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	☒ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**10/1/2025**

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

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 [Alcensa]), 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

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

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.

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)
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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

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

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

TOP

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

TOP

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.

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

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.

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

Target	FDA-Approved Targeted Therapies
EGFR	• Gefitinib (Iressa), • Erlotinib (Tarceva) alone or in combination with ramucirumab (Cyramza) • Afatinib (Gilotrif) • Osimertinib (Tagrisso) • Dacomitinib (Vizimpro) • Mobocertinib (Exkivity)
ALK	• Crizotinib (Xalkori) • Ceritinib (Zykadia) • Alectinib (Alecensa) • Brigatinib (Alunbrig) • Lorlatinib (Lorbrena)
BRAF	• Dabrafenib (Tafinlar) alone or in combination with trametinib (Mekinist) • Encorafenib (Braftovi) in combination with binimetinib (Mektovi)
ROS1	• Crizotinib (Xalkori)
KRAS	• Sotorasib (Lumakras) • Adagrasib (Krazati)
RET	• Selpercatinib (Retevmo) • Pralsetinib (Gavreto)
MET	• Capmatinib (Tabrecta) • Tepotinib (Tepmetko)
NTRK	• 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

Treatment	FDA-Approved Companion Diagnostic Tests	Biomarkers	NCCN Recommendation Level/Guideline
Adagrasib (Krazati)	• Agilent Resolution ctDx FIRST assay • therascreen KRAS RGQ PCR Kit	KRAS	2A or higher/ NSCLC Treatment (v.4.2023)
Afatinib (Gilotrif)	• 2013: therascreen EGFR RGQ PCR kit (Qiagen) • 2016: *therascreen* 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)	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: Ventana ALK (D5F3) CDx Assay • 2020: FoundationOne Liquid CDx	ALK	Same as above
Brigatinib (Alunbrig)	• 2020: Vysis ALK Break Apart FISH Probe Kit	ALK gene rearrangements	Same as above
Capmatinib (Tabrecta)	• 2020: FoundationOne CDx™ • 2021: FoundationOne Liquid CDx™	*MET* single nucleotide variants and indels that lead to *MET* exon 14 skipping	Same as above
Ceritinib (Zykadia)	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: VENTANA ALK (D5F3) CDx Assay	• ALK rearrangements, • ALK protein expression	Same as above
Crizotinib (Xalkori)	ALK tests:	ALK	Same as above

	• 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine) ROS tests: • 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)		
Dacomitinib (Vizimpro)	• 2018: therascreen EGFR RGQ PCR Kit • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)	EGFR	Same as above
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	• 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine)	BRAF V600E	Same as above
Erlotinib (Generic)	• 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

Gefitinib (Iressa)	• 2015: therascreen® 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)	• 2021: Ventana ALK (D5F3) CDx Assay	ALK	Same as above
Mobocertinib (Exkivity)	• 2021: Oncomine Dx Target Test	EGFR	Same as above
Osimertinib (Tagrisso)	• 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)	• 2020: Oncomine Dx Target Test	RET	Same as above
Selpercatinib (Retevmo)	• 2022: Oncomine Dx Target Test	RET	Same as above

	• 2024: TruSight Oncology Comprehensive (Illumina, Inc.)		
Sotorasib (Lumakras)	• 2021: Therascreen KRAS RGQ PCR kit • 2021: Guardant360 CDx	KRAS	Same as above
Tepotinib (Tepmetko)	• No approved companion diagnostic	MET exon 14 skipping alterations	Same as above
Encorafenib (Braftovi) plus Binimetinib (Mektovi)	• 2023: FoundationOne® CDx • 2023: FoundationOne® Liquid CDx	BRAF V600E	Same as above
Larotrectinib (Vitrakvi)	• 2020: FoundationOne CDx (Foundation Medicine, Inc.) • 2024: TruSight Oncology Comprehensive (Illumina, Inc.)	NTRK1, NTRK2, and NTRK3 fusions	Same as above
Entrectinib (Rozlytrek)	• 2022: FoundationOne CDx (Foundation Medicine, Inc.) • 2022: FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NTRK1, NTRK2, and NTRK3 fusions	Same as above

IV. RATIONALE

TOP

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

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

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.

