

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

EGFR Testing

- I. Analysis of tumor tissue for somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S678I, L861Q) within the epidermal growth factor receptor (*EGFR*) gene, may be considered **medically necessary** to predict treatment response to a U.S. Food and Drug Administration (FDA) -approved therapy (e.g., erlotinib [Tarceva] alone or in combination with ramucirumab [Cyramza], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], or osimertinib [Tagrisso]) in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous-cell non-small-cell lung cancer (NSCLC), and NSCLC not otherwise specified, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).

- II. 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).

- III. 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).

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

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

ALK Testing

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

BRAFV600E Testing

- IX. Analysis of tumor tissue for the somatic *BRAFV600E* 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).
- X. Analysis of tumor tissue for the somatic *BRAFV600E* variant is considered **investigational** in all other situations.
- XI. Analysis of plasma for the somatic *BRAFV600E* variant to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to BRAF and/or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar], trametinib [Mekinist]) in individuals with NSCLC.

ROS1 Testing

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

KRAS Testing

- XV. 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).
- XVI. Analysis of plasma for somatic variants of the *KRAS* gene (e.g., G12C) using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to sotorasib (Lumakras) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).
- XVII. All other uses of analysis of somatic variants of the *KRAS* gene in tissue or plasma are considered **investigational**.

RET Rearrangement Testing

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

MET Exon 14 Skipping Alteration

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

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

- XXIV. 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).
- XXV. 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).
- XXVI. All other uses of analysis of *NTRK* fusions in tissue or plasma are considered **investigational**.

Plasma Testing When Tissue is Insufficient

- XXVII. 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 **BOTH** of the following criteria:
- Individual does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue
 - Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing.

Testing for other variants may become available between policy updates.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

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

For expanded panel testing, see Blue Shield of California Medical Policy: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

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

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

For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (<https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion->

diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms. The most recent guidelines (v.10.2024) recommend that *EGFR* variants (category 1), *ALK* rearrangements (category 1), and PD-L1 testing (category 1) as well as *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET* exon 14 skipping alteration, *RET*, and *HER2* testing (all category 2A) be performed in the workup of NSCLC in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and NSCLC not otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling, defined as a single assay or a combination of a limited number of assays and that it is acceptable to have a tiered approach based on low-prevalence, co-occurring biomarkers. The guidelines additionally recommend identifying the emerging biomarker, high-level *MET* amplification, while noting that the definition of this biomarker is evolving and may differ according to the assay used.

The 2018 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology have recommended the following: "One set of genes must be offered" by all laboratories that test lung cancers, as an absolute minimum: *EGFR*, *ALK*, and *ROS1*. A second group of genes should be included in any expanded panel that is offered for lung cancer patients: *BRAF*, *MET*, *RET*, *ERBB2* (*HER2*), and *KRAS*, if adequate material is available. *KRAS* testing may also be offered as a single-gene test to exclude patients from expanded panel testing. All other genes are considered investigational at the time of publication."

Repeat Genomic Testing

There may be utility in repeated testing of gene variants for determining targeted therapy or immunotherapy in individuals with NSCLC, as tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making. For example, repeat testing (tissue or liquid based) of *EGFR* for T790M at progression on or after *EGFR* tyrosine kinase inhibitor therapy may be considered to select patients for treatment with osimertinib. T790M is an acquired resistance mutation that is rarely seen at initial diagnosis. The American Society of Clinical Oncology (ASCO) currently suggests repeat genomic testing for individuals on targeted therapy with suspected acquired resistance, especially if choice of next-line therapy would be guided. The ASCO guidance is not tumor specific, and it cautions to consider clinical utility (Chakravarty et al, 2022; PMID 35175857).

Concurrent Somatic Liquid-Based and Tissue-Based Genomic Testing

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

Recommended Testing Strategies

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

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

Coding

See the [Codes table](#) for details.

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.

Summary of Evidence

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

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

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

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

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

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

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

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

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

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

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

Additional Information

Not applicable.

