BlueCross BlueShield Federal Employee Program

FEP Medical Policy Manual

FEP 2.04.45 Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS)

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Related Policies:

2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
2.04.157 - Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)

Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS)

Description

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Over half of patients with non-small-cell lung cancer (NSCLC) present with advanced and therefore incurable disease. Treatment in this setting has been with platinum-based chemotherapy. 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 that may direct targeted therapy or immunotherapy depending on the presence of specific variants.

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, cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease.[1,] When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and 1-year survival of 30% to 45%.[2,3,] 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.

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.

EGFR Gene Variants

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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EGFR Variant Frequency

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).[4,] 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.[5,] Eberhard et al (2005)[6,] observed *EGFR* variants in 6.4% of patients with SCC and Rosell et al (2009)[7,] 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.[8,9,]

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.[10,] 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%.[10,] 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, polymerase chain reaction technologies, or next-generation sequencing.

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.[10,]*RET* fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.[10,]

MET Gene

MET alteration is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs.[10,]

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.

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Targeted Treatment

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 18, 2023. 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.)

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) • Amivantamab-vmjw (Rybrenant) • Mobocertinib (Exkivity)
ALK	• Crizotinib (Xalkori) • Ceritinib (Zykadia) • Alectinib (Alecensa) • Brigatinib (Alunbrig) • Lorlatinib (Lorbrena)
BRAF	• Dabrafenib (Tafinlar) alone or in combination with trametinib (Mekinist)
ROS1	• Crizotinib (Xalkori)
KRAS	• Sotorasib (Lumakras) • Adagrasib (Krazati)
RET	• Selpercatinib (Retevmo) • Pralsetinib (Gavreto)
MET	• Capmatinib (Tabrecta) • Tepotinib (Tepmetko)

Source: FDA (2023)11,

ALK: anaplastic lymphoma kinase; *EGFR*: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; MET: mesenchymal-epithelial transition.

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OBJECTIVE

The objective of this evidence review is to summarize the evidence and guidelines on testing for *EGFR*, *BRAF*, and*KRAS* variants ; *ALK*, *ROS1*, and *RET* rearrangements; or *MET* alterations to select targeted treatment for individuals with advanced-stage non-small-cell lung cancer.

POLICY STATEMENT

EGFR Testing

Analysis of tumor tissue for somatic variants in exons 18 through 21 (eg, 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 (eg, 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 (eg, insertion mutations) within the *EGFR* gene, may be considered **medically necessary** to predict treatment response to an FDA-approved therapy (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, crizotinib [Xalkori] or entrectinib) in individuals with NSCLC.

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KRAS Testing

Analysis of tumor tissue for somatic variants of the *KRAS* gene (eg, 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 (eg, 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 (eg, 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 (eg, 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**.

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 NTRK testing.

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

For expanded panel testing, see evidence review 2.04.115.

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.

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.4.2023) 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 evidence review 2.04.157.

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:

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"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.4.2023) state the following: "Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate; however, 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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Some Plans may have contract or benefit exclusions for genetic testing or have state mandates for biomarker testing coverage.

FDA REGULATORY STATUS

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 or Metastatic Colorectal Cancer and FDA Approved Companion Diagnostic Tests

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Adagrasib (Krazati)	• Adults with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy	• Agilent Resolution ctDx FIRST assay • therascreen KRAS RGQ PCR Kit	KRAS	• KRYSTAL-1 NCT03785249[12,	2A or higher/ NSCLC Treatment (v.4.2023)[13,