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

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		

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

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

VIII. REFERENCES

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1. *Fathi AT, Brahmer JR. Chemotherapy for advanced stage non-small cell lung cancer. Semin Thorac Cardiovasc Surg. 2008; 20(3): 210-6. PMID 19038730*
2. *Martoni A, Marino A, Sperandi F, et al. Multicentre randomised phase III study comparing the same dose and schedule of cisplatin plus the same schedule of vinorelbine or gemcitabine in advanced non-small cell lung cancer. Eur J Cancer. Jan 2005; 41(1): 81-92. PMID 15617993*
3. *Rudd RM, Gower NH, Spiro SG, et al. Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. J Clin Oncol. Jan 01 2005; 23(1): 142-53. PMID 15625369*
4. *Thunnissen E, van der Oord K, den Bakker M. Prognostic and predictive biomarkers in lung cancer. A review. Virchows Arch. Mar 2014; 464(3): 347-58. PMID 24420742*

5. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 7.2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.*
6. *Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. May 31 2018; 378(22): 2093-2104. PMID 29658845*
7. *Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools).*
8. *Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs.*
9. *Fang W, Zhang J, Liang W, et al. Efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors for Chinese patients with squamous cell carcinoma of lung harboring EGFR mutation. J Thorac Dis. Oct 2013; 5(5): 585-92. PMID 24255770*
10. *Mitsudomi T, Kosaka T, Yatabe Y. Biological and clinical implications of EGFR mutations in lung cancer. Int J Clin Oncol. Jun 2006; 11(3): 190-8. PMID 16850125*
11. *Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol. Sep 01 2005; 23(25): 5900-9. PMID 16043828*
12. *Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. Sep 03 2009; 361(10): 958-67. PMID 19692684*
13. *Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. Apr 15 2013; 19(8): 2240-7. PMID 23470965*
14. *Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. Mar 23 2011; 3(75): 75ra26. PMID 21430269*
15. *Mujoomdar M, Moulton K, Spry C. Epidermal Growth Factor Receptor Mutation Analysis in Advanced Non-Small Cell Lung Cancer: A Review of the Clinical Effectiveness and Guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010.*
16. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): therascreen EGFR RGQ PCR Kit. 2013*
17. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): cobas EGFR Mutation Test. 2013*
18. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): cobas EGFR Mutation Test v2. 2015*
19. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): OncomineTM Dx Target Test. 2017*
20. *Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol. Nov 2013; 31(11): 1023-31. PMID 24142049*

21. *Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst. May 01 2013; 105(9): 595-605. PMID 23594426*
22. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Epidermal growth factor receptor (EGFR) mutations and tyrosine kinase inhibitor therapy in advanced non-small-cell lung cancer. TEC Assessments. 2007;Volume 22:Tab 6.*
23. *Guetz GD, Landre T, Uzzan B, et al. Is There a Survival Benefit of First-Line Epidermal Growth Factor Receptor Tyrosine-Kinase Inhibitor Monotherapy Versus Chemotherapy in Patients with Advanced Non-Small-Cell Lung Cancer?: A Meta-Analysis. Target Oncol. Feb 2016; 11(1): 41-7. PMID 26092590*
24. *Kato T, De Marinis F, Spicer J, et al. The impact of first-line tyrosine kinase inhibitors (TKIs) on overall survival in patients with advanced non-small cell lung cancer (NSCLC) and activating epidermal growth factor receptor (EGFR) mutations: meta-analysis of major randomized trials by mutation type. Value Health. Nov 2015;18(7):A436. PMID 26532455*
25. *Kuan FC, Kuo LT, Chen MC, et al. Overall survival benefits of first-line EGFR tyrosine kinase inhibitors in EGFR-mutated non-small-cell lung cancers: a systematic review and meta-analysis. Br J Cancer. Nov 17 2015; 113(10): 1519-28. PMID 26461059*
26. *Greenhalgh J, Dwan K, Boland A, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev. May 25 2016; (5): CD010383. PMID 27223332*
27. *Petrelli F, Borgonovo K, Cabiddu M, et al. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small-cell lung cancer: a meta-analysis of 13 randomized trials. Clin Lung Cancer. Mar 2012; 13(2): 107-14. PMID 22056888*
28. *Wu YL, Zhou C, Liam CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol. Sep 2015; 26(9): 1883-1889. PMID 26105600*
29. *Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. Mar 2012; 13(3): 239-46. PMID 22285168*
30. *Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. Aug 2011; 12(8): 735-42. PMID 21783417*
31. *Zhou C, Wu YL, Chen G, et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol. Sep 2015; 26(9): 1877-1883. PMID 26141208*

