Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 04/12/2021

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: Circulating Tumor DNA Management of Non-Small Cell Lung is addressed separately in medical policy 00597.

EGFR 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 analysis of somatic variants in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (EGFR), to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) in patients with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified to be **eligible for coverage.****

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 analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC to be **investigational.***

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ALK 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 analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (ALK) gene to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori®], ceritinib [Zykadia], alectinib [Alecensa®], or brigatinib [Alunbrig™])‡ in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be **eligible for coverage.****

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 analysis of somatic rearrangement variants of the ALK gene in all other situations to be **investigational.***

BRAF V600E 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 analysis of the BRAF V600E variant to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar®] and

trametinib [Mekinist®])‡, in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be **eligible for coverage.****

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 analysis of the BRAF V600E variant in all other situations to be **investigational.***

ROS1 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 analysis of somatic rearrangement variants of the ROS1 gene to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be **eligible for coverage.****

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 analysis of somatic rearrangement variants of the ROS1 gene in all other situations to be **investigational.***

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NTRK Gene Fusion 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 analysis of gene fusions to predict treatment response to larotrectinib (Vitrakvi®)‡ or entrectinib (Rozlytrek™)‡ in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be **eligible for coverage.**** (see Policy Guidelines section).

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 analysis of NTRK gene fusions in all other situations to be **investigational.***

***RET* Rearrangement 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 analysis of genetic alteration in the RET gene to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) in patients with metastatic NSCLC to be **eligible for coverage.****

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 analysis of genetic alterations in the *RET* gene in all other situations to be **investigational.***

***MET* Exon 14 Skipping Alteration**

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 analysis of genetic alteration that leads to *MET* exon 14 skipping to predict treatment response to capmatinib (Tabrecta) in patients with metastatic NSCLC to be **eligible for coverage.****

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 analysis of genetic alterations of the MET gene in all other situations to be **investigational.***

Note: 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.

PD-L1 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 PD-L1 (immunohistochemistry) testing to predict treatment response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Yervoy), or pembrolizumab (Keytruda) in patients with metastatic NSCLC to be **eligible for coverage.****

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 PD-L1 testing in all other situations to be **investigational.***

KRAS TESTING

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 analysis of somatic variants of the KRAS gene as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase

inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab (Erbitux) in NSCLC to be **investigational.***

***HER2* Testing**

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 analysis of genetic alterations in the HER2 gene for targeted therapy in patients with NSCLC to be **investigational.***

Tumor Mutational Burden Testing

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 analysis of tumor mutational burden for targeted therapy in patients with NSCLC to be **investigational.***

Policy Guidelines

These gene tests are intended for use in patients with advanced non-small-cell lung cancer. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene are considered good candidates for treatment with erlotinib, gefitinib or afatinib. Patients with wild-type variants are unlikely to respond to erlotinib or afatinib; for these patients, other treatment options should be considered.

The 2020 guidelines from the National Comprehensive Cancer Network recommend that *EGFR* variants and *ALK* rearrangement testing (category 1) as well as *ROS1* and *BRAF* testing (category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not

otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling and should include the NTRK gene fusion.

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."

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 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. Testing for epidermal growth factor receptor (*EGFR*) variants and anaplastic lymphoma kinase (*ALK*) rearrangements is routine in clinical decision making for the

treatment of NSCLC. The use of testing for other variants to direct targeted therapy continues to evolve.

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.

Variants in 2 regions of the *EGFR* gene (exons 18-24)-small deletions in exon 19 and a point variant in exon 21 (L858R)-appear to predict tumor response to TKIs such as erlotinib. Likewise, tumors with an acquired exon 20 (T790M) substitution variant appear to respond to osimertinib following the failure of TKI therapy.

The prevalence of *EGFR* variants in NSCLC varies by population, with the highest prevalence in nonsmoking Asian women with adenocarcinoma, in whom *EGFR* variants have been reported to be up to 30% to 50%. The reported prevalence in the white population is approximately 10%.

ALK Gene

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

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

BRAF Gene

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the *BRAF* gene is the most frequently mutated in NSCLC, in 1%

to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. Most *BRAF* variants occur more frequently in smokers.