Related Policies

- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. 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.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

Cal. Health & Safety Code § 1367.665 and Insurance Code Section 10123.20

California laws that prohibit health plans and insurers from requiring prior authorization for biomarker testing for advanced or metastatic stage 3 or 4 cancer, and cancer progression or recurrence.

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09

California laws that requires insurers to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee’s disease or condition to guide treatment decisions, as prescribed.

FDA-Approved Targeted Therapies and Companion Diagnostic Tests for Advanced Non-Small-Cell Lung Cancer

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	<ul style="list-style-type: none"> 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. <u>Limitations of Use:</u> Safety and efficacy not established in patients whose tumors have resistant EGFR mutations Patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy	<ul style="list-style-type: none"> 2013: therascreen EGFR RGQ PCR kit (Qiagen) 2016: <i>therascreen</i> EGFR RGQ PCR Kit (Qiagen) 2017: FoundationOne CDx™ (Foundation Medicine) 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) 	EGFR	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 subgroup analysis) ¹⁶ , Previously Treated, Metastatic Squamous NSCLC: LUX-Lung 8 NCT01523587 ¹⁷ ,	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
Alectinib (Alecensa)	<ul style="list-style-type: none"> Patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 2020: Vysis ALK Break Apart FISH Probe Kit 	<i>ALK</i> gene rearrangements	ALTA 1L NCT02737501 ¹⁹ ,	Same as above
Capmatinib (Tabrecta)	Metastatic NSCLC whose tumors have a mutation that leads to <i>MET</i> exon 14 skipping as detected by an FDA-approved test.	<ul style="list-style-type: none"> 2020: FoundationOne CDx™ 2021: FoundationOne Liquid CDx™ 	<i>MET</i> single nucleotide variants and indels that lead to <i>MET</i> exon 14 skipping	GEOMETRY mono-1 NCT02414139 ²⁰ ,	Same as above
Ceritinib (Zykadia)	Adults with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test	<ul style="list-style-type: none"> 2017: FoundationOne CDx™ (Foundation Medicine) 2017: VENTANA ALK (D5F3) CDx Assay 	<ul style="list-style-type: none"> ALK rearrangements, ALK protein expression 	First-line: ASCEND-4 NCT01828099 ²¹ , Second-line: ASCEND-1, NCT01283516 ²² ,	Same as above
Crizotinib (Xalkori)	Adults with metastatic NSCLC whose tumors are ALK- or ROS1-positive as detected by an FDA-approved test	<p>ALK tests:</p> <ul style="list-style-type: none"> 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) 2017: FoundationOne CDx™ (Foundation Medicine) <p>ROS tests:</p> <ul style="list-style-type: none"> 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific) 	ALK	<p><i>ALK</i>-positive: PROFILE 1014 NCT01154140²³, NCT00932893²⁴,</p> <p><i>ROS1</i>-positive: PROFILE 1001 NCT00585195²⁵,</p>	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
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	<ul style="list-style-type: none"> 2018: theascreen 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-approved test	<ul style="list-style-type: none"> 2017: Oncomine™ Dx Target Test 2017: FoundationOne CDx™ (Foundation Medicine) 	BRAF V600E	Study BRF113928 NCT01336634 ²⁷ ,	Same as above
Erlotinib (Generic)	First-line and maintenance treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations. Locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.	<ul style="list-style-type: none"> 2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) 2016: cobas® EGFR Mutation Test v2 (tissue or blood test) (Roche Diagnostics) 2017: FoundationOne CDx™ (Foundation Medicine) 2020: FoundationOne® Liquid CDx 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) 	EGFR	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	<ul style="list-style-type: none"> 2015: theascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit 2017: Oncomine™ Dx Target Test 2017: FoundationOne CDx™ 	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
	Limitation of Use: Safety and efficacy of IRESSA have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations	<ul style="list-style-type: none"> • 2018: cobas® EGFR Mutation Test v2 (tissue or plasma test) (Roche Diagnostics) • 2020: cobas® EGFR Mutation Test v2 (tissue or plasma) (Roche Diagnostics) • 2020: FoundationOne® Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) 			
Lorlatinib (Lorbrena)	Adult patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 2021: Oncomine Dx Target Test 	EGFR	EXCLAIM NCT02716116 ³¹ ,	Same as above
Osimertinib (Tagrisso)	Adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.	<ul style="list-style-type: none"> • 2015-2020: cobas® EGFR Mutation Test v2 (tissue or plasma) • 2017-2019: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx 	EGFR	<ul style="list-style-type: none"> • Adjuvant treatment: ADAURA NCT02511106^{32, 33, 34}, • First-line, EGFR-Positive Metastatic NSCLC: FLAURA NCT02296125³⁵. 	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
	<p>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.</p> <p>Treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.</p>	<ul style="list-style-type: none"> 2020: FoundationOne® Liquid CDx 		<ul style="list-style-type: none"> Previously Treated EGFR T790M Mutation-Positive: AURA3³⁶. 	
Pralsetinib (Gavreto)	Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	<ul style="list-style-type: none"> 2020: Oncomine Dx Target Test 	RET	ARROW NCT03037385 ³⁷ ,	Same as above
Selpercatinib (Retevmo)	Adult patients with metastatic RET fusion-positive NSCLC	<ul style="list-style-type: none"> 2022: Oncomine Dx Target Test 2024: TruSight Oncology Comprehensive (Illumina, Inc.) 	RET	LIBRETTO-001 NCT03157128 ^{38, 39} ,	Same as above
Sotorasib (Lumkras)	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	<ul style="list-style-type: none"> 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.	<ul style="list-style-type: none"> No approved companion diagnostic 	MET exon 14 skipping alterations	VISION NCT02864992 ^{42, 43} ,	Same as above
Encorafenib plus Binimetinib (Braftovi)	Adult patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF	<ul style="list-style-type: none"> 2023: FoundationOne® CDx 	BRAF V600E	PHAROS NCT03915951 ^{44, 45} ,	Same as above