32. *Ahn MJ, Park BB, Ahn JS, et al. Are there any ethnic differences in molecular predictors of erlotinib efficacy in advanced non-small cell lung cancer?. Clin Cancer Res. Jun 15 2008; 14(12): 3860-6. PMID 18559606*
33. *Amann JM, Lee JW, Roder H, et al. Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 3503. J Thorac Oncol. Feb 2010; 5(2): 169-78. PMID 20035238*
34. *Felip E, Rojo F, Reck M, et al. A phase II pharmacodynamic study of erlotinib in patients with advanced non-small cell lung cancer previously treated with platinum-based chemotherapy. Clin Cancer Res. Jun 15 2008; 14(12): 3867-74. PMID 18559607*
35. *Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol. Mar 20 2008; 26(9): 1472-8. PMID 18349398*
36. *Schneider CP, Heigener D, Schott-von-Romer K, et al. Epidermal growth factor receptor-related tumor markers and clinical outcomes with erlotinib in non-small cell lung cancer: an analysis of patients from german centers in the TRUST study. J Thorac Oncol. Dec 2008; 3(12): 1446-53. PMID 19057271*
37. *Giaccone G, Gallegos Ruiz M, Le Chevalier T, et al. Erlotinib for frontline treatment of advanced non-small cell lung cancer: a phase II study. Clin Cancer Res. Oct 15 2006; 12(20 Pt 1): 6049-55. PMID 17062680*
38. *Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. J Clin Oncol. Mar 01 2007; 25(7): 760-6. PMID 17228019*
39. *Zhu CQ, da Cunha Santos G, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol. Sep 10 2008; 26(26): 4268-75. PMID 18626007*
40. *Yoshioka H, Hotta K, Kiura K, et al. A phase II trial of erlotinib monotherapy in pretreated patients with advanced non-small cell lung cancer who do not possess active EGFR mutations: Okayama Lung Cancer Study Group trial 0705. J Thorac Oncol. Jan 2010; 5(1): 99-104. PMID 19898258*
41. *Sim EH, Yang IA, Wood-Baker R, et al. Gefitinib for advanced non-small cell lung cancer. Cochrane Database Syst Rev. Jan 16 2018; 1: CD006847. PMID 29336009*
42. *Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. Sep 03 2009; 361(10): 947-57. PMID 19692680*
43. *Han B, Jin B, Chu T, et al. Combination of chemotherapy and gefitinib as first-line treatment for patients with advanced lung adenocarcinoma and sensitive EGFR mutations: A randomized controlled trial. Int J Cancer. Sep 15 2017; 141(6): 1249-1256. PMID 28560853*
44. *Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. Feb 2010; 11(2): 121-8. PMID 20022809*

45. *Wu YL, Saijo N, Thongprasert S, et al. Efficacy according to blind independent central review: Post-hoc analyses from the phase III, randomized, multicenter, IPASS study of first-line gefitinib versus carboplatin/paclitaxel in Asian patients with EGFR mutation-positive advanced NSCLC. Lung Cancer. Feb 2017; 104: 119-125. PMID 28212993*
46. *Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. Jun 24 2010; 362(25): 2380-8. PMID 20573926*
47. *Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol. Jan 2013; 24(1): 54-9. PMID 22967997*
48. *Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. Sep 20 2013; 31(27): 3327-34. PMID 23816960*
49. *Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol. Sep 20 2013; 31(27): 3342-50. PMID 23816967*
50. *Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. Feb 2014; 15(2): 213-22. PMID 24439929*
51. *Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. Lancet Oncol. May 2012; 13(5): 539-48. PMID 22452895*
52. *Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol. May 2012; 13(5): 528-38. PMID 22452896*
53. *Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol. Sep 20 2013; 31(27): 3335-41. PMID 23816963*
54. *Food and Drug Administration (FDA). TAGRISSOTM (osimertinib) Highlights of Prescribing Information. 2015*
55. *Yang J, Ramalingam SS, Janne PA, et al. LBA2_PR: Osimertinib (AZD9291) in pre-treated pts with T790M- positive advanced NSCLC: updated Phase 1 (P1) and pooled Phase 2 (P2) results. J Thorac Oncol. Apr 2016;11(4 Suppl):S152-153. PMID 27198353*
56. *Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. Aug 28 2018: JCO2018783118. PMID 30153097*

