BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.45 Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

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Related Policies:

2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
2.04.143- Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

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

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.

Treatment options for non-small-cell lung cancer (NSCLC) depend on disease stage and include various combinations of surgery, radiotherapy, systemic therapy, and best supportive care. Unfortunately, in up to 85% of cases, cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease.[1,] When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and 1-year survival of 30% to 45%.[2,3,] The identification of specific, targetable oncogenic “driver mutations” in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology. 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.[4,] 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%.[4,] Patients with *ROS1* fusions are typically never-smokers with adenocarcinoma.

KRAS Gene

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

KRAS variants can be detected by direct sequencing, PCR technologies, or NGS.

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

HER2 Gene

Human epidermal growth factor receptor 2 (*HER2*) is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. *HER2* is expressed in approximately 25% of NSCLC. *HER2* variants are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.[4,]

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.[4,]*RET* fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.[4,]

MET Gene

MET alteration is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs.[4,]

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.[5,]

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.[6,]

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 Non-Small-Cell Lung Cancer

Target	FDA-Approved Therapies
EGFR	• Gefitinib (Iressa), • Erlotinib (Tarceva), • Afatinib (Gilotrif) • Osimertinib (Tagrisso) • Dacomitinib (Vizimpro) • Amivantamab-vmjw (Rybrenant)
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	• Sotorasib (Lumakras)
HER2	• No FDA-approved targeted treatments
RET	• Selpercatinib (Retevmo) • Pralsetinib (Gavreto)
MET	• Capmatinib (Tabrecta) • Tepotinib (Tepmetko
NTRK	• Larotrectinib (Vitrakvi) • Entrectinib (Rozlytrek)
PD-L1	• Pembrolizumab (Keytruda) • Nivolumab (Opdivo) in combination with ipilimumab (Yervoy) • Atezolizumab (Tecentriq)

OBJECTIVE

The objective of this evidence review is to examine whether testing for *EGFR*, *BRAF*, *KRAS*, and *HER2* variants; *ALK*, *ROS1*, or *RET* rearrangements; *MET* alterations; NTRK gene fusions; or tumor mutational burden improves the net health outcome in individuals with advanced-stage non-small-cell lung cancer who are being considered for targeted therapy.

POLICY STATEMENT

EGFR Testing

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

Analysis of other *EGFR* variants within exons 22 to 24, or other applications related to NSCLC, is considered **investigational**.

At diagnosis, only analysis of somatic variants in exons 19 through 21 (eg, exon 19 deletions, L858R, T790M) within the *EGFR* gene, using the cobas EGFR Mutation Test v2, Guardant360 CDx test, OncoBEAM test, or InVisionFirst-Lung test with plasma specimens to detect circulating tumor DNA (ctDNA), may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], or osimertinib [Tagrisso]) in patients with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified.

At progression, analysis of the EGFR T790M resistance variant for targeted therapy with osimertinib using ctDNA using the cobas EGFR Mutation Test v2, Guardant360 CDx test, OncoBEAM test, or InVisionFirst-Lung test with plasma specimens to detect ctDNA , may be considered **medically necessary** in patients with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLD, and NSCLC not otherwise

specified when tissue biopsy to obtain new tissue is not feasible, e.g., in those who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, or cannot undergo biopsy. (see Policy Guidelines).

ALK Testing

Analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (*ALK*) gene in tissue may be considered **medically necessary** to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori], gefitinib [Zykadia], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of somatic rearrangement variants of the *ALK* gene is considered **investigational** in all other situations.

Analysis of somatic rearrangement variants of the ALK gene using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with NSCLC.

BRAF V600E Testing

Analysis of the somatic *BRAF* V600E variant in tissue may be considered **medically necessary** 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 (see Policy Guidelines section).

Analysis of the somatic *BRAF* V600E variant is considered **investigational** in all other situations.

Analysis of the somatic BRAF V600E variant using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar], trametinib [Mekinist]) in patients with NSCLC.

ROS1 Testing

Analysis of somatic rearrangement variants of the *ROS1* gene in tissue may be considered **medically necessary** 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 (see Policy Guidelines section).

Analysis of somatic rearrangement variants of the *ROS1* gene is considered **investigational** in all other situations.

Analysis of somatic rearrangement variants of the ROS1 gene using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with NSCLC.

KRAS Testing

Analysis of somatic variants of the *KRAS* gene in tissue may be considered **medically necessary** to predict treatment response to sotorasib (Lumakras) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of somatic variants of the KRAS gene using plasma specimens to detect ctDNA is considered **investigational** as a technique to predict treatment response to sotorasib (Lumakras).

All other uses of analysis of somatic variants of the *KRAS* gene are considered **investigational**.

HER2 Testing

Analysis of somatic alterations in the *HER2* gene in tissue for targeted therapy in patients with NSCLC is considered **investigational.**

Analysis of somatic alterations in the HER2 gene using plasma specimens to detect ctDNA for targeted therapy in patients with NSCLC is considered **investigational**.

