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

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 01/01/2023

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

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

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

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

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

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider initial analysis of tumor tissue for somatic variants within the **EGFR** gene, rearrangement variants of the **ALK** gene, **BRAF V600E** variant, rearrangement variants of the **ROS1** gene, variants of the **KRAS** gene, **NTRK** gene fusions, alteration in the **RET** gene, alteration that leads to **MET** exon 14 skipping, **HER2** and **PD-L1** expression by immunohistochemistry to predict treatment response to an FDA-approved targeted therapy or immunotherapy in individuals with advanced (stage III or IV) non-small-cell lung cancer (NSCLC) to be eligible for coverage.**

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

Patient Selection Criteria

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

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

LIQUID BIOPSY (PLASMA) TESTING WHEN TISSUE IS INSUFFICIENT

When Services May Be Eligible for Coverage

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

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

Based on review of available data, the Company may consider FDA-approved companion diagnostic plasma test in patients with advanced or metastatic NSCLC (stage IIIB or IV) to predict treatment response to an FDA-approved targeted therapy or immunotherapy for patients meeting the following criteria to be eligible for coverage:**
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Patient Selection Criteria

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

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

**REPEAT TESTING**

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

If a liquid biopsy is negative, tissue-based testing is strongly recommended.

*Note:
For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing (NGS), single available procedure code for the multi-gene panel test is to be utilized.*
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Per the AMA, when a PLA code is available to report a given proprietary laboratory service, the service should not be reported with any other CPT code(s).

Testing for other variants may become available between policy updates.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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

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

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

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

Policy Guidelines
Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.
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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.5.2022) recommend that EGFR variants (category 1), ALK rearrangements (category 1), and PD-L1 testing (category 1) as well as KRAS, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping alteration, RET, and HER2 testing (all category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling, defined as a single assay or a combination of a limited number of assays and that it is acceptable to have a tiered approach based on low-prevalence, co-occurring biomarkers. The guidelines additionally recommend identifying the emerging biomarker, high-level MET amplification, while noting that the definition of this biomarker is evolving and may differ according to the assay used.

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

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

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

**Concurrent Somatic Liquid-Based and Tissue-Based Genomic Testing**

Liquid biopsy testing uses blood samples and assesses cancer DNA and non-cancer DNA in the same blood sample. The goal is to identify options for genome-informed treatment. Some providers will order a liquid biopsy test and a tissue biopsy test at the same time to hasten time to treatment. If the intent of concurrent testing is to follow an individual over time to monitor for resistance variant T790M, then consideration could be given to doing liquid biopsy at diagnosis with the tissue biopsy to make sure that mutations that are going to be followed longitudinally can be detected by the liquid biopsy. Current NCCN guidelines for NSCLC (v. 5.2022) state the following: "Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate; however, data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection."

**Recommended Testing Strategies**

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

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

**Background/Overview**

**Non-Small-Cell Lung Cancer**

Treatment options for non-small-cell lung cancer (NSCLC) depend on disease stage and include various combinations of surgery, radiotherapy, systemic therapy, and best supportive care. Unfortunately, in up to 85% of cases, cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC
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have a median survival of 8 to 11 months and 1-year survival of 30% to 45%. The identification of specific, targetable oncogenic “driver mutations” in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology.

**EGFR Gene**

**EGFR,** a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit **EGFR** signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small-molecule tyrosine kinase inhibitors [TKIs]). These targeted therapies dampen signal transduction through pathways downstream to the **EGFR,** such as the RAS/RAF/MAPK cascade. RAS proteins are G proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors, such as **EGFR,** acting as binary switches between cell surface **EGFR** and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Somatic variants in the tyrosine kinase domain of the **EGFR** gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R, indicating substitution of leucine by arginine at codon position 858) are the most commonly found **EGFR** variants associated with sensitivity to **EGFR** tyrosine kinase inhibitors (TKIs; afatinib, erlotinib, gefitinib). These variants are referred to as sensitizing variants. Almost all patients who initially respond to an **EGFR** TKI experience disease progression. The most common of these secondary variants, called resistance variants, involves the substitution of methionine for threonine at position 790 (T790M) on exon 20.

Fang et al (2013) reported **EGFR** variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage squamous cell carcinoma (SCC). In a separate cohort of 63 Chinese patients with SCC who received erlotinib or gefitinib as second- or third-line treatment (63% never-smokers, 21% women), **EGFR** variant prevalence (all exon 19 deletion or L858R) was 23.8%.

