2021: Oncomine Dx Target Test 	EGFR	Same as above
Osimertinib (Tagrisso)	<ul style="list-style-type: none"> 2015-2020: cobas® EGFR Mutation Test v2 (tissue or plasma) 2017-2019: FoundationOne CDx™ (Foundation Medicine) 2020: Guardant360 CDx 2020: FoundationOne® Liquid CDx 	EGFR	Same as above
Pralsetinib (Gavreto)	<ul style="list-style-type: none"> 2020: Oncomine Dx Target Test 	RET	Same as above
Selpercatinib (Retevmo)	<ul style="list-style-type: none"> 2022: Oncomine Dx Target Test 	RET	Same as above

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	<ul style="list-style-type: none"> 2024: TruSight Oncology Comprehensive (Illumina, Inc.) 		
Sotorasib (Lumakras)	<ul style="list-style-type: none"> 2021: Therascreen KRAS RGQ PCR kit 2021: Guardant360 CDx 	KRAS	Same as above
Tepotinib (Tepmetko)	<ul style="list-style-type: none"> No approved companion diagnostic 	MET exon 14 skipping alterations	Same as above
Encorafenib (Braftovi) plus Binimetinib (Mektovi)	<ul style="list-style-type: none"> 2023: FoundationOne® CDx 2023: FoundationOne® Liquid CDx 	BRAF V600E	Same as above
Larotrectinib (Vitrakvi)	<ul style="list-style-type: none"> 2020: FoundationOne CDx (Foundation Medicine, Inc.) 2024: TruSight Oncology Comprehensive (Illumina, Inc.) 	NTRK1, NTRK2, and NTRK3 fusions	Same as above
Entrectinib (Rozlytrek)	<ul style="list-style-type: none"> 2022: FoundationOne CDx (Foundation Medicine, Inc.) 2022: FoundationOne Liquid CDx (Foundation Medicine, Inc.) 	NTRK1, NTRK2, and NTRK3 fusions	Same as above

IV. RATIONALE

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Summary of Evidence

For individuals with advanced or metastatic non-small-cell lung cancer (NSCLC) who are being considered for targeted therapy with tyrosine kinase inhibitors who undergo somatic testing for *EGFR* variants or *ALK* rearrangements using tissue biopsy specimens, the evidence includes U.S. Food and Drug Administration (FDA)-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with tyrosine kinase inhibitors who undergo somatic testing for *EGFR* variants or *ALK* rearrangements using circulating tumor DNA (ctDNA) (liquid biopsy), the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not

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extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with BRAF or ROS1 inhibitors who undergo somatic testing for *BRAF* variants or *ROS1* rearrangements using tissue biopsy specimens, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with BRAF or ROS1 inhibitors who undergo somatic testing for *BRAF* variants or *ROS1* rearrangements using ctDNA (liquid biopsy), no evidence was identified. No plasma tests have received FDA approval as companion diagnostics to select individuals with NSCLC for treatment with BRAF inhibitors and no studies were identified. FoundationOne Liquid CDx is FDA approved as a companion diagnostic to select treatment with entrectinib in individuals with *ROS1* positive NSCLC. No plasma tests have received FDA approval as companion diagnostics to select patients with *ROS1* rearrangements for treatment with crizotinib and no studies for this indication were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with RET or MET inhibitors who undergo somatic testing for *RET* rearrangements or *MET* alterations using tissue biopsy specimens, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with RET inhibitors who undergo somatic testing for *RET* rearrangements using ctDNA (liquid biopsy), no studies were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with MET inhibitors who undergo somatic testing for *MET* alterations using ctDNA (liquid biopsy), the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with a RAS inhibitor who undergo somatic testing for KRAS variants using tissue biopsy specimens, the evidence includes FDA-approved therapeutics with NCCN recommendations of

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2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with a RAS inhibitor who undergo somatic testing for KRAS variants using using ctDNA (liquid biopsy), the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with metastatic NSCLC who are being considered for targeted therapy with a TRK inhibitor who undergo somatic testing for NTRK gene fusion using tissue biopsy specimens, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with metastatic NSCLC who are being considered for targeted therapy with a TRK inhibitor who undergo somatic testing for NTRK gene fusion using ctDNA (liquid biopsy), the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

V. DEFINITIONS

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NA

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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VII. 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						

Investigational; therefore, not covered for cell-free DNA testing

Procedure Codes								
0388U	0409U	0436U	0485U	0530U	81479			

Covered when medically necessary (tissue testing):

Procedure Codes								
81191	81192	81193	81194	81210	81235	81275	81276	81401
81404	81405	81445	81450	81455	81457	81458	81459	81479
88342	88363	88365	0022U	0037U	0334U	0473U		

Covered when medically necessary for plasma/cell-free DNA testing OR for plasma testing when tissue is insufficient:

Procedure Codes								
0179U	0239U	0242U	0326U	0585U	81235	81277	81445	81450
81455	81462	81463	81464	81479	86152	86153		

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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

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IX. POLICY HISTORY

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MP 2.241	09/10/2020 Consensus Review. No changes made to the policy statement. Policy guidelines, product variation, description, rationale, benefit variation, disclaimer, and references updated. Coding reviewed.
	09/22/2020 Administrative Update. New codes 81191, 81192, 81193, 81194 added. Effective 01/01/2021.
	05/24/2021 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.
	02/02/2022 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; acoitinib 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.
	06/10/2022 Administrative Update. Added new code 0326U as MN effective 07/01/2022
	09/12/2022 Administrative Update. Added code 0334U effective 10/01/2022
	07/31/2023 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;

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	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 01/01/2024.
	06/12/2024 Administrative Update. Added code 0473U as MN. Eff 07/01/2024.
	09/30/2024 Administrative Update. New codes 0478U and 0485U added effective 10/01/2024
	10/28/2024 Minor Review. Added Lung HDPCR as INV with code 0478U eff 10/01/2024. Added code 0409U as INV. Updated references.
	12/27/2024 Administrative Update. Removed NCCN statement.
	03/28/2025 Minor Review. Extensive changes to policy statement with minor changes to intent. Agilent Resolution test with code 0179U will now be MN from INV. Removed statements regarding tumor mutational burden testing, PD-L1 testing as these are addressed in MP 2.388. Moved Lung HDPCR test and code 0478U to MP 2.326. Removed statement regarding HER2 testing. Policy guidelines, rationale, background updated. Added codes 0388U and 0530U as INV.
	07/14/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	09/09/2025 Administrative Update. New code 0585U added Effective 10/01/2025 as part of new code process.
	03/04/2026 Retirement Review. EviCore Delegation.

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