57. *Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. Feb 16 2017; 376(7): 629-640. PMID 27959700*
58. *Lin JZ, Ma SK, Wu SX, et al. A network meta-analysis of nonsmall-cell lung cancer patients with an activating EGFR mutation: Should osimertinib be the first-line treatment?. Medicine (Baltimore). Jul 2018; 97(30): e11569. PMID 30045282*
59. *Zhang W, Wei Y, Yu D, et al. Gefitinib provides similar effectiveness and improved safety than erlotinib for advanced non-small cell lung cancer: A meta-analysis. Medicine (Baltimore). Apr 2018; 97(16): e0460. PMID 29668619*
60. *De Mello RA, Escriu C, Castelo-Branco P, et al. Comparative outcome assessment of epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of advanced non-small-cell lung cancer: a network meta-analysis. Oncotarget. Feb 20 2018; 9(14): 11805-11815. PMID 29545937*
61. *Crequit P, Chaimani A, Yavchitz A, et al. Comparative efficacy and safety of second-line treatments for advanced non-small cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analysis. BMC Med. Oct 30 2017; 15(1): 193. PMID 29082855*
62. *Wu D, Duan C, Wu F, et al. Which treatment is preferred for advanced non-small-cell lung cancer with wild-type epidermal growth factor receptor in second-line therapy? A meta-analysis comparing immune checkpoint inhibitor, tyrosine kinase inhibitor and chemotherapy. Oncotarget. Sep 12 2017; 8(39): 66491-66503. PMID 29029530*
63. *Yang Z, Hackshaw A, Feng Q, et al. Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: A meta-analysis. Int J Cancer. Jun 15 2017; 140(12): 2805-2819. PMID 28295308*
64. *Zhang Y, Zhang Z, Huang X, et al. Therapeutic Efficacy Comparison of 5 Major EGFR-TKIs in Advanced EGFR-positive Non-Small-cell Lung Cancer: A Network Meta-analysis Based on Head-to-Head Trials. Clin Lung Cancer. Sep 2017; 18(5): e333-e340. PMID 28462807*
65. *Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. Jan 11 2018; 378(2): 113-125. PMID 29151359*
66. *Urata Y, Katakami N, Morita S, et al. Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L. J Clin Oncol. Sep 20 2016; 34(27): 3248-57. PMID 27022112*
67. *Yang JJ, Zhou Q, Yan HH, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. Br J Cancer. Feb 28 2017; 116(5): 568-574. PMID 28103612*
68. *Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. May 2016; 17(5): 577-89. PMID 27083334*
69. *Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. Clin Cancer Res. Apr 15 2011; 17(8): 2081-6. PMID 21288922*
70. *Food and Drug Administration (FDA). FDA approves crizotinib capsules. 2016*

71. *Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. Dec 04 2014; 371(23): 2167-77. PMID 25470694*
72. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Ventana ALK (D5F3) CDx Assay. 2015*
73. *Shaw AT, Kim TM, Crino L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. Jul 2017; 18(7): 874-886. PMID 28602779*
74. *Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. Mar 04 2017; 389(10072): 917-929. PMID 28126333*
75. *Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. Jul 01 2017; 390(10089): 29-39. PMID 28501140*
76. *Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol. Feb 2016; 17(2): 234-242. PMID 26708155*
77. *Peters S, Camidge DR, Shaw AT, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. Aug 31 2017; 377(9): 829-838. PMID 28586279*
78. *Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Ann Oncol. Nov 01 2018; 29(11): 2214-2222. PMID 30215676*
79. *Camidge DR, Kim DW, Tiseo M, et al. Exploratory Analysis of Brigatinib Activity in Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer and Brain Metastases in Two Clinical Trials. J Clin Oncol. Sep 10 2018; 36(26): 2693-2701. PMID 29768119*
80. *Ventana. VENTANA ALK (D5F3) CDx Assay - P140025. 2015*
81. *Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol. May 2016; 17(5): 642-50. PMID 27080216*
82. *Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol. Jul 2016; 17(7): 984-993. PMID 27283860*
83. *Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF V600E -mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. Oct 2017; 18(10): 1307-1316. PMID 28919011*
84. *Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med. Aug 20 2015; 373(8): 726-36. PMID 26287849*
85. *Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol. Oct 2012; 7(10): e23-4. PMID 22743296*