In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al (2006) reported **EGFR** variants in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies. Eberhard et al (2005) observed **EGFR** variants in 6.4% of patients with SCC and Rosell et al (2009)
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observed EGFR variants in 11.5% of patients with large cell carcinomas. Both studies had small sample sizes.

In 2 other studies, the acquired EGFR T790M variant has been estimated to be present in 50% to 60% of TKI-resistant cases in approximately 200 patients.

**ALK Gene**

*ALK* is a TK that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement that leads to a fusion gene and expression of a protein with constitutive TK activity that has been demonstrated to play a role in controlling cell proliferation. The *EML4-ALK* fusion gene results from an inversion within the short arm of chromosome 2.

The *EML4-ALK* rearrangement (“ALK-positive”) is detected in 3% to 6% of NSCLC patients, with the highest prevalence in never-smokers or light ex-smokers who have adenocarcinoma.

**BRAF Gene**

RAF proteins are serine/threonine kinases that are downstream of *RAS* in the RAS-RAF-ERK-MAPK pathway. In this pathway, the *BRAF* gene is the most frequently mutated in NSCLC, in 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. Most *BRAF* variants occur more frequently in smokers.

**ROS1 Gene**

*ROS1* codes for a receptor TK of the insulin receptor family and chromosomal rearrangements result in fusion genes. The prevalence of *ROS1* fusions in NSCLC varies from 0.9% to 3.7%. Patients with *ROS1* fusions are typically never-smokers with adenocarcinoma.

**KRAS Gene**

The *KRAS* gene (which encodes RAS proteins) can harbor oncogenic variants that result in a constitutively activated protein, independent of signaling from the *EGFR*, possibly rendering a tumor resistant to therapies that target the *EGFR*. Variants in the *KRAS* gene, mainly codons 12 and 13, have been reported in 20% to 30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers.
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KRAS variants can be detected by direct sequencing, PCR technologies, or NGS.

EGFR, ALK, ROS1, and KRAS driver mutations are considered to be mutually exclusive.

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

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

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

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

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

**Tumor Mutational Burden**
Tumor mutational burden, a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types, including lung cancer.
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Targeted Treatment and Immunotherapy
FDA-approved targeted treatments and immunotherapies for the variants described above are summarized in Table 1. (Note this information is current as of October 17, 2022. FDA maintains a list of oncology drug approval notifications at https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.).

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

<table>
<thead>
<tr>
<th>Target</th>
<th>FDA-Approved Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR</strong></td>
<td>Gefitinib (Iressa), Erlotinib (Tarceva) alone or in combination with ramucirumab (Cyramza) Afatinib (Gilotrif) Osimertinib (Tagrisso) Dacomitinib (Vizimpro) Amivantamab-vmjw (Rybrenant) Mobocertinib (Exkivity)</td>
</tr>
<tr>
<td><strong>ALK</strong></td>
<td>Crizotinib (Xalkori) Ceritinib (Zykadia) Alectinib (Alecensa) Brigatinib (Alunbrig) Lorlatinib (Lorbrena)</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td>Dabrafenib (Tafinlar) alone or in combination with trametinib (Mekinist)</td>
</tr>
<tr>
<td><strong>ROS1</strong></td>
<td>Crizotinib (Xalkori) Entrectinib (Rozlytrek)</td>
</tr>
<tr>
<td><strong>KRAS</strong></td>
<td>Sotorasib (Lumakras)</td>
</tr>
</tbody>
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| HER2 (ERBB2) | • Fam-trastuzumab deruxtecan-nxki (Enhertu) |
| RET          | • Selpercatinib (Retevmo)  
               | • Pralsetinib (Gavreto) |
| MET          | • Capmatinib (Tabrecta)  
               | • Tepotinib (Tepmetko) |
| NTRK1        | • Larotrectinib (Vitrakvi)  
               | • Entrectinib (Rozlytrek) |
| PD-L1        | • Pembrolizumab (Keytruda)  
               | • Nivolumab (Opdivo) in combination with ipilimumab (Yervoy)  
               | • Atezolizumab (Tecentriq)  
               | • Cemiplimab-rwlc (Libtayo) |

**FDA or Other Governmental Regulatory Approval**

Table 2 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved companion diagnostic tests. (Note this information is current as of October 17, 2022. FDA maintains a list of cleared or approved companion diagnostics at [https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-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.).)

