Medical Policy

BlueCross BlueShield Kansas
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Title: Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (*EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, NTRK*)

Related Policies:	▪ *Comprehensive Genetic Profiling for Selecting Targeted Cancer Therapies*

Professional / Institutional
Original Effective Date: September 28, 2014
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Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with tyrosine kinase inhibitors (TKIs)	Interventions of interest are: • Somatic testing for *EGFR* variants or *ALK* rearrangements using tissue biopsy specimens to guide treatment	Comparators of interest are: • Management without genetic testing for EGFR variants or ALK rearrangements	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include:

Populations	Interventions	Comparators	Outcomes
• With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with TKIs	• Somatic testing for *EGFR* variants or *ALK* rearrangements using circulating tumor DNA (ctDNA) (liquid biopsy) to guide treatment	• Biomarker testing using tissue to guide treatment	• Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with BRAF or ROS1 inhibitors	Interventions of interest are: • Somatic testing for *BRAF* variants or *ROS1* rearrangements using tissue biopsy specimens to guide treatment	Comparators of interest are: • Management without genetic testing for BRAF variants or ROS1 rearrangements	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with BRAF or ROS1 inhibitors	Interventions of interest are: • Somatic testing for BRAF variants or ROS1 rearrangements using ctDNA (liquid biopsy) to guide treatment	Comparators of interest are: • Biomarker testing using tissue to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with RET or MET inhibitors	Interventions of interest are: Somatic testing for *RET* rearrangements or MET alterations using tissue biopsy specimens to guide treatment	Comparators of interest are: • Management without genetic testing for RET rearrangements or MET alterations	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with RET inhibitors	Interventions of interest are: • Somatic testing for *RET* rearrangements using ctDNA (liquid biopsy) to guide treatment	Comparators of interest are: • Biomarker testing using tissue to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with MET inhibitors	Interventions of interest are: • Somatic testing for *MET* alterations using ctDNA (liquid biopsy) to guide treatment	Comparators of interest are: • Biomarker testing using tissue to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with a RAS inhibitor	Interventions of interest are: • Somatic testing for *KRAS* variants using tissue biopsy specimens to guide treatment	Comparators of interest are: • Management without genetic testing for KRAS variants	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy with a RAS inhibitor	Interventions of interest are: • Somatic testing for *KRAS* variants using ctDNA (liquid biopsy) to guide treatment	Comparators of interest are: • Biomarker testing using tissue to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With metastatic non-small-cell lung cancer who are being considered for targeted therapy with a *TRK* inhibitor	Interventions of interest are: • Somatic testing for *NTRK* gene fusion using tissue biopsy specimens to guide treatment	Comparators of interest are: • Management without genetic testing for *NTRK* gene fusion	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With metastatic non-small-cell lung cancer who are being considered for targeted therapy with a *TRK* inhibitor	Interventions of interest are: • Somatic testing for *NTRK* gene fusion using ctDNA (liquid biopsy) to guide treatment	Comparators of interest are: • Biomarker testing using tissue to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity

DESCRIPTION

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.

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; or NTRK gene fusion to select targeted treatment for individuals with advanced-stage non-small-cell lung cancer.

BACKGROUND

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.

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,]

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

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

Circulating Tumor DNA (Liquid Biopsy)

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

Targeted Treatment

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

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

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

Source: FDA (2023)12,

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

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 Non-Small-Cell Lung 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[13],	2A or higher/ NSCLC Treatment (v.4.2023)[14],
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,	• 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 15, • 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	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	squamous NSCLC progressing after platinum-based chemotherapy			subgroup analysis)[16], • Previously Treated, Metastatic Squamous NSCLC: LUX-Lung 8 NCT01523587[17],	
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[18],	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[19],	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[20],	Same as above
Ceritinib (Zykadia)	• Adults with metastatic NSCLC whose	• 2017: FoundationOne CDx™ (Foundation Medicine)	• ALK rearrangements,	First-line: ASCEND-4 NCT01828099[21],	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	tumors are ALK-positive as detected by an FDA-approved test	• 2017: VENTANA ALK (D5F3) CDx Assay	• ALK protein expression	Second-line: ASCEND-1, NCT01283516[22],	
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) • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine) ROS tests: • 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)	ALK	*ALK*-positive: PROFILE 1014 NCT01154140[23], NCT00932893[24], *ROS1*-positive: PROFILE 1001 NCT00585195[25],	Same as above
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[26],	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-	• 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine)	BRAF V600E	Study BRF113928 NCT01336634[27],	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	approved test				
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[28],	Same as above
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	• 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	Exon 19 deletion or exon 21 L858R substitution mutation	Study 1, Study 2 (Iressa Product Label)[29],	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations	• 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)			
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[30],	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[31],	Same as above
Osimertinib (Tagrisso)	• Adjuvant therapy aftertumor resection in	• 2015-2020: cobas® EGFR Mutation Test v2 (tissue or plasma	EGFR	• Adjuvant treatment: ADAURA NCT025111063	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	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	• 2017-2019: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx • 2020: FoundationOne® Liquid CDx		2, 33, 34, • First-line, EGFR-Positive Metastatic NSCLC: FLAURA NCT02296125 35, • Previously Treated EGFR T790M Mutation-Positive: AURA3[36],	