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

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

KRAS variants can be detected by direct sequencing, PCR technologies, or NGS. Although *KRAS* is the most common driver mutation in NSCLC, there are currently no targeted therapies specifically approved for this indication and, therefore, no U.S. Food and Drug Administration (FDA) approved companion diagnostics.

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.

There are currently no targeted therapies specifically approved for this indication.

***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 amplification 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.

Targeted Treatment and Immunotherapy

Targeted treatments and immunotherapy for the variants described above are summarized in Table 1.

Table 1. Targeted Treatments and Immunotherapy for NSCLC

Target	FDA-Approved Therapies
EGFR	• Gefitinib (Iressa), • Erlotinib (Tarceva), • Afatinib (Gilotrif) • Osimertinib (Tagrisso) • Dacomitinib (Vizimpro)
ALK	• Crizotinib (Xalkori)

	• Ceritinib (Zykadia) • Alectinib (Alecensa) • Brigatinib (Alunbrig) • Lorlatinib (Lorbrena)
BRAF	• Dabrafenib and trametinib combination
ROS1	• Crizotinib (Xalkori) • Ceritinib (Zykadia) • Lorlatinib (Lorbrena) • Entrectinib (Rozlytrek)
KRAS	• No FDA-approved targeted treatments
HER2	• No FDA-approved targeted treatements
RET	• Selpercatinib (Retevmo) • Pralsetinib (Gavreto)
MET	• Capmatinib (Tabrecta)
NTRK	• Larotrectinib (Vitrakvi) • Entrectinib (Rozlytrek)
PD-L1	• Pembrolizumab (Keytruda) • Nivolumab (Opdivo) in combination with ipilimumab (Yervoy) • Atezolizumab (Tecentriq)

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Table 2 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved companion diagnostic tests.

Table 2. Targeted Treatments and Immunotherapy for NSCLC and Companion Diagnostic Tests

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
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 (RGQ PCR) kit (Qiagen) • 2017: FoundationOne CDx™ (Foundation Medicine)
Alectinib (Alecensa)	• 2015: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: First line for patients with ALK-positive NSCLC who have not received prior systemic therapy for metastatic disease	• 2017: FoundationOne CDx™ (Foundation Medicine)

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		• 2017: Ventana ALK (D5F3) CDx Assay
Atezolizumab (Tecentriq)	• 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 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: VENTANA PD-L1

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
Brigatinib (Alunbrig)	• 2017: Second line for patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant of crizotinib	• 2020: Vysis ALK Break Apart FISH Probe Kit
Capmatinib (Tabrecta)	• 2020: metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to *MET* exon 14 skipping as detected by an FDA-approved test.	• 2020: FoundationOne CDx (Foundation Medicine)
Ceritinib (Zykadia)	• 2014: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: First line for patients with ALK-positive metastatic NSCLC	• 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: VENTANA ALK (D5F3) CDx Assay

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
Crizotinib (Xalkori)	• 2011: First line for patients with ALK- or ROS1-positive metastatic NSCLC	• 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine) • Oncomine Dx • 2017: VENTANA ALK (D5F3) CDx Assay
Crizotinib (Xalkori)	• 2016: Patients with ROS1-positive metastatic NSCLC	• 2017: Oncomine™ Dx Target Test (Thermo

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		Fisher Scientific)
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
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 o solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, o are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed	• No companiion diagnostic

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
	following treatment or have no satisfactory alternative therapy.	
Erlotinib (Tarceva)	• 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)
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

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		chain reaction (RGQ PCR) kit • 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2017: Oncomine Dx Target Test
Ipilimumab (Yervoy)	Treatment of adult patients with metastatic non-small cell lung cancer 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 nivolumab. (1.6) • Treatment of adult patients with metastatic or recurrent non-small cell	• PD-L1 IHC 28-8 PharmDx