**Table 2. FDA-Approved Targeted Treatments for NSCLC and Companion Diagnostic Tests**

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>FDA-Approved Companion Diagnostic Tests</th>
</tr>
</thead>
</table>
| Afatinib (Gilotrif) | - 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions  
|                  | - 2016: Second line for patients with metastatic squamous NSCLC  
|                  | - 2018: First line for patients with nonresistant EGFR variants other than exon 19 or exon 21 NSCLC | - 2013: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (ROQ PCR) kit (Qiagen)  
|                  |                                                                           | - 2017: FoundationOne CDx™ (Foundation Medicine)  
|                  |                                                                           | - 2017: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)                |
| Alectinib (Alecensa) | - 2015: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib  
|                  | - 2017: Patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test | - 2017: FoundationOne CDx™ (Foundation Medicine)  
|                  |                                                                           | - 2017: Ventana ALK (D5F3) CDx Assay                                         |
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<tr>
<td>Amivantamab-vmjw (Rybrenant)</td>
<td>• 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</td>
<td>• 2021: Guardant360 CDx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2021: Oncomine™† Dx Target Test</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>• 2020: First-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells covering ≥ 10% of the tumor area [IC ≥ 10%] ), as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations. o in combination with bevacizumab, paclitaxel, and carboplatin, for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations o in combination with paclitaxel protein-bound and carboplatin for the</td>
<td>• 2020: Ventana PD-L1</td>
</tr>
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| Brigatinib (Alunbrig)      | first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations  
  o for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.  | • 2020: Vysis ALK Break Apart FISH Probe Kit                                                                                                   |
|                            | • 2020: Treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test                                                                                                 |                                         |
| Capmatinib (Tabrecta)      | • 2020: Metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping as detected by an FDA-approved test.                                                                           | • 2020: FoundationOne CDx™
  • 2021: FoundationOne Liquid CDx™                                                                                                               |
| Cemiplimab-rwlc (Libtayo)  | • 2022: First-line treatment of patients with advanced NSCLC (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression | • 2021: PD-L1 IHC 22C3 pharmDx (Dako)                                                                                                           |
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<tr>
<td>Ceritinib (Zykadia)</td>
<td>(Tumor Proportion Score [TPS] &gt; 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations</td>
<td>North America, Inc.</td>
</tr>
<tr>
<td></td>
<td>• 2014: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2017: First line for patients with ALK-positive metastatic NSCLC</td>
<td></td>
</tr>
<tr>
<td>Crizotinib (Xalkor)</td>
<td>• 2011: First line for patients with ALK positive metastatic NSCLC</td>
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<tr>
<td>Crizotinib (Xalkori)</td>
<td>• 2016: Patients with ROS1-positive metastatic NSCLC</td>
<td>• 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)</td>
</tr>
</tbody>
</table>
| Dacomitinib (Vizimpro)   | • 2018: First line for patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitutions | • 2018: therascreen EGFR RGQ PCR Kit  
• 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) |

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| **Dabrafenib** *(Tafinlar)* plus **trametinib** *(Mekinist)* | • 2017: Used in combination for treatment of patients with metastatic NSCLC with BRAF V600E variant | • 2017: Oncomine™ Dx Target Test  
• 2017: FoundationOne CDx™‡ (Foundation Medicine) |
| **Entrectinib** *(Rozlytrek)*                  | • 2019:  
  o Adult patients with metastatic NSCLC whose tumors are ROS1-positive  
  o Adult and pediatric patients 12 years of age and older with  
    • solid tumors that have a NTRK gene fusion without a known acquired resistance mutation,  
    • are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy | • 2022: FoundationOne CDx™‡ (Foundation Medicine) |

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

Policy # 00452  
Original Effective Date: 05/20/2015  
Current Effective Date: 01/01/2023