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	on or after EGFR TKI therapy.				
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[37],	Same as above
Selpercatinib (Retevmo)	• Adult patients with metastatic RET fusion-positive NSCLC	• 2022: Oncomine Dx Target Test • 2024: TruSight Oncology Comprehensive (Illumina, Inc.)	RET	LIBRETTO-001 NCT03157128[38, 39],	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[40, 41],	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[42, 43],	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Encorafenib (Braftovi) plus Binimetinib (Mektovi)	• Adult patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, as detected by an FDA-approved test. Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF CRC, or wild-type BRAF NSCLC.	• 2023: FoundationOne® CDx • 2023: FoundationOne® Liquid CDx	BRAF V600E	PHAROS NCT03915951[44, 45]	Same as above
Larotrectinib (Vitrakvi)	Adult and pediatric patients with solid tumors that: • have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, • are metastatic or where	• 2020: FoundationOne CDx (Foundation Medicine, Inc.) • 2024: TruSight Oncology Comprehensive (Illumina, Inc.)	NTRK1, NTRK2, and NTRK3 fusions	Hong et al (2020)[46] - Pooled analysis of 3 studies: • LOXO-TRK-14001 NCT02122913 • SCOUT NCT02637687 • NAVIGATE NCT02576431	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	surgical resection is likely to result in severe morbidity, and • have no satisfactory alternative treatments or that have progressed following treatment.				
Entrectinib (Rozlytrek)	Adult and pediatric patients 12 years of age and older with solid tumors that: • have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have either progressed following	• 2022: FoundationOne CDx (Foundation Medicine, Inc.) • 2022: FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NTRK1, NTRK2, and NTRK3 fusions	STARTRK-2 NCT02568267 Doebele et al (2020)[47], STARTRK-1 NCT02097810 Drilon et al (2017)[48], Doebele et al (2020)[47], ALKA-372-001 Doebele et al (2020)[47], STARTRK-NG NCT02650401 Desai et al (2022)[49],	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	treatment or have no satisfactory alternative therapy.				

Sources: U.S. Food and Drug Administration (2023)[50]; U.S. Food and Drug Administration (n.d.)[12]
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.

POLICY

EGFR Testing

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

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

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

D. 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 circulating tumor DNA (ctDNA), may be considered **medically necessary** in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified, when tissue biopsy to obtain new tissue is not feasible (e.g., in those who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, or cannot undergo biopsy), and when the individual does not have any FDA-labeled contraindications to osimertinib and it is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

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

ALK Testing

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

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

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

BRAF V600E Testing

I. Analysis of tumor tissue for the somatic *BRAF* V600E variant may be considered **medically necessary** to predict treatment response to an FDA-approved BRAF and/or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar] and trametinib [Mekinist]), in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

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

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

ROS1 Testing

L. Analysis of tumor tissue for somatic rearrangement variants of the *ROS1* gene may be considered **medically necessary** to predict treatment response to an FDA-approvedROS1 inhibitor therapy (e.g., crizotinib [Xalkori] in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

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

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

KRAS Testing

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

P. Analysis of plasma for somatic variants of the KRAS gene (e.g., G12C) using an FDA-approved companion diagnostic plasma test to detect ctDNA is 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).