86. *Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. Nov 20 2014; 371(21): 1963-71. PMID 25264305*
87. *Lim SM, Kim HR, Lee JS, et al. Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. J Clin Oncol. Aug 10 2017; 35(23): 2613-2618. PMID 28520527*
88. *Mazieres J, Zalcman G, Crino L, et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. J Clin Oncol. Mar 20 2015; 33(9): 992-9. PMID 25667280*
89. *Kim HR, Lim SM, Kim HJ, et al. The frequency and impact of ROS1 rearrangement on clinical outcomes in never smokers with lung adenocarcinoma. Ann Oncol. Sep 2013; 24(9): 2364-70. PMID 23788756*
90. *Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer. N Engl J Med. Aug 27 2020; 383(9): 813-824. PMID 32846060*
91. *Skoulidis F, Li BT, Dy GK, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. N Engl J Med. Jun 24 2021; 384(25): 2371-2381. PMID 34096690*
92. *Pan W, Yang Y, Zhu H, et al. KRAS mutation is a weak, but valid predictor for poor prognosis and treatment outcomes in NSCLC: A meta-analysis of 41 studies. Oncotarget. Feb 16 2016; 7(7): 8373-88. PMID 26840022*
93. *Mao C, Qiu LX, Liao RY, et al. KRAS mutations and resistance to EGFR-TKIs treatment in patients with non-small cell lung cancer: a meta-analysis of 22 studies. Lung Cancer. Sep 2010; 69(3): 272-8. PMID 20022659*
94. *Linardou H, Dahabreh IJ, Kanaloupiti D, et al. Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. Lancet Oncol. Oct 2008; 9(10): 962-72. PMID 18804418*
95. *Papadimitrakopoulou V, Lee JJ, Wistuba II, et al. The BATTLE-2 Study: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. Oct 20 2016; 34(30): 3638-3647. PMID 27480147*
96. *Rulli E, Marabese M, Torri V, et al. Value of KRAS as prognostic or predictive marker in NSCLC: results from the TAILOR trial. Ann Oncol. Oct 2015; 26(10): 2079-84. PMID 26209642*
97. *Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. Jul 14 2005; 353(2): 123-32. PMID 16014882*
98. *Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med. Jan 2005; 2(1): e17. PMID 15696205*
99. *Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. Sep 01 2005; 23(25): 5892-9. PMID 16043829*
100. *Fiala O, Pesek M, Finek J, et al. Gene mutations in squamous cell NSCLC: insignificance of EGFR, KRAS and PIK3CA mutations in prediction of EGFR-TKI treatment efficacy. Anticancer Res. Apr 2013; 33(4): 1705-11. PMID 23564819*