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<tr>
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</table>
| Erlotinib (Tarceva) | • 2020: First-line treatment in combination with ramucirumab (Cyramza) for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions  
• 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions  
• 2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy  
• 2004: Second line for patients with locally advanced or metastatic NSCLC | • 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) |
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| Gefitinib (Iressa) | • 2015: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions  
• 2003: Second line for patients with locally advanced or metastatic NSCLC | • 2015: therascreen®‡ EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit  
• 2017: Oncomine™† Dx Target Test  
• 2017: FoundationOne CDx™‡ (Foundation Medicine)  
• 2017: cobas®‡ EGFR Mutation Test (tissue test) (Roche Diagnostics)  
• 2020: cobas®‡ EGFR Mutation Test v2 (tissue or plasma) (Roche Diagnostics)  
• 2020: FoundationOne®‡ Liquid CDx |
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<tr>
<td>Larotrectinib (Vitrakvi)</td>
<td>• 2018: Adult and pediatric patients with solid tumors that</td>
<td>• 2021: ONCO/Reveal Dx Lung &amp; Colon Cancer Assay (O/RDx-LCCA)</td>
</tr>
<tr>
<td></td>
<td>o have a NTRK gene fusion without a known acquired resistance mutation,</td>
<td>• 2020: FoundationOne CDx® (solid tumors, NTRK1/2/3 fusions)</td>
</tr>
<tr>
<td></td>
<td>o are metastatic or where surgical resection is likely to result in severe</td>
<td></td>
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<tr>
<td></td>
<td>morbidity, and</td>
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<tr>
<td></td>
<td>o have no satisfactory alternative treatments or that have progressed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>following treatment</td>
<td></td>
</tr>
<tr>
<td>Lorlatinib (Lorbrena)</td>
<td>• 2018: Patients with ALK-positive metastatic NSCLC whose disease has</td>
<td>• 2021: Ventana ALK (D5F3) CDx Assay</td>
</tr>
<tr>
<td></td>
<td>progressed on:</td>
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<tr>
<td></td>
<td>o crizotinib and at least 1 other ALK inhibitor for metastatic disease; or</td>
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</tr>
<tr>
<td></td>
<td>o alectinib as the first ALK inhibitor therapy for metastatic disease; or</td>
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<td>o ceritinib as the first ALK inhibitor therapy for metastatic disease</td>
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<td>Mobocertinib (Exkivity)</td>
<td>• 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</td>
<td>• 2021: Oncomine Dx Target Test</td>
</tr>
</tbody>
</table>
| Nivolumab (Opdivo) in combination with Ipilimumab (Yervoy) | • 2020:  
  o adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab  
  o adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy  
  o patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved  | • 2020: PD-L1 IHC 28-8 PharmDx                      |
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| Osimertinib (Tagrisso)     | • 2015: Second line for patients with metastatic NSCLC whose tumors have EGFR T790M variants as detected by an FDA-approved test, who have not responded to EGFR-blocking therapy  
                          | • 2018: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R variants  
                          | • 2019: EGFR exon 19 deletion and EGFR exon 21 L858R alterations  
                          | • 2020: 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                                                                 | • 2015-2020: cobas®‡ EGFR Mutation Test v2 (tissue or plasma)  
                          | • 2017-2019: FoundationOne CDx™ (Foundation Medicine)  
                          | • 2020: Guardant360 CDx  
                          | • 2020: FoundationOne®‡ Liquid CDx                                                                                                                                                                                                                                                                                                       |
| Pembrolizumab (Keytruda)   | • 2018: Monotherapy for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA- | • 2018: PD-L1 IHC 22C3 pharmDx  
                          |                                                                                                                                                                                                                                                                                                                                       | 2020: FoundationOne CDx (TMB)                                                                                                                                                                                                                                          |
### Treatment Indication

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</thead>
<tbody>
<tr>
<td><strong>approved therapy for these aberrations prior to receiving KEYTRUDA</strong></td>
<td>• 2020: For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) ( \geq 10 ) mutations/megabase (mut/Mb) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options</td>
<td></td>
</tr>
<tr>
<td>Pralsetinib (Gavreto)</td>
<td>• 2020: Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test</td>
<td>• 2020: Oncomine Dx Target Test</td>
</tr>
<tr>
<td>Selpercatinib (Rehevno)</td>
<td>• 2020: Adult patients with metastatic RET fusion-positive NSCLC</td>
<td>• 2022: Oncomine Dx Target Test</td>
</tr>
<tr>
<td>Sotorasib (Lumakras)</td>
<td>• 2021: 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</td>
<td>• 2021: Therascreen KRAS RGQ PCR kit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2021: Guardant360 CDx</td>
</tr>
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<tr>
<td>Tepotinib (Tepmetko)</td>
<td>• 2021: Adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.</td>
<td>• No approved companion diagnostic</td>
</tr>
<tr>
<td>Fam-trastuzumab deruxtecan-nxki (Enhertu)</td>
<td>• 2022: Adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy</td>
<td>• 2022: Oncomine Dx Target Test • 2022: Guardant360 CDx</td>
</tr>
</tbody>
</table>