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

RET Rearrangement Testing

R. 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).

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

T. Analysis of plasma for somatic alterations of the RET gene using plasma specimens to detect ctDNA is considered **experimental /investigational** as an alternative to tissue biopsy (see

Policy Guidelines) to predict treatment response to RET inhibitor therapy (e.g., selpercatinib [Retevmo], pralsetinib [Gavreto]) in individuals with NSCLC.

MET Exon 14 Skipping Alteration

U. 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).

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

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

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

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

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

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

Plasma Testing When Tissue is Insufficient

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

POLICY GUIDELINES

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

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

C. For expanded panel testing, see medical policy Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies.

D. This policy does not address *HER2* testing. 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.

E. 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.

F. 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 individuals: 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 individuals from expanded panel testing. All other genes are considered investigational at the time of publication."

Repeat Genomic Testing

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

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

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

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

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

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through September 26, 2025.

Testing for individual genes (not gene panels) associated with U.S. Food and Drug Administration (FDA)-approved therapeutics for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. The pivotal evidence is included in Table 2 for informational purposes. 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. Monoclonal antibody therapies such as amivantamab-vmjw (Rybrevant) are not reviewed.

SOMATIC BIOMARKER TESTING USING TISSUE BIOPSY TO SELECT TARGETED THERAPY FOR ADVANCED-STAGE NON-SMALL-CELL LUNG CANCER

REVIEW OF EVIDENCE

Testing for *EGFR* Variants or *ALK* Rearrangements with Tissue Biopsy
For individuals with advanced or metastatic non-small-cell lung cancer (NSCLC) who are being considered for targeted therapy with tyrosine kinase inhibitors (TKIs) who undergo somatic testing for epidermal growth factor receptor *(EGFR)* variants or anaplastic lymphoma kinase (*ALK*) rearrangements using tissue biopsy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing for *BRAF* Variants *or ROS1* Rearrangements with Tissue Biopsy
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, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing for *RET Rearrangementsor MET alterations* with Tissue Biopsy
For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with RET or mesenchymal-epithelial transition (MET) inhibitors who undergo somatic testing for *RET* rearrangements or *MET* alterations using tissue biopsy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing for *KRAS* Variants with Tissue Biopsy
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, 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.

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

BIOMARKER TESTING USING CIRCULATING TUMOR DNA (LIQUID BIOPSY) TO SELECT TARGETED THERAPY FOR ADVANCED-STAGE NON-SMALL-CELL LUNG CANCER

Testing for *EGFR* Variants or *ALK* Rearrangements with Circulating Tumor DNA (Liquid Biopsy)
For individuals with advanced-stage NSCLC who receive somatic testing for *EGFR* variants or ALK rearrangements using circulating tumor DNA (ctDNA) (liquid biopsy) to guide targeted treatment with TKIs, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing *BRAF* Variants or ROS1 Rearrangements with Circulating Tumor DNA (Liquid Biopsy)

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.

In December 2022, FoundationOne Liquid CDx was FDA approved as a companion diagnostic to select treatment with entrectinib in individuals with 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.

Testing for *MET* Exon 14 Skipping Alterations with Circulating Tumor DNA (Liquid Biopsy)

For individuals with advanced-stage NSCLC who receive somatic testing for *MET* Exon 14 skipping alterations using ctDNA (liquid biopsy) to guide targeted treatment with MET inhibitors, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing for *RET* Rearrangements with Circulating Tumor DNA (Liquid Biopsy)

No plasma tests have received FDA approval as companion diagnostics to select individuals with NSCLC for treatment with RET inhibitors and no studies were identified.

Testing for *KRAS* Variants with Circulating Tumor DNA (Liquid Biopsy)

For individuals with advanced-stage NSCLC who receive somatic testing for *KRAS* variants using ctDNA (liquid biopsy) to guide targeted treatment with RAS inhibitors, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated.

Testing for *NTRK* Gene Fusion with Circulating Tumor DNA (Liquid Biopsy)

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

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).[51,] 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. [52,] 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.[53,]

In 2022, the ASCO published a guideline on the management of stage III NSCLC.[54,] 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.[55,] 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.[56,] *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 (v8.2025) include the following recommendations and statements related to testing for molecular biomarkers:[14,]

- 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;
    - *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 (v8.2025) include the following recommendations related to plasma cell-free/circulating tumor DNA testing.[14,]

- Plasma cell free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis.
- ctDNA is not routinely recommended in settings other than advanced/metastatic disease. For stages I–III, tissue-based testing is preferred. Metastatic disease confined to the thorax may have a higher yield with tissue-based testing.
- Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation, most commonly in processed plasma.