NTRK Gene Fusion Testing

Analysis of somatic *NTRK* gene fusions in tissue may be considered **medically necessary** to predict treatment response to entrectinib (Rozlytrek) or larotrectinib (Vitrakvi) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of somatic *NTRK* gene fusions is considered **investigational** in all other situations.

RET Rearrangement Testing

Analysis of somatic alteration in the *RET* gene in tissue may be considered **medically necessary** to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) in patients with metastatic NSCLC.

Analysis of somatic alterations in the *RET* gene is considered **investigational** in all other situations.

Analysis of somatic alterations of the RET gene using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to RET inhibitor therapy (eg, selpercatinib [Retevmo], pralsetinib [Gavreto]) in patients with NSCLC.

MET Exon 14 Skipping Alteration

Analysis of somatic alteration in tissue that leads to *MET* exon 14 skipping may be considered **medically necessary** to predict treatment response to capmatinib (Tabrecta) in patients with metastatic NSCLC.

Analysis of somatic alterations of the *MET* gene is considered **investigational** in all other situations.

Analysis of somatic alteration that leads to *MET* exon 14 skipping using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to MET inhibitor therapy (capmatinib [Tabrecta]) in patients with NSCLC.

PD-L1 Testing

PD-L1 testing may be considered **medically necessary** to predict treatment response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Yervoy), or pembrolizumab (Keytruda) in patients with metastatic NSCLC.

PD-L1 testing is considered **investigational** in all other situations.

Tumor Mutational Burden Testing

Analysis of tumor mutational burden for targeted therapy in patients with NSCLC is considered **investigational.**

Plasma Testing When Tissue is Insufficient

Plasma tests for oncogenic driver variants deemed **medically necessary** on tissue biopsy may be considered **medically necessary** to predict treatment response to targeted therapy for patients meeting the following criteria:

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

POLICY GUIDELINES

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

Guidelines from the National Comprehensive Cancer Network on non-small-cell lung cancer provide recommendations for biomarker testing. Guidelines are updated frequently; refer to the source document for current recommendations. The most recent guidelines (v.6.2021) recommend that *EGFR* variants, *ALK* rearrangement, and PD-L1 testing (category 1) as well as *KRAS*, *ROS1*, *BRAF, NTRK1/2/3, MET* Exon 14 skipping alteration, and *RET* testing (category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling.

The 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 (see policy 2.04.143).

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

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 September 29, 2021. 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

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

FEP Pharmacy Policy	**Treatment**	**Indication**	**FDA-Approved Companion Diagnostic Tests**
5.21.39	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) • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
5.21.75	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 • 2020: FoundationOne Liquid CDx
	Amivantamab-vmjw (Rybrenant)	• 2021: adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy	• 2021: Guardant360 CDx
5.21.80	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. ◦ 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 ◦ 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 ◦ for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.	• 2020: VENTANA PD-L1
5.21.92	Brigatinib (Alunbrig)	• 2017: Second line for patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant of crizotinib • 2020: Treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test	• 2020: Vysis ALK Break Apart FISH Probe Kit • 2020: FoundationOneCDX
	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 (Foundation Medicine) • 2021: FoundationOne Liquid CDx
5.21.46	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
5.21.12	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
5.21.12	Crizotinib (Xalkori)	• 2016: Patients with ROS1-positive metastatic NSCLC	• 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)
5.21.117	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)

5.21.37	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)

5.21.134	Entrectinib (Rozlytrek)	• 2019:
		  ○ Adult patients with metastatic NSCLC whose tumors are ROS1-positive
		  ○ 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
			• No companion diagnostic

5.21.82	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) • 2020: FoundationOne Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
5.21.59	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) • 2017: Oncomine Dx Target Test • 2020: FoundationOne Liquid CDx • 2021: ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA)
5.21.13	Ipilimumab (Yervoy)	• Treatment of 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 nivolumab • Treatment of adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum doublet chemotherapy	• PD-L1 IHC 28-8 PharmDx

5.21.122	Larotrectinib (Vitrakvi)	• 2018: Adult and pediatric patients 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 no satisfactory alternative treatments or that have progressed following treatment
			• FoundationOne CDx (solid tumors, NTRK1/2/3 fusions)

5.21.120	Lorlatinib (Lorbrena)	• 2018: Patients with ALK-positive metastatic NSCLC whose disease has progressed on:
		  ○ crizotinib and at least 1 other ALK inhibitor for metastatic disease; or
		  ○ alectinib as the first ALK inhibitor therapy for metastatic disease; or
		  ○ ceritinib as the first ALK inhibitor therapy for metastatic disease
			• No companion diagnostic

5.21.53	Nivolumab (Opdivo) in combination with Ipilimumab (Yervoy)	• 2020:
		  ○ 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
		  ○ 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
			• PD-L1 IHC 28-8 PharmDx