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Afatinib (Gilotrif)	• First-line for patients with metastatic NSCLC whose tumors have non-resistant EGFR mutations as detected by an FDA-approved test. Limitations of Use: Safety and efficacy not established in patients whose tumors have resistant EGFR mutations • Patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy	• 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	• EGFR Mutation-Positive, Metastatic NSCLC: LUX-Lung 3 NCT00949650[14], • Non-resistant EGFR mutations (S768I, L861Q, and G719X) other than exon 19 deletions or exon 21 L858R substitutions: LUX-Lung 2 (NCT00525148), LUX-Lung 3 (NCT00949650), and LUX-Lung 6 (NCT01121393) (pooled subgroup analysis) [15], • Previously Treated, Metastatic Squamous NSCLC: LUX-Lung 8 NCT01523587[16],	Same as above
Alectinib (Alecensa)	• Patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: Ventana ALK (D5F3) CDx Assay • 2020: FoundationOne Liquid CDx	ALK	ALEX NCT02075840[17],	Same as above
Brigatinib (Alunbrig)	• Treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2020: Vysis ALK Break Apart FISH Probe Kit	*ALK* gene rearrangements	ALTA 1L NCT02737501[18],	Same as above
Capmatinib (Tabrecta)	• Metastatic NSCLC whose tumors have a mutation that leads to *MET* exon 14 skipping as detected by an FDA-approved test.	• 2020: FoundationOne CDx™ • 2021: FoundationOne Liquid CDx™	*MET* single nucleotide variants and indels that lead to *MET* exon 14 skipping	GEOMETRY mono-1 NCT02414139[19],	Same as above
Ceritinib (Zykadia)	• 2 • Adults with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: VENTANA ALK (D5F3) CDx Assay	• ALK rearrangements, • ALK protein expression	First-line: ASCEND-4 NCT01828099[20], Second-line: ASCEND-1, NCT01283516[21],	Same as above
Crizotinib (Xalkori)	• Adults with metastatic NSCLC whose tumors are ALK- or ROS1-positive as detected by an FDA-approved test	ALK tests: • 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories)	ALK	*ALK*-positive: PROFILE 1014 NCT01154140[22], NCT00932893[23],	Same as above

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		• 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine) ROS tests: • 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)		*ROS1*-positive: PROFILE 1001 NCT00585195[24],	
Dacomitinib (Vizimpro)	• First line for patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitutions as detected by an FDA-approved test	• 2018: therascreen EGFR RGQ PCR Kit • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)	EGFR	ARCHER 1050 NCT01774721[25],	Same as above
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	• Used in combination for treatment of patients with metastatic NSCLC with BRAF V600E mutation as detected by an FDA-approved test	• 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine)	BRAF V600E	Study BRF113928 NCT01336634[26],	Same as above
Erlotinib (Generic)	• First-line and maintenance treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations. • Locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.	• 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*	NCT00874419[27],	Same as above

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Gefitinib (Iressa)	• First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions as detected by an FDA-approved test Limitation of Use: Safety and efficacy of IRESSA have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations	• 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	Study 1, Study 2 (Iressa Product Label)[28],	Same as above
Lorlatinib (Lorbrena)	• Adult patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test	• 2021: Ventana ALK (D5F3) CDx Assay	ALK	CROWN NCT03052608[29],	Same as above
Mobocertinib (Exkivity)	• 2021: Adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy	• 2021: Oncomine Dx Target Test	EGFR	EXCLAIM NCT02716116[30],	Same as above
Osimertinib (Tagrisso)	• • Adjuvant therapy aftertumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. • First-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. • Treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.	• 2015-2020: cobas EGFR Mutation Test v2 (tissue or plasma • 2017-2019: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx • 2020: FoundationOne Liquid CDx	EGFR	• Adjuvant treatment: ADAURA NCT02511106[31], [32], [33], • First-line, EGFR - Positive Metastatic NSCLC: FLAURA NCT02296125[34], • Previously Treated EGFR T790M Mutation-Positive: AURA3[35],	Same as above
Pralsetinib (Gavreto)	• Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	• 2020: Oncomine Dx Target Test	RET	ARROW NCT03037385[36],	Same as above

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Selpercatinib (Retevmo)	• Adult patients with metastatic RET fusion-positive NSCLC	• 2022: Oncomine Dx Target Test	RET	LIBRETTO-001 NCT03157128[37, 38,]	Same as above
Sotorasib (Lumakras)	• Adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least 1 prior systemic therapy	• 2021: Therascreen KRAS RGQ PCR kit • 2021: Guardant360 CDx	KRAS	CodeBreaK 100 NCT03600883[39, 40,]	Same as above
Tepotinib (Tepmetko)	• Adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.	• No approved companion diagnostic	MET exon 14 skipping alterations	VISION NCT02864992[41, 42,]	Same as above

Sources: U.S. Food and Drug Administration (2023)[43,]; U.S. Food and Drug Administration (n.d.)[11,]
ALK: anaplastic lymphoma kinase; CDx: companion diagnostic;*EGFR*: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; ; MET: mesenchymal-epithelial transition; NCCN: National Comprehensive Cancer Network; NSCLC: non-small-cell lung cancer; PCR: polymerase chain reaction; TKI: tyrosine kinase inhibitor.