- Studies have demonstrated ctDNA and tissue testing to have very high specificity. Both ctDNA and tissue testing have appreciable false-negative rates, supporting the complementarity of these approaches, and data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.
    - Limitations of ctDNA testing that can impact interpretation include:
        - Low tumor fraction/ctDNA; some assays include a measure of ctDNA fraction, which can aid in identification of situations in which low ctDNA fraction might suggest compromised sensitivity
        - The presence of mutations from sites other than the target lesion, most commonly clonal hematopoiesis of indeterminate potential (CHIP) or postchemotherapy marrow clones. KRAS and TP53 can be seen in either of these circumstances
        - The inherent ability of the assay to detect fusions or other genomic variation of relevance
    - Limitations of tissue testing that can impact interpretation include:
        - Low tumor percent in a sample not sufficiently mitigated by tumor enrichment or high analytic sensitivity methods
        - The inherent ability of the assay to detect fusions or other genomic variation of relevance

U.S. Preventive Services Task Force Recommendations

Not applicable.

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			
NCT03915951[a]	A Phase 2, Open-label Study of Encorafenib + Binimetinib in Patients With BRAFV600-mutant Non-small Cell Lung Cancer	98 (actual)	Oct 2025
NCT03576937	Achieving Value in Cancer Diagnostics: Blood Versus Tissue Molecular Profiling - a Prospective Canadian Study (VALUE)	207 (actual)	Apr 2023
NCT01306045	Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	647 (actual)	Jul 2024
NCT03225664	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer	37 (actual)	Dec 2025
NCT02622581	Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP)	12400	Dec 2027
NCT02117167[a]	Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: SAFIR02_Lung - Evaluation of the Efficacy of High	999	Dec 2023

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer		
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Dec 2026
NCT02576431[a]	A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-positive Tumors	215 (actual)	Oct 2025
NCT02568267[a]	An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements	534 (actual)	Dec 2025
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 2026
NCT03199651	Beating Lung Cancer in Ohio (BLCIO) Protocol	3584	Dec 2028
NCT04863924	Accelerating Lung Cancer Diagnosis Through Liquid Biopsy (ACCELERATE)	170	Jun 2025
NCT04912687[a]	Implementing Circulating Tumor DNA Analysis at Initial Diagnosis to Improve Management of Advanced Non-small Cell Lung Cancer Patients (NSCLC) (CIRCULAR)	580	Aug 2027
NCT03037385[a]	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	590 (actual)	Mar 2024
NCT03178552[a]	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	Oct 2026
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	400 (actual)	Jun 2025
NCT04180176[a]	A Multicenter, Low-Interventional Study to Evaluate the Feasibility of a Prospective Clinicogenomic Program (PCG)	945 (actual)	Nov 2023

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

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81191	NTRK1 (Neurotrophic Receptor Tyrosine Kinase 1) (e.g., solid tumors) translocation analysis
81192	NTRK2 (Neurotrophic Receptor Tyrosine Kinase 2) (e.g., solid tumors) translocation analysis
81193	NTRK3 (Neurotrophic Receptor Tyrosine Kinase 3) (e.g., solid tumors) translocation analysis
81194	NTRK (Neurotrophic-Tropomyosin receptor Tyrosine Kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis
81210	BRAF (B-RAF Proto-Oncogene, Serine/Threonine Kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
81235	EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion L858R, T790M, G719A, G719S, L861Q)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis, variants in exon 2 (e.g., codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
81445	Solid organ neoplasm, genomic sequence analysis panel 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

CPT/HCPCS	
81479	Unlisted molecular pathology procedure
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
88364	In situ hybridization (e.g., FISH), per specimen; each additional single probe stain procedure
88365	In situ hybridization (e.g., FISH), per specimen; initial single probe stain procedure
88366	In situ hybridization (e.g., FISH), per specimen; each multiplex probe stain procedure
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence or absence of variants and associated therapy(ies) to consider.
0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0388U	Oncology (non-small cell lung cancer), next generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer related genes, plasma, with report of alterations detected
0478U	Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2 and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection

REVISIONS	
09-28-2014	Policy added to the bcbsks.com web site on 08-29-2014. Effective on 09-28-2014, 30 days after posting.
02-08-2015	Title of policy changed from "Epidermal Growth Factor Receptor Mutation Analysis for Patients with Non-Small Cell Lung Cancer"
	Updated Description section.
	In Policy section:

REVISIONS	
	▪ Added "D. Analysis of somatic mutations of the KRAS gene is considered experimental / investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC." ▪ Added "E. Testing for genetic alterations in the genes ROS, RET, MET, BRAF, and HER2, for targeted therapy in patients with NSCLC, is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ The following CPT codes were added: 81275, 81404, 81405, 81406, 81479, 88342, 88365.
	Updated References section.
05-14-2015	Updated Description section.
	In Policy section: ▪ Added Item D, "Analysis of somatic rearrangement mutations of the ALK gene may be considered medically necessary to predict treatment response to crizotinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)." ▪ Added Item E, " Analysis of somatic rearrangement mutations of the ALK gene is considered experimental / investigational in all other clinical situations." ▪ In Item G, added "Analysis" and removed "Testing", to read " Analysis for genetic alterations in the genes ROS, RET, MET, BRAF, and HER2, for targeted therapy in patients with NSCLC, is considered experimental / investigational." ▪ In Policy Guidelines, Item 2, added "The 2015", "as a category 1 recommendation that", and "and ALK rearrangement testing be performed in the workup of NSCLC in patients with histologic subtypes adenocarcinomas, large-cell carcinoma, and NSCLC not otherwise specified," and removed "a) for patients with advanced lung cancer, nonsquamous cell type, or b) when biopsy specimens are small and histology is mixed," to read, "2. The 2015 guidelines from the National Comprehensive Cancer Network recommend as a category 1 recommendation that EGFR mutation testing and ALK rearrangement testing be performed in the workup of NSCLC in patients with histologic subtypes adenocarcinoma, large-cell carcinoma, and NSCLC not otherwise specified." ▪ In Policy Guidelines, Item 3, added "The", "and ALK rearrangement" and "and ALK", and removed "Current", to read, "The 2014 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology recommend: a) EGFR mutation and ALK rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (e.g., smoking history); b) In the setting of fully excised lung cancer specimens, EGFR and ALK mutation testing is not recommended in lung cancers when an adenocarcinoma component is lacking (such as pure squamous cell lacking any immunohistochemical evidence of adenocarcinomatous differentiation); and c) In the setting of more limited lung cancer specimens (e.g., biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous cell histology. Clinical criteria (e.g., young age, lack of smoking history) may be useful to select a subset of these samples for testing."
	Updated Rationale section.
	Updated References section.
01-01-2016	Updated Description section.

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	Updated Rationale section.
	In Coding section: ▪ Revised nomenclature to CPT code: 81275. ▪ Revised bullets under CPT/HCPCS coding.
	Updated References section.
	Added Appendix section.
11-22-2016	Updated Description section.
	In Policy section: ▪ In Item A, added "an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g.,", "[Tarceva®], gefitinib [Iressa®],", and "[Gilotrif®])" to read, "Except as noted below, analysis of 2 types of somatic mutation within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)." ▪ Added new Item B, "Analysis for the T790M mutation in the gene for the EGFR is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy." ▪ In Policy Guidelines, revised guideline dates for Items 2 and 3 and added "Genetic Counseling."
	Updated Rationale section.
	In Coding section: ▪ Added CPT code: 81276. ▪ Updated coding bullets.
	Updated References section.
10-01-2017	In Policy section: ▪ Removed Genetic Counseling information from Policy Guidelines.
	In Coding section: ▪ Added CPT code: 0022U.
03-14-2018	Updated Description section.
	In Policy section: ▪ In Item A, removed "mutation", "point mutation", and "with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)" and added "variants", "single-nucleotide variant", and "with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified" to read, "Except as noted below, analysis of 2 types of somatic variants within the EGFR gene – small deletions in exon 19 and a single-nucleotide variant in exon 21 (L85I4) – may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item B, removed "mutation" and added "variants" to read, "Analysis of the T790M variants in the EGFR gene is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy."