101. *Guan JL, Zhong WZ, An SJ, et al. KRAS mutation in patients with lung cancer: a predictor for poor prognosis but not for EGFR-TKIs or chemotherapy. Ann Surg Oncol. Apr 2013; 20(4): 1381-8. PMID 23208128*
102. *Boldrini L, Ali G, Gisfredi S, et al. Epidermal growth factor receptor and K-RAS mutations in 411 lung adenocarcinoma: a population-based prospective study. Oncol Rep. Oct 2009; 22(4): 683-91. PMID 19724844*
103. *Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol. Feb 20 2010; 28(6): 911-7. PMID 20100966*
104. *Khambata-Ford S, Harbison CT, Hart LL, et al. Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. J Clin Oncol. Feb 20 2010; 28(6): 918-27. PMID 20100958*
105. *Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet. May 02 2009; 373(9674): 1525-31. PMID 19410716*
106. *O'Byrne KJ, Gatzemeier U, Bondarenko I, et al. Molecular biomarkers in non-small-cell lung cancer: a retrospective analysis of data from the phase 3 FLEX study. Lancet Oncol. Aug 2011; 12(8): 795-805. PMID 21782507*
107. *Janne PA, van den Heuvel MM, Barlesi F, et al. Selumetinib Plus Docetaxel Compared With Docetaxel Alone and Progression-Free Survival in Patients With KRAS-Mutant Advanced Non-Small Cell Lung Cancer: The SELECT-1 Randomized Clinical Trial. JAMA. May 09 2017; 317(18): 1844-1853. PMID 28492898*
108. *Blumenschein GR, Smit EF, Planchard D, et al. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC). Ann Oncol. May 2015; 26(5): 894-901. PMID 25722381*
109. *Mok T, Ladrera G, Srimuninnimit V, et al. Tumor marker analyses from the phase III, placebo-controlled, FASTACT-2 study of intercalated erlotinib with gemcitabine/platinum in the first-line treatment of advanced non-small-cell lung cancer. Lung Cancer. Aug 2016; 98: 1-8. PMID 27393499*
110. *Shen H, Du G, Liu Z, et al. Assessment and prognostic analysis of EGFR mutations or/and HER2 overexpression in Uygur's Non-small Cell Lung Cancer. Int J Clin Exp Med. 2015; 8(12): 22300-9. PMID 26885207*
111. *Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. Jun 01 2013; 31(16): 1997-2003. PMID 23610105*
112. *Food and Drug Administration Center for Drug Evaluation and Research. Multi-Discipline Review of Pralsetinib (2020).*
113. *Wolf J, Seto T, Han JY, et al. Capmatinib in MET Exon 14-Mutated or MET -Amplified Non-Small-Cell Lung Cancer. N Engl J Med. Sep 03 2020; 383(10): 944-957. PMID 32877583*

114. *Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. Feb 22 2018; 378(8): 731-739. PMID 29466156*
115. *Food and Drug Administration (FDA). NDA Multidisciplinary Review and Evaluation NDA 210861 and NDA 211710 VITRAKVI (larotrectinib), 2018.*
116. *Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. Apr 2020; 21(4): 531-540. PMID 32105622*
117. *Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. Feb 2020; 21(2): 271-282. PMID 31838007*
118. *Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. N Engl J Med. Oct 01 2020; 383(14): 1328-1339. PMID 32997907*
119. *Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. Nov 10 2016; 375(19): 1823-1833. PMID 27718847*
120. *Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. Nov 21 2019; 381(21): 2020-2031. PMID 31562796*
121. *Rizvi H, Sanchez-Vega F, La K, et al. Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing. J Clin Oncol. Mar 01 2018; 36(7): 633-641. PMID 29337640*
122. *Singal G, Miller PG, Agarwala V, et al. Association of Patient Characteristics and Tumor Genomics With Clinical Outcomes Among Patients With Non-Small Cell Lung Cancer Using a Clinicogenomic Database. JAMA. Apr 09 2019; 321(14): 1391-1399. PMID 30964529*
123. *Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. Oct 2020; 21(10): 1353-1365. PMID 32919526*
124. *Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. Aug 04 2011; 365(5): 395-409. PMID 21714641*
125. *Lee JK, Hahn S, Kim DW, et al. Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis. JAMA. Apr 09 2014; 311(14): 1430-7. PMID 24715074*
126. *Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. Apr 30 2015; 372(18): 1689-99. PMID 25923549*