		○ 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 therapy for these aberrations prior to receiving OPDIVO.	
5.21.69	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: cobas EGFR Mutation Test v2 (blood test) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx • 2020: FoundationOne Liquid CDx
5.21.50	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-approved therapy for these aberrations prior to receiving KEYTRUDA • 2020: For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥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	• 2018: PD-L1 IHC 22C3 pharmDx • 2020: FoundationOne CDx
5.21.162	Pralsetinib (Garret)	• Adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test	• 2020: Oncomine Dx Target Test
5.21.148	Selpercatinib (Retevmo)	• Adult patients with metastatic RET fusion-positive NSCLC	• No companion diagnostic specified
	Sotorasib (Lumakras)	• Adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least 1 prior systemic therapy	• 2021: Therascreen KRAS RGQ PCR kit • 2021: Guardant360 CDx
	Tepotinib (Tempietto)	• Adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.	• No companion diagnostic

Sources: U.S. Food and Drug Administration (2020)[7]; U.S. Food and Drug Administration (n.d.)[8].
ALK: anaplastic lymphoma kinase; *EGFR*: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; MET: mesenchymal-epithelial transition; NSCLC: non-small-cell lung cancer; NTRK neurotrophic receptor tyrosine kinase; PCR: polymerase chain reaction.

RATIONALE

Summary of Evidence

For individuals who have advanced-stage non-small-cell lung cancer (NSCLC) who are being considered for targeted therapy who receive testing for epidermal growth factor receptor (*EGFR)* variants and anaplastic lymphoma kinase (*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 an 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 (ORR) 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 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 progression-free survival (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 an 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* 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 are being considered for targeted therapy who receive neurotrophic receptor tyrosine kinase (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 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 are being considered for immunotherapy who receive tumor mutational burden (TMB) testing, the evidence includes a randomized controlled trial (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 (≥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 that the technology results in an improvement in the net health outcome.

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).[162,] 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. [163,] 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 ROS-1 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.

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.[164,] 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.[165,]*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.6.2021) 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.6.2021) 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.
- To minimize tissue use and potential wastage, the NCCN NSCLC Panel recommends that broad molecular profiling be done as part of biomarker testing using a validated test(s) that assesses potential genetic variants:
    - EGFR mutations
    - BRAF mutations
    - MET exon 14 skipping mutations
    - RET rearrangements
- Both FDA and laboratory-developed test platforms are available that address the need to evaluate these and other analytes
- Broad molecular profiling is also recommended to identify rare driver mutations for which effective therapy may be available, such as NTRK gene fusions, high-level MET amplification, ERBB2 mutations, and TMB.
- Clinicopathologic features should not be used to select patients for testing
- The guidelines do not endorse any specific commercially available biomarker assays.

Plasma Cell-Free/Circulating Tumor DNA Testing:

The NCCN guidelines on NSCLC (v.6.2021) include the following recommendations related to plasma cell-free/circulating tumor DNA testing.[166,]

- 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 should not be used in lieu of a histologic tissue diagnosis, but cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, notably:
    - If the patient is medically unfit for invasive tissue sampling; or
    - 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.

The guidelines also state:

- Standards for analytic performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare and Medicaid Services will cover diagnostic testing with next-generation sequencing for beneficiaries with recurrent, relapsed, refractory, metastatic cancer, or advanced stages III or IV cancer if the beneficiary has not been previously tested using the same next-generation sequencing test, unless a new primary cancer diagnosis is made by the treating physician, and if the patient has decided to seek further cancer treatment. The test must have a U.S. Food and Drug Administration approved or cleared indication as an in vitro diagnostic, with results and treatment options provided to the treating physician for patient management.[167,]

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2018	New policy	Analysis of somatic variants in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (EGFR), may be considered medically necessary 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. Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered investigational. Analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (ALK) gene may be considered medically necessary 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 (see Policy Guidelines section). Analysis of somatic rearrangement variants of the ALK gene is considered investigational in all other situations. Analysis of the BRAF V600E variant may be considered medically necessary 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. Analysis of somatic rearrangement variants of the ROS1 gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. Analysis of somatic variants of the KRAS gene is considered investigational as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the antiEGFR monoclonal antibody cetuximab in NSCLC. Analysis of genetic alterations in the genes HER2, RET, and MET for targeted therapy in patients with NSCLC is considered investigational.
December 2019	Replace policy	Policy updated with literature review through August 26, 2019; references added. FEP related pharmacy policies added. 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; other policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 9, 2020; references added. 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. 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.
March 2022	Replace policy	Policy updated with literature review through September 29, 2021; references added. Policy No. 2.04.143 (Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer [Liquid Biopsy]) was merged with this policy and Policy 2.04.143 archived. New indication and medically necessary policy statement added for KRAS testing to select patients for treatment with sotorasib. New indications and investigational policy statements added for ALK rearrangement and MET exon 14 skipping alteration testing using FoundationOne Liquid. Corrected terminology from "MET amplifications" to "MET alterations" in the evidence review.