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	▪ In Item C, removed "mutation" and added "variants" to read, "Analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—is considered experimental / investigational for patients with advanced squamous cell NSCLC." ▪ In Item D, removed "mutations" and added "variants" to read, "Analysis of other *EGFR* variants within exons 18 to 24, or other applications related to NSCLC, is considered experimental / investigational." ▪ In Item E, removed "mutations" and "with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)" and added "variants", "ALK inhibitor therapy (e.g.," "[Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™])", and "with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified" to read, "Analysis of somatic rearrangement variants of the *ALK* gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item F, removed "mutations" and "clinical" and added "variants" to read, "Analysis of somatic rearrangement variants of the *ALK* gene is considered experimental / investigational in all other situations." ▪ Added new Item G, "Analysis of the *BRAF* V600E variant may be considered medically necessary to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ Added new Item H, "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 metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In previous Item G (now Item I), removed "mutations" and added "variants" to read, "Analysis of somatic variants of the *KRAS* gene is considered experimental / investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC." ▪ In Previous Item H (now Item J), removed "ROS" and "BRAF" to read, "Analysis for genetic alterations in the genes RET, MET, and HER2 for targeted therapy in patients with NSCLC is considered experimental / investigational." ▪ Added new Item K, "Programmed death receptor 1 (PD-1) or its ligand (PD-L1) expression analysis may be considered medically necessary as a technique to predict treatment response to drug therapy." ▪ Updated Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Updated nomenclature for CPT codes: 88342, 88365. ▪ Updated coding bullets. ▪ Removed ICD-9 codes.
	Updated References section.
09-12-2018	In Policy section:

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	▪ In Item A, removed "metastatic" and added "stage III or IV" to read, "Except as noted below, analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a single-nucleotide variant in exon 21 (L858R)—may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item E, removed "metastatic" and added "stage III or IV" to read, "Analysis of somatic rearrangement variants of the ALK gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [ZykadiaTM], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item G, removed "metastatic" and added "stage III or IV" to read, "Analysis of the BRAF V600E variant may be considered medically necessary to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with stage III or IV metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item H, removed "metastatic" and added "stage III or IV" to read, "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 stage III or IV metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified."
	Updated References section.
02-01-2019	Policy posted 01-04-2019 with an effective date of 02-01-2019.
	Updated Description section.
	In Policy section: ▪ In Item A, removed "Except as noted below," "2 types of," "small deletions in exon 19 and a single nucleotide variant in exon 21 (L858R)" and added "in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q)" and "osimertinib [Tagrisso]" to read, "Analysis of somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the EGFR gene may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (e.g., erlotinib [Tarceva], gefitinib [Iressa}, afatinib [Gilotrif], or osimertinib [Tagrisso]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ Removed Item B, "Analysis of the T790M variants in the EGFR gene is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy." ▪ Removed Item C, "Analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—is considered experimental / investigational for patients with advanced squamous cell NSCLC." ▪ In previous Item D, now Item B, removed "18" and added "22" to read, "Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered experimental / investigational." ▪ Updated Policy Guidelines.
	Updated Rationale section.

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	Updated References section.
	Removed Appendix section.
03-29-21	Policy Title change from *"Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer"* to *"Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer"*
	Updated Description section
	In the Policy section: • Added F. Analysis of BRAF V600E variant is considered **experimental /investigationa**l in all other situations H. Analysis of somatic rearrangement variants of the ROS1 gene is considered **experimental / investigational** in all other situations. J. Analysis of genetic alterations in the *HER2* gene for targeted therapy in patients with NSCLC is considered **experimental / investigational.** K. Analysis of NTRK gene fusions may be considered **medically necessary** to predict treatment response to entrectinib (Rozlytrek) or larotrectinib (Vitrakvi) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified. L. Analysis of NTRK gene fusions is considered **experimental / investigational** in all other situations. M. Analysis of genetic alteration in the RET gene may be considered **medically necessary** to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) in patients with metastatic NSCLC. N. Analysis of genetic alterations in the RET gene is considered **experimental / investigational** in all other situations. O. Analysis of genetic alteration that leads to MET exon 14 skipping may be considered **medically necessary** to predict treatment response to capmatinib (Tabrecta) in patients with metastatic NSCLC. P. Analysis of genetic alterations of the MET gene is considered **experimental / investigational** in all other situations Q. PD-L1 testing may be considered **medically necessary** to predict treatment response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Yervoy), or pembrolizumab (Keytruda) in patients with metastatic NSCLC. R. PD-L1 testing is considered **experimental /investigational** in all other situations S. Analysis of tumor mutational burden for targeted therapy in patients with NSCLC is considered **experimental / investigational.** • Deleted Analysis for genetic alterations in the genes *RET*, *MET*, and *HER2* for targeted therapy in patients with NSCLC is considered **experimental / investigational**. Programmed death receptor 1 (PD-1) or its ligand (PD-L1) expression analysis may be considered **medically necessary** as a technique to predict treatment response to drug therapy.
	Updated Reference section
	In Coding section o Added CPT codes: 81191, 81192, 81193, 81194, 81210, 88364, 88366 o Removed CPT code 81406
	Updated Rationale section
02-04-2022	Updated Description Section
	Updated Policy Section ▪ Added Section B