Treatment	Indications in Advanced NSCLC	FDA-Approved Companion Diagnostic Tests	Biomarkers	Pivotal Studies	NCCN Recommendation Level/Guideline
b (Mektovi)	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.	<ul style="list-style-type: none"> 2023: FoundationOne® Liquid CDx 			
Larotrectinib (Vitrakvi)	Adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (<i>NTRK</i>) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> LOXO-TRK-14001 NCT02122913 SCOUT NCT02637687 NAVIGATE NCT02576431 	Same as above
Entrectinib (Rozlytrek)	Adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (<i>NTRK</i>) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely	<ul style="list-style-type: none"> 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
	to result in severe morbidity, and have either progressed following 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.

Rationale

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	<ul style="list-style-type: none"> Gefitinib (Iressa), Erlotinib (Tarceva) alone or in combination with ramucirumab (Cyramza) Afatinib (Gilotrif) Osimertinib (Tagrisso) Dacomitinib (Vizimpro) Mobocertinib (Exkivity)
ALK	<ul style="list-style-type: none"> Crizotinib (Xalkori) Ceritinib (Zykadia) Alectinib (Alecensa) Brigatinib (Alunbrig) Lorlatinib (Lorbrena)
BRAF	<ul style="list-style-type: none"> Dabrafenib (Tafinlar) alone or in combination with trametinib (Mekinist)

Target	FDA-Approved Targeted Therapies
<i>ROS1</i>	<ul style="list-style-type: none"> • Encorafenib (Braftovi) in combination with binimetinib (Mektovi)
<i>KRAS</i>	<ul style="list-style-type: none"> • Crizotinib (Xalkori)
<i>RET</i>	<ul style="list-style-type: none"> • Sotorasib (Lumakras) • Adagrasib (Krazati)
<i>MET</i>	<ul style="list-style-type: none"> • Selpercatinib (Retevmo) • Pralsetinib (Gavreto)
<i>NTRK</i>	<ul style="list-style-type: none"> • Capmatinib (Tabrecta) • Tepotinib (Tepmetko) • 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.