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
	lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum doublet chemotherapy. (1.6)	
Larotrectinib (Vitrakvi)	• 2018: Adult and pediatric patients with solid tumors that o have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, o are metastatic or where surgical resection is likely to result in severe morbidity, and o have no satisfactory alternative treatments or that have progressed following treatment.	• FoundationOne CDx (solid tumors, NTRK1/2/3 fusions)
Lorlatinib (Lorbrena)	• 2018: Patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer whose disease has progressed on o crizotinib and at least one other ALK inhibitor for metastatic disease; or o alectinib as the first ALK inhibitor therapy for metastatic disease; or o ceritinib as the first ALK inhibitor therapy for metastatic disease.	• No companion diagnostic

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
Nivolumab (Opdivo) in combination with Ipilimumab (Yervoy)	• 2020: ○ adult patients with metastatic non-small cell lung cancer 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. ○ adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy. ○ patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.	• PD-L1 IHC 28-8 PharmDx
Osimertinib (Tagrisso)	• 2015: Second line for patients with metastatic NSCLC whose tumors have EGFR T790M variants as detected by FDA-approved test, who have not responded to EGFR-blocking therapy	• 2015: cobas® EGFR Mutation Test v2 (blood test)

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
	• 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	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx
Pembrolizumab (Keytruda)	• 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-approved therapy for these aberrations prior to receiving KEYTRUDA	• PD-L1 IHC 22C3 pharmDx
Pralsetinib (Gavreto)	• Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	• 2020: Oncomine Dx Target Test
Selpercatinib (Retevmo)	• Adult patients with metastatic RET fusion-positive NSCLC	• No companion diagnostic specified

Sources: U.S. Food and Drug Administration (2020); U.S. Food and Drug Administration (n.d.) ALK: anaplastic lymphoma kinase; *EGFR*: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; NSCLC: non-small-cell lung cancer; PCR: polymerase chain reaction.

Rationale/Source

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 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 testing for *EGFR* variants and *ALK* rearrangements, the evidence includes phase 3 studies comparing tyrosine kinase inhibitors (TKIs) (e.g., afatinib, erlotinib, gefitinib, osimertinib, et al) with chemotherapy. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive 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 a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive 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 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 a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for *KRAS* or *HER2* variants, 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 a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive NTRK gene fusion testing, the evidence includes nonrandomized trials of larotrectinib and entrectinib in patients with solid tumors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In 55 patients with consecutively and prospectively identified tropomyosin receptor kinase fusion-positive solid tumors who received larotrectinib, including 4 patients with lung tumors, the overall response rate was 80% (95% CI, 67 to 90). The median PFS had not been reached after a median follow-up duration of 9.9 months (range, 0.7 to 25.9). Responses were observed regardless of tumor type or age of the patient. In an integrated

analysis of 3 phase 1-2 trials in patients with NTRK solid tumors who received entrectinib, 10 of whom had NSCLC, response was 57% (95% CI 43.2% to 70.8%) with an acceptable safety profile. The evidence is sufficient to determine that the technology results in a meaningful 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 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 overall survival 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 a meaningful improvement in the net health outcome.

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive tumor mutational burden (TMB) testing, the evidence includes a RCT and retrospective observational studies. 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 ($\geq$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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

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 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 2014, the American Society of Clinical Oncology (ASCO) reviewed and endorsed the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (2013) guidelines, and highlighted 3 evolving areas: advances in *ALK* testing methodology, considerations for selecting appropriate populations for molecular testing, and the emergence of other targeted molecular alterations. The ASCO recommendations stated that testing for *EGFR* should be prioritized over other molecular markers in lung adenocarcinoma, and that, after *EGFR* testing, testing for *ALK* should be prioritized over other proposed molecular markers in lung adenocarcinomas, for which published evidence is insufficient to support testing guideline development at the present time.

In 2018, the ASCO reviewed and endorsed, with minor modifications, the guidelines from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (2018; see above). The ASCO differed from the guidelines in its recommendation of stand-alone *BRAF* testing in patients with advanced lung adenocarcinoma, irrespective of clinical characteristics (expert consensus opinion).

In 2017, the ASCO also updated its evidence-based recommendations on systemic therapy for patients with stage IV NSCLC. Table 3 summarizes the recommendations and associated quality and strength of evidence.