Sources: U.S. Food and Drug Administration (2022) U.S. Food and Drug Administration (n.d.) ALK: anaplastic lymphoma kinase; CDx: companion diagnostic; EGFR: epidermal growth factor receptor; ERBB2: erythroblastic oncogene B 2 receptor tyrosine kinase; FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; MET: mesenchymal-epithelial transition; NSCLC: non-small-cell lung cancer; NTRK neurotrophic receptor tyrosine kinase; PCR: polymerase chain reaction.

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

Over half of patients with non-small-cell lung cancer (NSCLC) present with advanced and therefore incurable disease. Treatment in this setting has been with platinum-based chemotherapy. The identification of specific, targetable oncogenic “driver mutations” in a subset of NSCLCs has
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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 who have advanced-stage NSCLC who are being considered for targeted therapy who receive somatic testing for EGFR variants and ALK rearrangements, the evidence includes nonrandomized studies and phase 3 studies comparing tyrosine kinase inhibitors (TKIs) (eg, afatinib, erlotinib, gefitinib, osimertinib, dacomitinib, et al) with chemotherapy or alternate TKIs. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, quality of life (QOL), and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and progression-free survival (PFS), with a reduction in toxicity and improvement in QOL. Recent data has also shown that patients with EGFR exon 20 insertion mutations may benefit from immunotherapy with amivantamab-vmjw following disease progression on platinum-based chemotherapy or ramucirumab in combination with erlotinib as first-line treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive somatic testing for BRAF variants and ROS1 rearrangements, the evidence includes nonrandomized trials and observational studies of BRAF and MEK inhibitors and crizotinib or ceritinib, respectively. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown that combination therapy with dabrafenib and trametinib for BRAF V600E- variant NSCLC and crizotinib for NSCLC with ROS1 rearrangements result in response rates of 60% and 70%, respectively, with acceptable toxicity profiles. In an analysis of 53 patients with ROS-1 fusion-positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib, the objective response rate was 77%, with a median duration of response of 24.6 months and acceptable toxicity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive somatic testing for RET or MET gene testing, the evidence includes nonrandomized trials of kinase inhibitors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown efficacy in PFS and duration of response for
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selpercatinib and pralsetinib in patients with RET-fusion positive NSCLC, and for capmatinib in patients with MET Exon 14 skipping alterations, with acceptable toxicity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive somatic testing for KRAS as a technique to predict treatment nonresponse to anti-EGFR therapy with TKIs or testing for HER2 variants to select the use of the anti-EGFR monoclonal antibody cetuximab (Erbitux), the evidence includes post hoc analysis of trials, observational studies, and meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Data on the role of KRAS variants in NSCLC and response to erlotinib are available from post hoc analysis of trials, observational studies, and meta-analyses. Although studies have shown that KRAS variants in patients with NSCLC confer a high level of resistance to TKIs, data are insufficient to assess any additional benefit to KRAS testing beyond EGFR testing. In 2 randomized trials with post hoc analyses of KRAS variant status and use of the anti-EGFR monoclonal antibody cetuximab with chemotherapy, KRAS variants did not identify patients who would benefit from anti-EGFR antibodies, because outcomes with cetuximab were similar regardless of KRAS variant status. Studies for HER2 variant testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive somatic testing for KRAS variants to select targeted treatment, the evidence includes a phase 2, open-label trial of sotorasib in patients with KRAS variant NSCLC. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Presence of the KRAS alteration in tissue was confirmed on central laboratory testing with the use of the therascreen KRAS RGQ PCR Kit. Among 124 patients evaluated for the primary outcome, 4 (3.2%) had a complete response and 42 (33.9%) had a partial response, with an acceptable safety profile. Median duration of response was 11.1 months (95% confidence interval [CI]: 6.9 to not evaluable). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy with fam-trastuzumab deruxtecan-nxki who receive somatic testing for HER2 variants, the evidence includes a multicenter, blinded, and randomized dose-optimization trial. Relevant outcomes are OS,
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disease-specific survival, test validity, QOL, and treatment-related morbidity. In the DESTINY-Lung02 trial, patients with activating HER2 mutations who have received prior systemic therapy demonstrated an objective response rate (ORR) of 58% (95% CI, 43% to 71%) and median duration of response of 8.7 months (95% CI, 7.1 months to not estimable) when treated with the novel antibody-drug conjugate trastuzumab deruxtecan. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals who have advanced-stage NSCLC who receive testing for biomarkers of EGFR TKIs sensitivity using ctDNA with the cobas EGFR Mutation Test v2, Guardant360 CDx, FoundationOne Liquid CDx, OncoBEAM, or InVision tests, the evidence includes numerous studies assessing the diagnostic characteristics of liquid biopsy compared with tissue biopsy. Relevant outcomes are OS,
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disease-specific survival, and test validity. Current evidence does not permit determining whether cobas or tissue biopsy is more strongly associated with patient outcomes or treatment response. No evidence identified in RCTs providing the clinical utility of cobas. The cobas, Guardant360 CDx, and FoundationOne Liquid CDx tests have received FDA-approval as companion diagnostics for EGFR-sensitizing variants and are therefore not subject to extensive evidence review. The OncoBEAM and InVision tests have adequate evidence of clinical validity for the EGFR TKI-sensitizing variants. A chain of evidence demonstrates that the reflex testing strategy with these tests should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with EGFR TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who receive testing for biomarkers of EGFR TKIs sensitivity using ctDNA (liquid biopsy) with tests other than the cobas EGFR Mutation Test v2, Guardant360 CDx, FoundationOne Liquid CDx, OncoBEAM or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with reference standard. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the other commercially available tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. No evidence was found in RCTs providing the clinical utility of these methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who progressed on EGFR TKIs who receive testing for biomarkers of EGFR TKI resistance using ctDNA (liquid biopsy) with the cobas EGFR Mutation Test v2, Guardant360 CDx, OncoBEAM, or InVision tests the evidence includes studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are OS, disease-specific survival, and test validity. Both cobas and Guardant360 CDx tests have been FDA-approved as companion diagnostic plasma tests for selection of osimertinib treatment in patients with T790M-mutated NSCLC on the basis of clinical bridging studies and are therefore not subject to extensive