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	▪ Added Section C ▪ Added Section G ▪ Section H added word "somatic" ▪ Added Section J ▪ Added Section M ▪ Added Section N ▪ Section O added "using plasma specimens to detect ctDNA", "sotorasib (Lumakras)"and removed "anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab (Erbitux) in NSCLC." ▪ Added Section P ▪ Section Q replaced "genetic" with "somatic" ▪ Section U replaced "genetic" with "somatic" ▪ and added "in tissue" ▪ Section V replaced "genetic" with "somatic" ▪ Added Section W ▪ Section X replaced "genetic" with "somatic" ▪ Section Y replaced "genetic" with "somatic" ▪ Added Section Z
	Updated Policy Guidelines
	Updated Rationale Section
	Updated Coding Section ▪ Added code: 0239U
	Updated References Section
	The *Circulating Tumor DNA for Management of NSCLC (Liquid Biopsy)* medical policy has been incorporated into this policy and archived.
10-28-2022	Updated Coding Section ▪ Added 0338U (effective 10-01-2022)
02-09-2023	Updated Title 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*)"
	Updated Description Section
	Updated Policy Section ▪ 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 policy statements 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. ▪ *NTRK* testing was removed. ▪ 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.
	Updated Policy Guideline Section ▪ Added: o This policy does not address germline testing for inherited risk of developing cancer. o Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer

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	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. ○ 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. 5.2022) 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." ▪ Removed: ○ These gene tests are intended for use in patients with advanced (stage III or IV) non-small-cell lung cancer. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene are considered good candidates for treatment with erlotinib, gefitinib or afatinib. Patients with wild-type variants are unlikely to respond to erlotinib or afatinib; for these patients, other treatment options should be considered. ○ Guidelines from the National Comprehensive Cancer Network on non-small-cell lung cancer provide recommendations for biomarker testing. Guidelines are updated frequently; refer to the source document for current recommendations. The most recent guidelines (v.6.2021) recommend that EGFR variants, ALK rearrangement, and PD-L1 testing (category 1) as well as KRAS, ROS1, BRAF, NTRK1/2/3, MET Exon 14 skipping alteration, and RET testing (category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling. ○ The tests discussed herein, cobas EGFR Mutation Test v2, Guardant360 CDx test, Oncobeam test, or InVisionFirst-Lung, are intended for use in patients with advanced (stage III or IV) non-small-cell lung cancer. These tests include variants beyond exons 19 through 21 of the epidermal growth factor receptor (EGFR) gene, and some tests additionally include variants in numerous other genes. Patients with sensitizing variants of the tyrosine kinase domain of the EGFR gene are considered good candidates for treatment with erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib. The U.S. Food and Drug Administration approval for the cobas EGFR Mutation Test v2 states that patients who are negative for EGFR exon 19 deletions or L858R variant based on the plasma test should be reflexed to routine biopsy and testing using formalin-fixed paraffin-embedded tissue. Plasma tests for other oncogenic driver variants deemed medically necessary on