127. *Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med. Jun 14 2018; 378(24): 2288-2301. PMID 29863955*
128. *Wu Y, Liu H, Shi X, et al. Can EGFR mutations in plasma or serum be predictive markers of non-small-cell lung cancer? A meta-analysis. Lung Cancer. Jun 2015; 88(3): 246-53. PMID 25837799*
129. *Supplee JG, Milan MSD, Lim LP, et al. Sensitivity of next-generation sequencing assays detecting oncogenic fusions in plasma cell-free DNA. Lung Cancer. Aug 2019; 134: 96-99. PMID 31320002*
130. *Papadimitrakopoulou VA, Han JY, Ahn MJ, et al. Epidermal growth factor receptor mutation analysis in tissue and plasma from the AURA3 trial: Osimertinib versus platinum-pemetrexed for T790M mutation-positive advanced non-small cell lung cancer. Cancer. Jan 15 2020; 126(2): 373-380. PMID 31769875*
131. *Jenkins S, Yang JC, Ramalingam SS, et al. Plasma ctDNA Analysis for Detection of the EGFR T790M Mutation in Patients with Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. Jul 2017; 12(7): 1061-1070. PMID 28428148*
132. *Food and Drug Administration (FDA). cobas EGFR Mutation Test v2 (P150047). 2016;*
133. *Karlovich C, Goldman JW, Sun JM, et al. Assessment of EGFR Mutation Status in Matched Plasma and Tumor Tissue of NSCLC Patients from a Phase I Study of Rociletinib (CO-1686). Clin Cancer Res. May 15 2016; 22(10): 2386-95. PMID 26747242*
134. *Thress KS, Brant R, Carr TH, et al. EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of leading technologies to support the clinical development of AZD9291. Lung Cancer. Dec 2015; 90(3): 509-15. PMID 26494259*
135. *Mok T, Wu YL, Lee JS, et al. Detection and Dynamic Changes of EGFR Mutations from Circulating Tumor DNA as a Predictor of Survival Outcomes in NSCLC Patients Treated with First-line Intercalated Erlotinib and Chemotherapy. Clin Cancer Res. Jul 15 2015; 21(14): 3196-203. PMID 25829397*
136. *Weber B, Meldgaard P, Hager H, et al. Detection of EGFR mutations in plasma and biopsies from non-small cell lung cancer patients by allele-specific PCR assays. BMC Cancer. Apr 28 2014; 14: 294. PMID 24773774*
137. *Palmero R, Taus A, Viteri S, et al. Biomarker Discovery and Outcomes for Comprehensive Cell-Free Circulating Tumor DNA Versus Standard-of-Care Tissue Testing in Advanced NonSmall-Cell Lung Cancer. JCO Precis Oncol. 2021;(5):93-102.*
138. *Food and Drug Administration. Guardant360 CDx. 2020;*
139. *Leighl NB, Page RD, Raymond VM, et al. Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-small Cell Lung Cancer. Clin Cancer Res. Aug 01 2019; 25(15): 4691-4700. PMID 30988079*
140. *Schwaederle MC, Patel SP, Husain H, et al. Utility of Genomic Assessment of Blood-Derived Circulating Tumor DNA (ctDNA) in Patients with Advanced Lung Adenocarcinoma. Clin Cancer Res. Sep 01 2017; 23(17): 5101-5111. PMID 28539465*

141. *Thompson JC, Yee SS, Troxel AB, et al. Detection of Therapeutically Targetable Driver and Resistance Mutations in Lung Cancer Patients by Next-Generation Sequencing of Cell-Free Circulating Tumor DNA. Clin Cancer Res. Dec 01 2016; 22(23): 5772-5782. PMID 27601595*
142. *Villaflor V, Won B, Nagy R, et al. Biopsy-free circulating tumor DNA assay identifies actionable mutations in lung cancer. Oncotarget. Oct 11 2016; 7(41): 66880-66891. PMID 27602770*
143. *Ramalingam SS, Yang JC, Lee CK, et al. Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. Mar 20 2018; 36(9): 841-849. PMID 28841389*
144. *Mellert H, Foreman T, Jackson L, et al. Development and Clinical Utility of a Blood-Based Test Service for the Rapid Identification of Actionable Mutations in Non-Small Cell Lung Carcinoma. J Mol Diagn. May 2017; 19(3): 404-416. PMID 28433077*
145. *Paweletz CP, Sacher AG, Raymond CK, et al. Bias-Corrected Targeted Next-Generation Sequencing for Rapid, Multiplexed Detection of Actionable Alterations in Cell-Free DNA from Advanced Lung Cancer Patients. Clin Cancer Res. Feb 15 2016; 22(4): 915-22. PMID 26459174*
146. *Pritchett MA, Camidge DR, Patel M, et al. Prospective Clinical Validation of the InVisionFirst-Lung Circulating Tumor DNA Assay for Molecular Profiling of Patients With Advanced Nonsquamous NonSmall-Cell Lung Cancer. JCO Precision Oncology 2019 :3, 1-15.*
147. *Remon J, Lacroix L, Jovelet C, et al. Real-World Utility of an Amplicon-Based Next-Generation Sequencing Liquid Biopsy for Broad Molecular Profiling in Patients With Advanced NonSmall-Cell Lung Cancer. JCO Precision Oncology 2019 :3, 1-14*
148. *Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED) FoundationOne Liquid CDx. 2020*
149. *Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED) Guardant360 CDx. 2020*
150. *Sacher AG, Paweletz C, Dahlberg SE, et al. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. JAMA Oncol. Aug 01 2016; 2(8): 1014-22. PMID 27055085*
151. *Guo QM, Wang L, Yu WJ, et al. Detection of Plasma EGFR Mutations in NSCLC Patients with a Validated ddPCR Lung cfDNA Assay. J Cancer. 2019; 10(18): 4341-4349. PMID 31413754*
152. *Zhang Y, Xu Y, Zhong W, et al. Total DNA input is a crucial determinant of the sensitivity of plasma cell-free DNA EGFR mutation detection using droplet digital PCR. Oncotarget. Jan 24 2017; 8(4): 5861-5873. PMID 28052016*
153. *Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED) cobas EGFR Mutation Test v2. 2016*