Table 3. Recommendations on Systemic Therapy for Stage IV NSCLC

Recommendation	QOE	SOR
First-line therapy		
Sensitizing *EGFR* variants: afatinib, erlotinib, or gefitinib	High	Strong
ALK rearrangements: crizotinib	Intermediate	Moderate
ROS1 rearrangement: crizotinib	Low	Weak

Second-line therapy		
Sensitizing *EGFR* variants and T790M resistance variant: osimertinib	High	Strong
ROS1 rearrangement who have not received prior crizotinib: crizotinib	Low	Moderate
BRAF variants who have received prior immune checkpoint therapy: dabrafenib alone or in combination with trametinib	Insufficient	Moderate

NSCLC: non-small-cell lung cancer; QOE: quality of evidence; SOR: strength of recommendation.

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

***EGFR* Testing**

The NCCN guidelines (v.8.2020) for the treatment of metastatic non-small-cell lung cancer (NSCLC) recommend the following on epidermal growth factor receptor (*EGFR*) testing:

- *EGFR* mutation testing is recommended (category 1) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified, because erlotinib or afatinib (category 1 for both) is recommended for patients who are positive for *EGFR* variants.

- When an *EGFR* variant is discovered prior to first-line chemotherapy, erlotinib (category 1), afatinib (category 1), dacomitinnib (category 1), gefitinib (category 1), or osimertinib (category 1, preferred) are recommended.
- When an *EGFR* variant is discovered during first-line chemotherapy, interrupt or continue chemotherapy, then follow with erlotinib, afatinib, or gefitinib.
- If progression occurs following first-line treatment, *EGFR* T790M testing is recommended (category 2A). If T790M-positive, osimertinib (category 1), local therapy, or continuing with erlotinib, afatinib, or gefitinib are recommended (depending on symptoms, the location of metastases, and a number of lesions).
- Tyrosine kinase inhibitors are not recommended as first-line therapy or subsequent therapy following progression for patients negative for *EGFR* variants or with unknown *EGFR* status.
- In patients with squamous cell carcinoma (SCC), *EGFR* variant testing should be considered in never-smokers; when histology is assessed using small biopsy specimens (rather than surgically resected samples); or when histology is mixed adenosquamous (category 2A).

***ALK* Testing**

The NCCN guidelines (v.8.2020) state the following on anaplastic lymphoma kinase (*ALK*) rearrangement testing:

- *ALK*-rearrangement testing is recommended (category 1) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.
- If *ALK*-positive status is discovered before first-line chemotherapy, alectinib (category 1; preferred), brigatinib (category 1), crizotinib (category 1), or ceritinib (category 1) is recommended.
- If *ALK* rearrangement is discovered during first-line chemotherapy, interrupt or complete planned chemotherapy and start alectinib (preferred), brigatinib, crizotinib or ceritinib.
- If there is progression on first-line therapy, continue alectinib, crizotinib, or ceritinib, switch to ceritinib, alectinib, lorlatinib, or brigatinib, or consider local therapies are recommended (depending on symptoms, the location of metastases, and the number of lesions).
- In patients with SCC, *ALK*-rearrangement testing should be considered in never-smokers; when histology is assessed using small biopsy specimens (rather than surgically resected samples); or when histology is mixed adenosquamous (category 2A).

- Flare phenomenon has been seen in a subset of patients who discontinue *ALK* inhibitors. If disease flare occurs, restart *ALK* inhibitor.

BRAF Testing

The NCCN guidelines (v.8.2020) state the following on *BRAF* testing:

- *BRAF* testing is recommended (category 2A) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.
- *BRAF* testing may be considered in patients with SCC.
- If *BRAF*V600E variant-positive status is discovered, combination dabrafenib and trametinib or other first-line cytotoxic therapy options are recommended.

ROS1 Testing

The NCCN guidelines (v.8.2020) state the following on *ROS1*-rearrangement testing:

- *ROS1*-rearrangement testing is recommended (category 2A) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.
- *ROS1*-rearrangement testing may be considered in patients with SCC.
- If *ROS1*-positive status is discovered, crizotinib (preferred), entrictinib (preferred) or ceritinib is recommended.