Literature Review

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* Rearrangements or *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.

Summary of Evidence

For individuals with advanced or metastatic non-small-cell lung cancer (NSCLC) who are being considered for targeted therapy with tyrosine kinase inhibitors who undergo somatic testing for *EGFR* variants or *ALK* rearrangements using tissue biopsy specimens, the evidence includes U.S. Food and Drug Administration (FDA)-approved therapeutics with National Comprehensive Cancer

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

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

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

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

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

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

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

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

For individuals with advanced or metastatic NSCLC who are being considered for targeted therapy with a RAS inhibitor who undergo somatic testing for KRAS variants using using ctDNA (liquid biopsy), the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and

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

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

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

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 (e.g., 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 (v.10.2024) 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;
 - *NTRK1/2/3* gene fusions;
 - *ROS1* rearrangements.
- Both U.S. Food and Drug Administration (FDA) and laboratory-developed test platforms are available that address the need to evaluate these and other analytes.
- Broad molecular profiling is also recommended to identify emerging biomarkers for which effective therapy may be available, such as high-level *MET* amplifications.
- Clinicopathologic features should not be used to select patients for testing.
- The guidelines do not endorse any specific commercially available biomarker assays or commercial laboratories.

Plasma Cell-Free/Circulating Tumor DNA Testing:

The NCCN guidelines on NSCLC (v.10.2024) 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.

Medicare National Coverage

The Centers for Medicare and Medicaid Services will cover diagnostic testing with next-generation sequencing for beneficiaries with recurrent, relapsed, refractory, metastatic cancer, or advanced stages III or IV cancer if the beneficiary has not been previously tested using the same next-generation sequencing test, unless a new primary cancer diagnosis is made by the treating physician, and if the patient has decided to seek further cancer treatment. The test must have an FDA-approved or cleared indication as an in vitro diagnostic, with results and treatment options provided to the treating physician for patient management.⁵⁷

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
<i>Ongoing</i>			
NCT03915951 ^a	A Phase 2, Open-label Study of Encorafenib + Binimetinib in Patients With BRAFV600-mutant Non-small Cell Lung Cancer	98 (actual)	Dec 2024
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 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
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: SAFIRO2_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer	999	Dec 2023
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Dec 2025
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)	Apr 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	2994	Dec 2027
NCT04863924	Accelerating Lung Cancer Diagnosis Through Liquid Biopsy (ACCELERATE)	170	Dec 2024
NCT04912687 ^a	Implementing Circulating Tumor DNA Analysis at Initial Diagnosis to Improve Management of Advanced Non-small Cell Lung Cancer Patients (NSCLC) (CIRCULAR)	580	Jan 2026
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	589	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	Aug 2028
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.

References

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
- Diagnosis and cancer type and stage
- Previous treatment plan(s) and response(s)
- Current treatment plan
- Clinical justification for analysis testing

- Previous biopsies and any tissue limitations or contraindications to repeat biopsy

Post Service (in addition to the above, please include the following):

- Analysis testing results

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	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)
	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 [InVisionFirst®-Lung Liquid Biopsy by Inivata, Inc]
	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 (v-raf murine sarcoma viral oncogene homolog B1) (e.g., colon cancer), gene analysis, V600E variant
	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)
	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)	