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evidence review. Given the moderate clinical sensitivity and specificity of liquid biopsy for the remaining tests, using liquid biopsy alone or in combination with tissue biopsy might result in the selection of different patients testing positive for EGFR TKI resistance. It cannot be determined whether patient outcomes are improved. Although there is higher discordance in the liquid versus tissue results for the resistance variant, retrospective analyses have suggested that patients positive for T790M in liquid biopsy have outcomes with osimertinib that appear to be similar overall to patients positive by a tissue-based assay. Additionally, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published joint guidelines endorsed by American Society of Clinical Oncology with an expert consensus opinion that physicians may use liquid biopsy (cell-free DNA) to identify EGFR T790M variants in patients with progression or resistance to EGFR-targeted TKIs and that testing of the tumor sample is recommended if the liquid biopsy result is negative. Similarly, the National Comprehensive Cancer Network guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when testing for the T790M resistance variant, liquid biopsy should be considered. When a liquid biopsy is negative, tissue-based testing is strongly recommended. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who progressed on EGFR TKIs who receive testing for biomarkers of EGFR TKI resistance using ctDNA (liquid biopsy) with tests other than the cobas EGFR Mutation Test v2, Guardant360 CDx, OncoBEAM, or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the other commercially available tests have multiple studies of adequate quality to estimate the performance characteristics for detection of the EGFR T790M variant with sufficient precision. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. No RCTs was found providing evidence of the clinical utility of these methods of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
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For individuals with advanced-stage NSCLC who are being considered for targeted therapy who undergo testing for ALK rearrangements or MET exon 14 skipping alterations using FoundationOne Liquid CDx, the evidence includes clinical bridging studies. Relevant outcomes are OS, disease-specific survival, and test validity. FoundationOne Liquid CDx has received FDA-approval as a companion diagnostic plasma test for alectinib and capmatinib and is therefore not subject to extensive evidence review. FDA approval was based on sufficient sensitivity against clinical trial assays as reference standard to support a reflex testing strategy and favorable overall response rates in the liquid-positive subpopulation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced-stage NSCLC who are being considered for targeted therapy who undergo testing for KRAS variants or ROS1 rearrangements using FoundationOne Liquid CDx, the evidence includes several retrospective and prospective studies assessing the diagnostic characteristics of liquid biopsy compared with tissue reference standard. Relevant outcomes are OS, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. Studies have had small sample sizes and have failed to focus on the actionable KRAS G12C variant. Multiple studies of adequate quality to estimate the performance characteristics with sufficient precision are lacking. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. No evidence was found in RCTs providing the clinical utility of this method of liquid biopsy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with advanced-stage NSCLC who are being considered for targeted therapy or immunotherapy who undergo testing for KRAS or HER2 variants using Guardant360 CDx, the evidence includes clinical bridging studies. Relevant outcomes are OS, disease-specific survival, and test validity. Guardant360 CDx received FDA-approval as a companion diagnostic plasma test for sotorasib and fam-trastuzumab deruxtecan-nxki and is therefore not subject to extensive evidence review. FDA approval was based on sufficient sensitivity against clinical trial assays as reference standard to support a reflex testing strategy and favorable overall response rates in the liquid-positive subpopulation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.
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Supplemental Information
Practice Guidelines and Position Statements