Laboratory-Developed Tests

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed under CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

RATIONALE

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.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Chest Physicians Guidelines

In 2013, the American College of Chest Physicians updated its evidence-based practice guidelines on the treatment of stage IV non-small-cell lung cancer (NSCLC).[44,] Based on a review of the literature, the College reported improved response rates, progression-free survival, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with *EGFR* variants, especially exon 19 deletion and L858R. The College recommended, "testing patients with NSCLC for *EGFR* mutations at the time of diagnosis whenever feasible, and treating with first-line EGFR TKIs [tyrosine kinase inhibitors] if mutation-positive."

American Society of Clinical Oncology

In 2021, the American Society of Clinical Oncology (ASCO) and Ontario Health published updated guidelines on therapy for stage IV NSCLC with driver alterations. [45,] The updated recommendations were based on a systematic review of randomized controlled trials from December 2015 to January 2020 and meeting abstracts from ASCO 2020. The recommendations include the following:

- All patients with nonsquamous NSCLC should have the results of testing for potentially targetable mutations (alterations) before implementing therapy for advanced lung cancer, regardless of smoking status, when possible.
- Targeted therapies against ROS1 fusions, BRAF V600E mutations, RET fusions, MET exon 14 skipping mutations, and NTRK fusions should be offered to patients, either as initial or second-line therapy when not given in the first-line setting.
- Chemotherapy is still an option at most stages.

The above guidelines were updated in 2023 to add amivantamab monotherapy and mobocertinib monotherapy for second-line treatment in advanced NSCLC with an *EGFR* exon 20 insertion, and sotorasib monotherapy for second-line treatment in advanced NSCLC with a *KRAS*-G12C mutation.[46,]

In 2022, the ASCO published a guideline on the management of stage III NSCLC.[47,] The recommendations were based on a literature search of systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2021. Relevant recommendations include the following:

- Presence of oncogenic driver alterations, available therapies, and patient characteristics should be taken into account.
- Patients with resected stage III NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutation may be offered adjuvant osimertinib after platinum-based chemotherapy.

College of American Pathologists et al

In 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR and ALK TKI therapy.[48,] Based on excellent quality evidence (category A), the guidelines recommended *EGFR* variant and *ALK* rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (eg, smoking history).

In 2018, updated guidelines were published and added new *EGFR* and *ALK* recommendations.[49,]*ROS1* testing is recommended for all patients with lung adenocarcinoma irrespective of clinical characteristics (strong recommendation). *BRAF*, *RET*, *HER2*, *KRAS*, and *MET* testing are not recommended as routine stand-alone tests, but may be considered as part of a larger testing panel or if *EGFR*, *ALK*, and *ROS1* are negative (expert consensus opinion).

National Comprehensive Cancer Network Guidelines

Testing for Molecular Biomarkers

National Comprehensive Cancer Network (NCCN) guidelines on NSCLC provide recommendations for individual biomarkers that should be tested, and recommend testing techniques. Guidelines are updated frequently; refer to the source document for current recommendations. The most recent guidelines (v.4.2023) include the following recommendations and statements related to testing for molecular biomarkers:[13,]

- Broad molecular profiling systems may be used to simultaneously test for multiple biomarkers.
- To minimize tissue use and potential wastage, the NCCN NSCLC Panel recommends that broad molecular profiling be done as part of biomarker testing using a validated test(s) that assesses potential genetic variants:
    - *ALK* rearrangements
    - *EGFR* mutations
    - *BRAF* mutations
    - *MET* exon 14 skipping mutations

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  - *RET* rearrangements
  - *ERBB2* (*HER2*) mutations
  - *KRAS* mutations
  - *NTRK* 1/2/3 gene fusions
  - *ROS1* rearrangements
- Both U.S. Food and Drug Administration (FDA) and laboratory-developed test platforms are available that address the need to evaluate these and other analytes.
- Broad molecular profiling is also recommended to identify emerging biomarkers for which effective therapy may be available, such as high-level *MET* amplifications.
- Clinicopathologic features should not be used to select patients for testing.
- The guidelines do not endorse any specific commercially available biomarker assays or commercial laboratories.