Type	Code	Description
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81479	Unlisted molecular pathology procedure
	88341	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
	88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
	88364	In situ hybridization (e.g., FISH), per specimen; initial 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; initial single probe stain procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
11/26/2014	BCBSA Medical Policy adoption
08/31/2015	Policy title change from Molecular Analysis for Targeted Therapy for Non-Small-Cell Lung Cancer Policy revision without position change
06/01/2016	Policy revision without position change
12/01/2016	Policy revision without position change
12/01/2017	Policy revision without position change
12/01/2018	Policy revision without position change
12/01/2019	Policy revision without position change
12/01/2020	Annual review. Policy statement updated
01/01/2021	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer to current one. Coding update.
03/01/2022	Annual review. No change to policy statement.
04/01/2022	Policy statement, guidelines and literature review updated to combine with Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy) 2.04.143. Policy title changed from Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer to current one.
09/01/2022	Coding update
02/01/2023	Annual review. Policy statement, guidelines and literature review updated. Policy title changed from Molecular Analysis (Including Liquid Biopsy) for

Effective Date	Action
	Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer to current one.
11/01/2025	Policy reactivated. Previously archived from 06/01/2023 to 10/31/2025

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

- A. The technology must have final approval from the appropriate government regulatory bodies.
 - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
 - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
 - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.
- B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
 - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
 - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.
- C. The technology must improve the net health outcome.
 - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.
- D. The technology must be as beneficial as any established alternatives.
 - The technology should improve the net health outcome as much as, or more than, established alternatives.
- E. The improvement must be attainable outside the investigational setting.
 - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER
<p>Reactivated Policy</p> <p>Policy Statement: N/A</p>	<p style="text-align: center;"><u>Blue font: Verbiage Changes/Additions</u></p> <p>Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, NTRK) 2.04.45</p> <p>Policy Statement: <i>EGFR</i> Testing</p> <ol style="list-style-type: none"> I. Analysis of tumor tissue for somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S678I, L861Q) within the epidermal growth factor receptor (<i>EGFR</i>) gene, may be considered medically necessary to predict treatment response to a U.S. Food and Drug Administration (FDA) -approved therapy (e.g., erlotinib [Tarceva] alone or in combination with ramucirumab [Cyramza], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], or osimertinib [Tagrisso]) in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous-cell non-small-cell lung cancer (NSCLC), and NSCLC not otherwise specified, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines). II. Analysis of tumor tissue for somatic variants in exon 20 (e.g., insertion mutations) within the <i>EGFR</i> 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). III. At diagnosis, analysis of plasma for somatic variants in exons 19 through 21 (e.g., exon 19 deletions, L858R, T790M) within

POLICY STATEMENT	
BEFORE	AFTER
	<p style="text-align: center;">Blue font: Verbiage Changes/Additions</p> <p>the <i>EGFR</i> 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).</p> <p>IV. At progression, analysis of plasma for the EGFR T790M resistance variant for targeted therapy with osimertinib using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered medically necessary in individuals with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified, when tissue biopsy to obtain new tissue is not feasible (e.g., in those who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, or cannot undergo biopsy), and when the individual does not have any FDA-labeled contraindications to osimertinib and it is intended to be used consistently with the FDA-approved label (see Policy Guidelines).</p> <p>V. Analysis of somatic variants in the <i>EGFR</i> gene in tissue or plasma, including variants within exons 22 to 24, is considered investigational in all other situations.</p> <p>ALK Testing</p> <p>VI. Analysis of tumor tissue for somatic rearrangement variants of the anaplastic lymphoma kinase (<i>ALK</i>) 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</p>

POLICY STATEMENT	
BEFORE	AFTER
	<p style="text-align: center;"><u>Blue font: Verbiage Changes/Additions</u></p> <p>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).</p> <p>VII. Analysis of plasma for somatic rearrangement variants of the ALK gene using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered medically necessary as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an FDA-approved ALK inhibitor therapy in individuals with NSCLC (e.g., alectinib [Alecensa]), if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).</p> <p>VIII. Analysis of somatic rearrangement variants of the <i>ALK</i> gene in tissue or plasma is considered investigational in all other situations.</p> <p><i>BRAFV600E</i> Testing</p> <p>IX. Analysis of tumor tissue for the somatic <i>BRAFV600E</i> 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).</p> <p>X. Analysis of tumor tissue for the somatic <i>BRAFV600E</i> variant is considered investigational in all other situations.</p>