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

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

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

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

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

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

**College of American Pathologists et al**

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

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

**National Comprehensive Cancer Network Guidelines**

**Testing for Molecular Biomarkers**

NCCN guidelines on NSCLC (v.3.2022) 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.3.2022) include the following recommendations and statements related to testing for molecular biomarkers:

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

- NSCLC Panel recommends that broad molecular profiling be done as part of biomarker testing using a validated test(s) that assesses a minimum of the following potential genetic variants: ALK rearrangements, BRAF mutations, EGFR mutations, KRAS mutations, METex14 skipping mutations, NTRK 1/2/3 gene fusions, RET rearrangements, ROS1 rearrangements, and IHC testing for PD-L1 expression levels.
- The NCCN Panel recently deleted TMB as an emerging immune biomarker based on clinical trial data and other issues. In addition to the lack of clinical data to support use of TMB as an immune biomarker, there are technical problems with measuring TMB (e.g., lack of agreement on the definition of a cut off for designating high TMB levels; lack of standardization of TMB measurements across laboratories).
- Biomarker testing should be done at properly accredited laboratories (minimum of Clinical Laboratory Improvement Amendments [CLIA] accreditation). Both FDA and laboratory-developed test platforms are available that evaluate these and other analytes.
- The guidelines do not endorse any specific commercially available biomarker assays.

Plasma Cell-Free/Circulating Tumor DNA Testing:
The NCCN guidelines on NSCLC (v.3.2022) include the following recommendations related to plasma cell-free/circulating tumor DNA testing.

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

The guidelines also state:

- Standards for analytic performance characteristics of cell-free tumor DNA have not been established, there is up to a 30% false-negative rate, and variants can be detected that are not related to the tumor (e.g., clonal hematopoiesis of indeterminate potential [CHIP]). Rare examples of CHIP with KRAS mutations have been described, suggesting caution in
the interpretation of cfDNA findings. In addition, CHIP can be identified following prior chemotherapy or radiotherapy, further confounding interpretation of variants such as in TP53. Given the previous caveats, careful consideration is required to determine whether cfDNA findings reflect a true oncogenic driver or an unrelated finding. In contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.

U.S. Preventive Services Task Force Recommendations
Not applicable.

