Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 01/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Medical policy 00597 Circulating Tumor DNA Management of Non-Small Cell Lung Cancer (Liquid Biopsy) was retired effective 04/11/2022 and merged with this medical policy.

Note: Medical policy 00423 Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Note: Medical policy 00497 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Note: Medical policy 00731 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer

EGFR, ALK, BRAF, ROS1, KRAS, NTRK, RET, MET, HER2, PD-L1 AND MICROSATELLITE INSTABILITY TUMOR SPECIMEN TESTING

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider initial analysis of tumor tissue for somatic variants within the *EGFR* gene, rearrangement variants of the *ALK* gene, *BRAF V600E* variant, rearrangement variants of the *ROS1* gene, variants of the *KRAS* gene, *NTRK* gene fusions, alteration in the *RET* gene, alteration that leads to *MET* exon 14 skipping, *HER2* and *PD-L1*

expression by immunohistochemistry to predict treatment response to an FDA-approved targeted therapy or immunotherapy in individuals with advanced (stage III or IV) non-small-cell lung cancer (NSCLC) to be **eligible for coverage.****

Based on review of available data, the Company may consider microsatellite instability (*MSI*) testing for selecting immunotherapy cancer treatment with pembrolizumab (Keytruda) in patients with metastatic or unresectable NSCLC to be **eligible for coverage.***

Patient Selection Criteria

Coverage eligibility for MSI testing for selecting treatment with pembrolizumab (Keytruda) will be considered when **ALL** of the following criteria are met:

- Individual has metastatic or unresectable stage III NSCLC (is not a candidate for surgical resection or definitive chemoradiation); **AND**
- Pembrolizumab is being considered; **AND**
- The panel test has a U.S. Food and Drug Administration (FDA) approved or cleared indication as an in vitro companion diagnostic (i.e., FoundationOne CDx™‡ assay); **AND**
- Individual has not been previously tested using the same test, unless a new primary cancer diagnosis is made, and further cancer treatment is being considered, or as noted below under repeat testing.

LIQUID BIOPSY (PLASMA) TESTING WHEN TISSUE IS INSUFFICIENT

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider FDA- approved companion diagnostic plasma test in patients with advanced or metastatic NSCLC (stage IIIB or IV) to predict

treatment response to an FDA-approved targeted therapy or immunotherapy for patients meeting the following criteria to be **eligible for coverage:****

Patient Selection Criteria

Coverage eligibility will be considered when **ALL** the following criteria are met:

- Tissue-based somatic genomic profiling test is not feasible (i.e., tumor tissue quantity is not sufficient for standard molecular testing using formalin-fixed paraffin-embedded tissue or invasive biopsy is medically contraindicated); AND
- Liquid biopsy test must have a U.S. Food and Drug Administration (FDA) approved or cleared indication as an in vitro companion diagnostic for use in NSCLC (i.e., FoundationOne®‡ Liquid CDx, Guardant360®‡ CDx; see also Policy Guidelines): AND
- Requested panel test needs to include relevant oncogenic driver variants with National Comprehensive Cancer Network (NCCN) recommendation of 2A or higher (i.e., *EGFR, ALK, BRAF V600E, ROS1, KRAS, NTRK* gene fusion, *RET* rearrangement, *MET* exon 14 skipping, MSI, *HER2*); AND
- Individual has not been previously tested using the same liquid biopsy panel, unless a new primary cancer diagnosis is made, and further cancer treatment is being considered, or as noted below under repeat testing; AND
- Follow-up tissue-based analysis will be considered if no driver variant is detected by plasma genotyping, or if circulating tumor DNA (ctDNA) is insufficient and not detected.

REPEAT TESTING

Based on review of available data, the Company may consider repeat tissue or plasma based analysis of the *EGFR* gene for T790M variant to guide treatment with FDA approved medications (e.g., osimertinib) in individuals with advanced (stage III or IV) NSCLC and progression or resistance to EGFR-targeted tyrosine kinase inhibitors (e.g., erlotinib, afatinib, gefitinib or dacomitinib) to be **eligible for coverage.****

Note:
For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing (NGS), single available procedure code for the multi-gene panel test is to be utilized.

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Per the AMA, when a PLA code is available to report a given proprietary laboratory service, the service should not be reported with any other CPT code(s).