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	tissue biopsy may also be appropriate for patients who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; however, this is only appropriate if follow-up tissue-based analysis is planned should no driver variant be identified.
	Updated Rationale Section
	Update Coding Section ▪ Added: 81445, 81455, 88341 and 0326U ▪ Removed Coding bullet ○ ICD-10-CM does not have specific coding for non-small-cell lung cancer. The malignant neoplasm of lung codes above would be used.
	Updated References Section
04-03-2023	Updated Coding Section ▪ Updated nomenclature for 0022U ▪ Removed ICD-10 Codes
07-03-2023	Updated Coding Section ▪ Added 0388U, 0397U
10-02-2023	Updated Coding Section ▪ Removed Deleted code 0397U
02-04-2024	Updated Title to: "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (*EGFR, ALK, BRAF, ROS1, RET, MET, KRAS)"*
	Updated Description Section
	Updated Policy Section • Section B removed: "or amivantamab [Rybrevant])" • Section C removed: "the cobas EGFR Mutation Test v2, Guardant360 CDx test, FoundationOne Liquid CDx, OncoBEAM test, or InVisionFirst-Lung test" and added "an FDA-approved companion diagnostic plasma test" • Section D removed: "the cobas EGFR Mutation Test v2, Guardant360 CDx test, OncoBEAM test, or InVisionFirst-Lung test to detect ctDNA" and added "an FDA-approved companion diagnostic plasma test to detect circulating tumor DNA" • Section E removed: " Analysis of plasma for somatic variants in exon 20 (e.g., insertion mutations) within the EGFR 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 therapy in individuals in NSCLC (e.g., amivantamab [Rybrevant]), 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)." • Section M removed: "or entrectinib [Rozlytrek])" • Section O removed: "[Rozlytrek])" • Section S, T and U removed: "HER2 Testing S. Analysis of tumor tissue for somatic alterations in the HER2(ERBB2) gene may be considered medically necessary to predict treatment response to an FDA-approved therapy (e.g., fam-trastuzumab deruxtecan-nxki [Enhertu]) in individuals with unresectable or 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). T. Analysis of plasma for somatic alterations in the HER2(ERBB2) gene using an FDA-approved companion diagnostic plasma test to detect ctDNA is considered medically necessary as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved therapy (e.g., fam-trastuzumab deruxtecan-nxki [Enhertu]) in individuals with unresectable or metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test

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	are intended to be used consistently with their FDA-approved labels (see Policy Guidelines). U. All other uses of analysis of somatic variants of the HER2 (ERBB2) gene in tissue or plasma are considered experimental / investigational." • Section V added: "RET inhibitor therapy (e.g.," • Section BB, CC, DD removed: PD-L1 Testing BB. PD-L1 testing of tissue may be considered medically necessary to predict treatment response to an FDA-approved therapy (e.g., atezolizumab [Tecentriq], nivolumab [Opdivo] in combination with ipilimumab [Yervoy], pembrolizumab [Keytruda], or cemiplimab-rwlc [Libtayo]) 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). CC. PD-L1 testing is considered experimental /investigational in all other situations Tumor Mutation Burden Testing DD. Analysis of tumor mutational burden to predict treatment response to immunotherapy in individuals with NSCLC is considered experimental / investigational.
	Updated Policy Guidelines • Added B: "This policy does not address HER2 testing. 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."
	Updated Rationale Section
	Updated Coding Section ▪ Removed 0338U ▪ Added 0179U ▪ Updated nomenclature for 81445 and 81455 (eff. 01-01-2024)
	Updated Reference Section
10-01-2024	Updated Coding Section ▪ Added 0478U (eff. 10-01-2024)
Posted 12-23-2024 Effective 01-22-2025	Updated Title ▪ Added NTRK to title: "Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (*EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, NTRK*)
	Updated Description Section
	Updated Policy Section ▪ Added Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Testing Section: X. Analysis of tumor tissue for *NTRK* gene fusions may be considered medically necessary to predict treatment response to TRK inhibitor therapy (e.g., larotrectinib [Vitrakvi] or entrectinib [Rozlytrek]) in individuals with metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines). Y. Analysis of plasma for *NTRK* gene fusions using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered medically necessary as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to TRK inhibitor therapy (e.g., larotrectinib [Vitrakvi] or entrectinib [Rozlytrek]) in individuals with metastatic NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).

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	Z. All other uses of analysis of *NTRK* fusions in tissue or plasma are considered investigational.
	Updated Policy Guideline Section ▪ Added: "This policy does not address monoclonal antibody therapies such as amivantamab-vmjw (Rybrevant)." ▪ "For expanded panel testing, see medical policy Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies."
	Updated Rationale Section
	Updated References Section
01-13-2026	Updated Description Section
	Updated Rationale Section
	Updated Reference Section

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