POLICY STATEMENT	
BEFORE	AFTER
	<p style="text-align: center;"><u>Blue font: Verbiage Changes/Additions</u></p> <p>XI. Analysis of plasma for the somatic <i>BRAF</i>V600E variant to detect ctDNA is considered investigational as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to BRAF and/or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar], trametinib [Mekinist]) in individuals with NSCLC.</p> <p><i>ROS1</i> Testing</p> <p>XII. Analysis of tumor tissue for somatic rearrangement variants of the <i>ROS1</i> gene may be considered medically necessary to predict treatment response to an FDA-approved ROS1 inhibitor therapy (e.g., crizotinib [Xalkori]) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label (see Policy Guidelines).</p> <p>XIII. Analysis of tumor tissue for somatic rearrangement variants of the <i>ROS1</i> gene is considered investigational in all other situations.</p> <p>XIV. Analysis of plasma for somatic rearrangement variants of the <i>ROS1</i> gene to detect ctDNA is considered investigational as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to ROS1 inhibitor therapy (e.g., crizotinib [Xalkori] or entrectinib) in individuals with NSCLC.</p> <p><i>KRAS</i> Testing</p> <p>XV. Analysis of tumor tissue for somatic variants of the <i>KRAS</i> 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>

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	<p>XVI. Analysis of plasma for somatic variants of the KRAS gene (e.g., G12C) using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered medically necessary as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to sotorasib (Lumakras) in individuals with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).</p> <p>XVII. All other uses of analysis of somatic variants of the <i>KRAS</i> gene in tissue or plasma are considered investigational.</p> <p><i>RET</i> Rearrangement Testing</p> <p>XVIII. Analysis of tumor tissue for somatic alterations in the <i>RET</i> 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).</p> <p>XIX. Analysis of tumor tissue for somatic alterations in the <i>RET</i> gene is considered investigational in all other situations.</p> <p>XX. Analysis of plasma for somatic alterations of the RET gene using plasma specimens to detect ctDNA is considered investigational as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to RET inhibitor therapy (e.g., selpercatinib [Retevmo], pralsetinib [Gavreto]) in individuals with NSCLC.</p> <p><i>MET</i> Exon 14 Skipping Alteration</p>

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	<p style="text-align: center;">Blue font: Verbiage Changes/Additions</p> <p>XXI. Analysis of tumor tissue for somatic alterations in tissue that leads to <i>MET</i> 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).</p> <p>XXII. Analysis of plasma for somatic alteration that leads to <i>MET</i> exon 14 skipping using an FDA-approved companion diagnostic plasma test to detect ctDNA may be considered medically necessary as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to MET inhibitor therapy (e.g., capmatinib [Tabrecta]) in individuals with NSCLC, if the individual does not have any FDA-labeled contraindications to the requested agent and both the agent and ctDNA test are intended to be used consistently with their FDA-approved labels (see Policy Guidelines).</p> <p>XXIII. All other uses of analysis of somatic variants of the <i>MET</i> gene in tissue or plasma are considered investigational.</p> <p>Neurotrophic Receptor Tyrosine Kinase (<i>NTRK</i>) Gene Fusion Testing</p> <p>XXIV. Analysis of tumor tissue for <i>NTRK</i> 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).</p> <p>XXV. Analysis of plasma for <i>NTRK</i> 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</p>

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	<p style="text-align: center;"><u>Blue font: Verbiage Changes/Additions</u></p> <p>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).</p> <p>XXVI. All other uses of analysis of <i>NTRK</i> fusions in tissue or plasma are considered investigational.</p> <p>Plasma Testing When Tissue is Insufficient</p> <p>XXVII. 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 BOTH of the following criteria:</p> <ul style="list-style-type: none"> A. Individual does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; AND B. Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing. <p>Testing for other variants may become available between policy updates.</p>