154. *Karachaliou N, Mayo-de las Casas C, Queralt C, et al. Association of EGFR L858R Mutation in Circulating Free DNA With Survival in the EURTAC Trial. JAMA Oncol. May 2015; 1(2): 149-57. PMID 26181014*
155. *Oxnard GR, Thress KS, Alden RS, et al. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. Oct 01 2016; 34(28): 3375-82. PMID 27354477*
156. *Helman E, Nguyen M, Karlovich CA, et al. Cell-Free DNA Next-Generation Sequencing Prediction of Response and Resistance to Third-Generation EGFR Inhibitor. Clin Lung Cancer. Nov 2018; 19(6): 518-530.e7. PMID 30279111*
157. *Chen Y, Han T, Zhou Y, et al. Comparing the efficacy of targeted next-generation sequencing in the identification of somatic mutations in circulating tumor DNA from different stages of lung cancer. Neoplasma. Jul 23 2019; 66(4): 652-660. PMID 31058536*
158. *Tran VT, Phan TT, Nguyen ST, et al. Smoking habit and chemo-radiotherapy and/or surgery affect the sensitivity of EGFR plasma test in non-small cell lung cancer. BMC Res Notes. Aug 03 2020; 13(1): 367. PMID 32746896*
159. *Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol. Jun 01 2018; 36(16): 1631-1641. PMID 29504847*
160. *Food and Drug Administration. Summary of Safety and Effectiveness Data. FoundationOne Liquid CDx. 2020.*
161. *Dziadziuszko R, Mok T, Peters S, et al. Blood First Assay Screening Trial (BFAST) in Treatment-Naive Advanced or Metastatic NSCLC: Initial Results of the Phase 2 ALK-Positive Cohort. J Thorac Oncol. Jul 24 2021. PMID 34311110*
162. *Socinski MA, Evans T, Gettinger S, et al. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. May 2013; 143(5 Suppl): e341S-e368S. PMID 23649446*
163. *Hanna NH, Robinson AG, Temin S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. J Clin Oncol. Mar 20 2021; 39(9): 1040-1091. PMID 33591844*
164. *Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Arch Pathol Lab Med. Jun 2013; 137(6): 828-60. PMID 23551194*
165. *Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Mol Diagn. Mar 2018; 20(2): 129-159. PMID 29398453*
166. *Protean BioDiagnostics, LungHDPCR, www.proteanbiodx.com/lung-hdpcr*

167. *National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 7.2024.*
168. *Rolfo C, Mack P, Scagliotti GV, et al. Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer. J Thorac Oncol. 2021;16(10):1647-1662. doi:10.1016/j.jtho.2021.06.017*
169. *Aggarwal C, Marmarelis ME, Hwang WT, et al. Association Between Availability of Molecular Genotyping Results and Overall Survival in Patients With Advanced Nonsquamous Non-Small-Cell Lung Cancer. JCO Precis Oncol. 2023;7:e2300191. doi:10.1200/PO.23.00191*
170. *Centers for Medicare and Medicaid Services. Next Generation Sequencing. 2020.*

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; 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.
	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;

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

	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.

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