Testing for other variants may become available between policy updates.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers tissue based analysis of somatic variants that are eligible for coverage (i.e., *EGFR, ALK, BRAF, ROS1, KRAS, NTRK, RET, MET, HER2,* and MSI and *PD-L1* expression by immunohistochemistry) in all other situations to be **investigational.***

Based on review of available data, the Company considers analysis for all other somatic genetic alterations for selection of NSCLC targeted therapy or immunotherapy, including but not limited to analysis of tumor mutational burden (TMB), to be **investigational.***

Based on review of available data, the Company considers use of concurrent liquid based test in addition to tumor based genomic profiling to be **investigational.***

Based on review of available data, the Company considers liquid biopsy testing when selection criteria are not met and in all other situations not mentioned above to be **investigational.***

Policy Guidelines

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

For expanded panel testing, see medical policy 00423 Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapy and Immunotherapy.

Agents targeted against HER2 in 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 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 non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling, defined as a single assay or a combination of a limited number of assays and that it is acceptable to have a tiered approach based on low-prevalence, co-occurring biomarkers. The guidelines additionally recommend identifying the emerging biomarker, high-level MET amplification, while noting that the definition of this biomarker is evolving and may differ according to the assay used.

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

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

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
Patients 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.

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Background/Overview

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. 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%. 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 tyrosine kinase 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 tyrosine kinase inhibitors (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.

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). 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.

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

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

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

NTRK Gene Fusions

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

PD-1/PD-L1

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

Tumor Mutational Burden

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

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 and Immunotherapy

FDA-approved targeted treatments and immunotherapies for the variants described above are summarized in Table 1. (Note this information is current as of November 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.).

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Table 1. Targeted Treatments and Immunotherapy 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) • Entrectinib (Rozlytrek)
KRAS	• Sotorasib (Lumakras) • Adagrasib (Krazati)
HER2 (ERBB2)	• Fam-trastuzumab deruxtecan-nxki (Enhertu)
RET	• Selpercatinib (Retevmo) • Pralsetinib (Gavreto)

MET	• Capmatinib (Tabrecta) • Tepotinib (Tepmetko)
NTRK	• Larotrectinib (Vitrakvi) • Entrectinib (Rozlytrek)
PD-L1	• Pembrolizumab (Keytruda) • Nivolumab (Opdivo) in combination with ipilimumab (Yervoy) • Atezolizumab (Tecentriq) • Cemiplimab-rwlc (Libtayo)

FDA or Other Governmental Regulatory Approval

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 November 18, 2023. An up-to-date 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. FDA-Approved Targeted Treatments for NSCLC and Companion Diagnostic Tests

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
dMMR/MSI-H	Pembrolizumab (Keytruda®)	Adult and pediatric patients with unresectable or metastatic dMMR or MSI-H solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no	Ventana MMR RxDx (dMMR) FoundationOne CDx (MSI-H)

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
		satisfactory alternative treatment options* *Safety and effectiveness in pediatric patients with MSI-H central nervous system cancers have not been established*	
dMMR	Dostarlimab (Jemperli®)	Adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options*	Ventana MMR RxDx Panel
PD-L1	Pembrolizumab (Keytruda)	First-line treatment of patients with NSCLC expressing PD-L1 as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is: • stage III where patients are not candidates for surgical resection or definitive chemoradiation, or • metastatic Patients with metastatic NSCLC whose tumors express PD-L1 as	PD-L1 IHC 22C3 pharmDx

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
		determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy	
PD-L1	Cemiplimab (Libtayo®)	First-line treatment of adult patients with NSCLC whose tumors have high PD-L1 expression (TPS≥ 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations, and is: • locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or • metastatic	PD-L1 IHC 22C3 pharmDx
PD-L1	Nivolumab (Opdivo) + Ipilimumab (Yervoy)	Patients with metastatic NSCLC expressing PD-L1 as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations	PD-L1 IHC 28-8 pharmDx
PD-L1	Atezolizumab (Tecentriq)	Adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells,	Ventana PD-L1 (SP263) Assay

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
		as determined by an FDA-approved test	
TMB	Pembrolizumab (Keytruda)	Adult and pediatric patients with unresectable or metastatic TMB-high (≥10 mutations/megabase) solid tumors, as determined by an FDA-approved test that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx
KRAS	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
EGFR	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	2013: therascreen EGFR (RGQ PCR) kit (Qiagen) 2016: therascreen EGFR RGQ PCR Kit (Qiagen) 2017: FoundationOne

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
		Patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy	CDx™ (Foundation Medicine) 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
ALK	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 gene rearrangements	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
MET single nucleotide variants and indels that lead	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™

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
to MET exon 14 skipping			2021: FoundationOne Liquid CDx™
ALK rearrangements, ALK protein expression	Ceritinib (Zykadia)	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	Crizotinib (Xalkori)	Adults with metastatic NSCLC whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test	ALK tests: 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) 2017: FoundationOne CDx™ (Foundation Medicine)