KRAS Testing

The NCCN guidelines (v.8.2020) state that "The presence of a KRAS mutation is prognostic of poor survival when compared to patients with tumors without KRAS mutation. Mutations in KRAS have been associated with reduced responsiveness to EGFR TKI [tyrosine kinase inhibitor] therapy. Owing to the low probability of overlapping targetable alterations, the presence of a mutation in KRAS may identify patients who will not benefit from further molecular testing." Targeted therapy for patients with the *KRAS* variants is currently unavailable.

RET Testing

The NCCN guidelines (v.8.2020) recommend testing for RET rearrangements (category 2A) in eligible patients with metastatic NSCLC.

MET Exon 14 Skipping Alterations

The NCCN guidelines (v.8.2020) recommend testing for *MET* Exon 14 skipping mutations (category 2A) in eligible patients with metastatic NSCLC.

NTRK Testing
NCCN guidelines (v.8.2020) recommend NTRK gene fusion testing in patients with metastatic NSCLC. The Panel recommends larotrectinib and entrectinib (category 2A) as either first-line or subsequent therapy options for patients with NTRK gene fusion-positive metastatic NSCLC based on data and the U.S. Food and Drug Administration approvals.

Immunotherapy and Tumor Mutational Burden
In the NCCN guideline (v.8.2020), nibolumab/ipilimumab is recommended for patients with metastatic NSCLC, regardless of PD-L1 levels or histology; negative test results for EGFR, ALK, ROS1, MET exon 14 skipping, RET, or BRAF variants, and no contraindications to immunotherapy. The guidelines state that first line therapy with nivolumab/ipilimumab is useful in certain circumstances (e.g., renal impairment) for patients with PD-L1 levels of 1% or more and is an "other recommended" first-line therapy option for patients with PD-L1 levels less than 1%.

TMB is considered to be an emerging biomarker that may be useful in selecting patients for nivolumab with or without ipilimumab; however, there is no consensus on how to measure TMB.

Other Biomarkers
The NCCN guidelines (v.8.2020) identify high-level *MET* amplification, *ERBB2* (*HER2*) mutations, and tumor mutational burden as emerging biomarkers to identify novel therapies for patients with metastatic NSCLC:

Plasma Cell-Free/Circulating Tumor DNA Testing:
The NCCN guidelines (v.8.2020) support limited use of liquid biopsy.

- Plasma cell-free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis.
- The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, including: in the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified.

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01306045	Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	469	Dec 2021
NCT03225664[a]	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer	102	Sep 2020
NCT02622581[a]	Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP)	7500	Dec 2025
NCT02117167[a]	Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: SAFIR02_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer	999	Feb 2021
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Jun 2022

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02576431[a]	A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-positive Tumors	203	May 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	300	Dec 2024
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	68	Jul 2021
NCT03469960	A Randomized Phase 3 Trial Comparing Continuation Nivolumab-Ipilimumab Doublet Immunotherapy Until Progression Versus Observation in Treatment-naive Patients With PDL1-positive Stage IVNon-Small Cell Lung Cancer (NSCLC) After Nivolumab-Ipilimumab Induction Treatment	1360	May 2023
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	647	Feb 2024
Unpublished			
NCT01248247[a]	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated	334	Jun 2020

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Patients With Advanced Non-Small Cell Lung Cancer		

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

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Policy History

Original Effective Date: 05/20/2015
Current Effective Date: 04/12/2021

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

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 04/12/2021

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.

Next Scheduled Review Date: 03/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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

Code Type	Code
CPT	0022U, 0037U, 81235, 81275, 81276, 81404, 81405, 81406, 81445, 81479, 88364, 88365 Codes added eff 1/1/2021: 81191, 81192, 81193, 81194
HCPCS	No codes
ICD-10 Diagnosis	C34.00-C34.02, C34.10-C34.12, C34.2, C34.30-C34.32, C34.80-C34.82, C34.90-C34.92

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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

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

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

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