Plasma Cell-Free/Circulating Tumor DNA Testing:

The NCCN guidelines on NSCLC (v.4.2023) include the following recommendations related to plasma cell-free/circulating tumor DNA testing.[13,]

- Plasma cell free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis.
- Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation, most commonly in processed plasma (sometimes referred to as "liquid biopsy").
- Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate; however, data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.
- Published guidelines elaborating standards for analytical performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.
- Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example, clonal hematopoiesis of indeterminate potential (CHIP).
- The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably:
  - If a patient is medically unfit for invasive tissue sampling
  - In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA can be used, however, follow-up tissue-based analysis for all patients in which an oncogenic driver is not identified should be planned.
  - In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available, consider repeat biopsy and/or cell-free/circulating tumor DNA testing.
  - In the initial diagnostic setting, if the feasibility of timely tissue-based testing is uncertain, concurrent circulating tumor DNA testing may aid in biomarker evaluation for treatment selection, provided negative results are considered per above limitations.

The guidelines also state:

- Standards for analytic performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare and Medicaid Services will cover diagnostic testing with next-generation sequencing for beneficiaries with recurrent, relapsed, refractory, metastatic cancer, or advanced stages III or IV cancer if the beneficiary has not been previously tested using the same next-generation sequencing test, unless a new primary cancer diagnosis is made by the treating physician, and if the patient has decided to seek further cancer treatment. The test must have an FDA- approved or cleared indication as an in vitro diagnostic, with results and treatment options provided to the treating physician for patient management.[50,]

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2018	New policy	Analysis of somatic variants in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (EGFR), may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) in patients with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified. Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered investigational. Analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (ALK) gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section). Analysis of somatic rearrangement variants of the ALK gene is considered investigational in all other situations. Analysis of the BRAF V600E variant may be considered medically necessary to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar] and trametinib [Mekinist]), in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. Analysis of somatic rearrangement variants of the ROS1 gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. Analysis of somatic variants of the KRAS gene is considered investigational as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the antiEGFR monoclonal antibody cetuximab in NSCLC. Analysis of genetic alterations in the genes HER2, RET, and MET for targeted therapy in patients with NSCLC is considered investigational.
December 2019	Replace policy	Policy updated with literature review through August 26, 2019; references added. FEP related pharmacy policies added. New indications for NTRK testing and tumor mutational burden (TMB) testing added. Medically necessary statement for NTRK testing and investigational statement for TMB testing added; other policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 9, 2020; references added. Separated out KRAS, HER2, RET and MET into 2 indications. RET and MET testing are medically necessary under specified conditions. KRAS and HER2 indications remain investigational. Added an indication and MN policy statement for PD-L1 testing. Updated Policy Guidelines section with recommended testing strategies. Updated Regulatory Status section and Policy statements with new FDA indications. "or Immunotherapy" added to the policy title.
March 2022	Replace policy	Policy updated with literature review through September 29, 2021; references added. Policy No. 2.04.143 (Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer [Liquid Biopsy]) was merged with this policy and Policy 2.04.143 archived. New indication and medically necessary policy statement added for KRAS testing to select patients for treatment with sotorasib. New indications and investigational policy statements added for ALK rearrangement and MET exon 14 skipping alteration testing using FoundationOne Liquid. Corrected terminology from "MET amplifications" to "MET alterations" in the evidence review.
March 2023	Replace policy	Policy updated with literature review through October 17, 2022; references added. Policy title changed to: "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)." Policy extensively revised as full evidence review is no longer included for somatic tests of individual genes (not gene panels) associated with U.S. Food and Drug Administration (FDA)-approved therapeutics (ie, as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher. New evidence reviews added addressing testing of HER2 variants in tissue to select patients for immunotherapy and testing of KRAS, ROS1, and HER2 variants in plasma for targeted therapy or immunotherapy. New medically necessary policy statements added with criteria for testing of: EGFR exon 20 insertions in tissue and plasma, ALK in plasma, KRAS G12C in plasma, HER2 in tissue and plasma, and MET exon 14 skipping alterations in plasma.
March 2024	Replace policy - coding update only	Removed NTRK codes 81191-81194 as NTRK testing is not addressed in this review. Policy updated with literature search through October 18, 2023; references added. Evidence opinion extensively pruned; evidence review is not included for somatic tests of individual genes (not gene panels) associated with FDA-approved therapies with NCCN recommendations of 2A or higher. Pivotal studies added to Table 2. Indications related to immunotherapy and tumor mutational burden testing removed and added to policy 2.04.157. Indication on HER2 removed as out of scope. Title changed accordingly. Policy statements revised for clarity and to align with indications; intent unchanged.

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