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
			ROS tests: 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)
EGFR	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)
BRAF V600E	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)
EGFR	Erlotinib (Generic)	First-line and maintenance treatment of patients with locally advanced or metastatic NSCLC	2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics)

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
		with EGFR activating mutations. Locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.	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)
Exon 19 deletion or exon 21 L858R substitution mutation	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	2015: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
		established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations	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)

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
ALK	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
EGFR	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	Osimertinib (Tagrisso)	Adjuvant therapy aftertumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (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.	2015-2020: cobas® EGFR Mutation Test v2 (tissue or plasma 2017-2019: FoundationOne CDx™ (Foundation Medicine) 2020: Guardant360 CDx 2020: FoundationOne® Liquid CDx

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion 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.	
RET	Pralsetinib (Gavreto)	Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	2020: Oncomine Dx Target Test
RET	Selpercatinib (Retevmo)	Adult patients with metastatic RET fusion-positive NSCLC	2022: Oncomine Dx Target Test
KRAS	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
MET exon 14 skipping alterations	Tepotinib (Tepmetko)	Adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.	No approved companion diagnostic

Abbreviations: ALK, anaplastic lymphoma kinase; CPS, combined positive score; CRC, colorectal cancer; dMMR, mismatch repair-deficient; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; MSI-H, microsatellite instability-high; NSCLC, non-small cell lung cancer; pMMR, mismatch repair-proficient; ROS1, c-ros oncogene1; TNBC, triple-negative breast cancer; TMB, tumor mutational burden; TPS, tumor proportion score.

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Source: U.S. Food & Drug Administration (2023). *This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

Summary of Evidence

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 tissue biopsy specimens, the evidence includes 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 National Comprehensive Cancer Network (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 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 National Comprehensive Cancer Network (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 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 National Comprehensive Cancer Network (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 circulating tumor DNA (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 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 National Comprehensive Cancer Network (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 circulating tumor DNA (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 circulating tumor DNA (ctDNA) (liquid biopsy), the evidence includes 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 National Comprehensive Cancer Network (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 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 National Comprehensive Cancer Network (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 circulating tumor DNA (ctDNA) (liquid biopsy), the evidence includes 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 National Comprehensive Cancer Network (NCCN) recommendations.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive PD-L1 testing, the evidence includes randomized controlled trials (RCTs) comparing immunotherapy to chemotherapy. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In RCTs, patients with high PD-L1 expression had longer PFS and fewer adverse events when treated with anti-PD-L1 monoclonal antibodies than with platinum chemotherapy. In the KEYNOTE trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level. Based on clinical trial data, PD-L1 testing has received FDA approval and NCCN recommendations to select immune checkpoint inhibitor therapy in individuals with metastatic NSCLC. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy with fam-trastuzumab deruxtecan-nxki who receive somatic testing for HER2 variants, the evidence includes a multicenter, blinded, and randomized dose-optimization trial. Relevant outcomes are OS,

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

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive tumor mutational burden (TMB) testing, the evidence includes a RCT and retrospective observational studies. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In a subgroup analysis of the KEYNOTE trial, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high TMB (≥10 mutations per megabase). In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies. Additionally, there is no consensus on how to measure TMB, and current NCCN guidelines no longer recognize it as an emerging biomarker for NSCLC. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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). 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 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. 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.

In 2022, the ASCO published a guideline on the management of stage III NSCLC. 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. 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. *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
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:

- Broad molecular profiling systems may be used to simultaneously test for multiple biomarkers. The Panel added a definition for broad molecular profiling for NSCLC as molecular testing that identifies all of the classic actionable biomarkers (e.g., *ALK, BRAF, EGFR, KRAS, METex14 skipping, NTRK 1/2/3, RET, ROS1*) using either a single assay or a combination of a limited number of assays, and optimally also identifies the emerging biomarkers (e.g., high-level MET amplification, ERBB2 mutations).
- NSCLC Panel recommends that broad molecular profiling be done as part of biomarker testing using a validated test(s) that assesses a minimum of the following potential genetic variants: *ALK* rearrangements, *BRAF* mutations, EGFR mutations, KRAS mutations,

METex14 skipping mutations, *NTRK* 1/2/3 gene fusions, RET rearrangements, ROS1 rearrangements, and IHC testing for PD-L1 expression levels.

- The NCCN Panel recently deleted TMB as an emerging immune biomarker based on clinical trial data and other issues. In addition to the lack of clinical data to support use of TMB as an immune biomarker, there are technical problems with measuring TMB (e.g., lack of agreement on the definition of a cut off for designating high TMB levels; lack of standardization of TMB measurements across laboratories).
- Biomarker testing should be done at properly accredited laboratories (minimum of Clinical Laboratory Improvement Amendments [CLIA] accreditation). Both FDA and laboratory-developed test platforms are available that evaluate these and other analytes.
- The guidelines do not endorse any specific commercially available biomarker assays.
- 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
  - RET rearrangements
  - ERBB2 (HER2) mutations
  - KRAS mutations
  - NTRK 1/2/3 gene fusions
  - ROS1 rearrangements

- Both 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.