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

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

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT03576937</td>
<td>Achieving Value in Cancer Diagnostics: Blood Versus Tissue Molecular Profiling - a Prospective Canadian Study (VALUE)</td>
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<tr>
<td>NCT01306045</td>
<td>Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung</td>
<td>471</td>
<td>Dec 2024</td>
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<tr>
<td>NCT03225664</td>
<td>BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer</td>
<td>37 (actual)</td>
<td>Sep 2024</td>
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<td>NCT02622581</td>
<td>Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP)</td>
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<tr>
<td>NCT02117167a</td>
<td>Intergroup Trial UNICANCER UC 0105-1305/IFCT 1301: SAFIR02_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer</td>
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<td>NCT02465060</td>
<td>Molecular Analysis for Therapy Choice (MATCH)</td>
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<td>NCT02576431a</td>
<td>A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-positive Tumors</td>
<td>204</td>
<td>Aug 2025</td>
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<tr>
<td>NCT02568267a</td>
<td>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</td>
<td>700</td>
<td>Apr 2025</td>
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<tr>
<td>NCT01639508</td>
<td>A Phase II Study of Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes:</td>
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<td>Jul 2023</td>
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</table>
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<tr>
<td>NCT03469960</td>
<td>A Randomized Phase 3 Trial Comparing Continuation Nivolumab-Ipilimumab Doublet Immunotherapy Until Progression Versus Observation in Treatment-naive Patients With PDL1-positive Stage IV Non-Small Cell Lung Cancer (NSCLC) After Nivolumab-Ipilimumab Induction Treatment</td>
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<td>May 2023</td>
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<td>NCT03199651</td>
<td>Beating Lung Cancer in Ohio (BLCIO) Protocol</td>
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<td>NCT04863924</td>
<td>Accelerating Lung Cancer Diagnosis Through Liquid Biopsy (ACCELERATE)</td>
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<td>NCT04912687a</td>
<td>Implementing Circulating Tumor DNA Analysis at Initial Diagnosis to Improve Management of Advanced Non-small Cell Lung Cancer Patients (NSCLC) (CIRCULAR)</td>
<td>580</td>
<td>Jan 2024</td>
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<tr>
<td>NCT03037385a</td>
<td>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</td>
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<td>Feb 2024</td>
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<tr>
<td>NCT03178552a</td>
<td>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)</td>
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<td>NCT04591431</td>
<td>The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy</td>
<td>384</td>
<td>Aug 2024</td>
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<tr>
<td>NCT04180176a</td>
<td>A Multicenter, Low-Interventional Study to Evaluate the Feasibility of a Prospective Clinicogenomic Program (PCG)</td>
<td>1000</td>
<td>Mar 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References
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52. Food and Drug Administration (FDA). TAGRISSOTM (osimertinib) Highlights of Prescribing Information. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208065s000lbl.pdf.


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05/07/2015 Medical Policy Committee review
05/20/2015 Medical Policy Implementation Committee approval. New policy. Replaced policy 00122 and 00289.
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016 Medical Policy Committee review
12/21/2016 Medical Policy Implementation Committee approval. Added coverage statement for analysis for the T790M mutation and added brand names to the coverage statements.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
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12/07/2017 Medical Policy Committee review
12/20/2017 Medical Policy Implementation Committee approval. Added ROS1 and BRAF testing to medically necessary statement. Rationale reorganized. Criteria reformatted.
12/06/2018 Medical Policy Committee review
12/19/2018 Medical Policy Implementation Committee approval. The policy section on EGFR Testing was changed given the new evidence in support of testing for additional variants in the EGFR gene.
12/05/2019 Medical Policy Committee review
12/11/2019 Medical Policy Implementation Committee approval. New indications for NTRK testing and tumor mutational burden (TMB) testing added. Medically necessary statement for NTRK testing and investigational statement for TMB testing added.
05/07/2020 Medical Policy Committee review
05/13/2020 Medical Policy Implementation Committee approval. No change to coverage.
02/04/2021 Medical Policy Committee review
02/10/2021 Medical Policy Implementation Committee approval. Separated out KRAS, HER2, RET and MET into 2 indications. RET and MET testing are medically necessary under specified conditions. KRAS and HER2 indications remain investigational. Added an indication and MN policy statement for PD-L1 testing. Added a new PICO for immunotherapy. Updated Policy Guidelines section with recommended testing strategies. Updated Regulatory Status section and Policy statements with new FDA indications. "or Immunotherapy" added to the policy title.
03/04/2021 Medical Policy Committee review
03/10/2021 Medical Policy Implementation Committee approval. Added Small panel testing including the genes listed as eligible for coverage may be considered as an alternative to individual testing and may be preferred when there is limited tissue available for testing.
For 5 or more gene tests being run on a tumor specimen on the same platform, such as multi-gene panel next generation sequencing, an available procedure code for the multi-gene panel test is to be utilized.
03/03/2022 Medical Policy Committee review
03/09/2022 Medical Policy Implementation Committee approval. New indication and eligible for coverage policy statement added for KRAS testing to select patients for
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treatment with sotorasib. New indications and investigational policy statements added for ALK rearrangement and MET exon 14 skipping alteration testing using FoundationOne Liquid. Title changed to “Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer.”

Coding update 06/07/2022
Coding update 09/01/2022
Medical Policy Committee review 09/14/2022
Medical Policy Implementation Committee approval. Coverage extensively revised due to senate bill update.
12/01/2022
Medical Policy Committee review
12/14/2022
Medical Policy Implementation Committee approval. Senate bill update. No change to coverage.

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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

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

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