- Plasma cell free/circulating tumor DNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC.
- Plasma cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, notably:
    - the patient is not medically fit for invasive tissue sampling; or
    - There is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified.
- 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 ~~is~~ for all patients in which an oncogenic driver is not identified.

- 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 cfDNA 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 a U.S. Food and Drug Administration approved or cleared indication as an in vitro diagnostic, with results and treatment options provided to the treating physician for patient management.

Ongoing and Unpublished Clinical Trials
Some currently ongoing trials that might influence this review are listed in Table 3

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03576937	Achieving Value in Cancer Diagnostics: Blood Versus Tissue Molecular Profiling - a Prospective Canadian Study (VALUE)	207	Sep 2022
NCT01306045	Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	471	Dec 2024
NCT03225664	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer	37 (actual)	Sep 2024
NCT02622581	Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP)	12400	Dec 2027
NCT02117167a	Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: SAFIR02_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer	999	Dec 2023
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Dec 2025
NCT02576431a	A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-positive Tumors	204	Aug 2025
NCT02568267a	An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic	700	Apr 2025

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements		
NCT01639508	A Phase II Study of Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	86	Jul 2023
NCT03199651	Beating Lung Cancer in Ohio (BLCIO) Protocol	2994	Dec 2023
NCT04863924	Accelerating Lung Cancer Diagnosis Through Liquid Biopsy (ACCELERATE)	170	Dec 2023
NCT04912687a	Implementing Circulating Tumor DNA Analysis at Initial Diagnosis to Improve Management of Advanced Non-small Cell Lung Cancer Patients (NSCLC) (CIRCULAR)	580	Jan 2024
NCT03037385a	A Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors	589	Feb 2024
NCT03178552a	A Phase II/III Multicenter Study Evaluating the Efficacy and Safety of Multiple Targeted Therapies as Treatments for Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring Actionable Somatic Mutations Detected in Blood (B-FAST: Blood-First Assay Screening Trial)	1000	Apr 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	384	Aug 2024
NCT04180176a	A Multicenter, Low-Interventional Study to Evaluate the Feasibility of a Prospective Clinicogenomic Program (PCG)	1000	Mar 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 01/01/2024

Policy History

Original Effective Date: 05/20/2015
Current Effective Date: 01/01/2024

05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. New policy. Replaced policy 00122 and 00289.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Added coverage statement for analysis for the T790M mutation and added brand names to the coverage statements.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Added ROS1 and BRAF testing to medically necessary statement. Rationale reorganized. Criteria reformatted.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. The policy section on EGFR Testing was changed given the new evidence in support of testing for additional variants in the EGFR gene.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. 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.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. No change to coverage.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. 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. Added a new

	PICO for immunotherapy. 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.
03/04/2021	Medical Policy Committee review
03/10/2021	Medical Policy Implementation Committee approval. Added Small panel testing including the genes listed as eligible for coverage may be considered as an alternative to individual testing and may be preferred when there is limited tissue available for testing. For 5 or more gene tests being run on a tumor specimen on the same platform, such as multi-gene panel next generation sequencing, an available procedure code for the multi-gene panel test is to be utilized.
03/03/2022	Medical Policy Committee review
03/09/2022	Medical Policy Implementation Committee approval. New indication and eligible for coverage 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. Title changed to “Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer.” Coding update
06/07/2022	Coding update
09/01/2022	Medical Policy Committee review
09/14/2022	Medical Policy Implementation Committee approval. Coverage extensively revised due to senate bill update.
12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. Senate bill update. No change to coverage.
06/06/2023	Coding update
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Senate bill review. 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. Policy

	statements revised for clarity and to align with indications; intent unchanged. New codes effective 01/01/2024 added to policy.
02/01/2024	Coding update

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0022U, 0037U, 0179U, 0239U, 0242U, 0326U, 0388U, 81191, 81192, 81193, 81194, 81210, 81235, 81275, 81276, 81401, 81404, 81405, 81406, 81445, 81479, 88365 Delete code effective 01/01/2023: 88364 Delete code effective 10/01/2023: 0397U Add code effective 01/01/2024: 81457, 81458, 81459, 81462, 81463, 81464, 88366 Add code effective 02/01/2024: 81455
HCPCS	No codes
ICD-10 Diagnosis	C34.00-C34.92

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.