FEP Medical Policy Manual

FEP 2.04.45 Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Effective Policy Date: April 1, 2021

Original Policy Date: December 2018

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)
*See targeted therapies under FDA Regulations section for a list of related FEP Pharmacy policies

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

Description

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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. 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.[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 amplification 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 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 treatments
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)

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* amplifications; 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*), 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**.

ALK Testing

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.

BRAF V600E Testing

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 (see Policy Guidelines section).

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

ROS1 Testing

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 (see Policy Guidelines section).

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

KRAS Testing

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 anti-EGFR monoclonal antibody cetuximab (Erbitux) in NSCLC.

HER2 Testing

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

NTRK Gene Fusion Testing

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

RET Rearrangement Testing

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

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

MET Exon 14 Skipping Alteration

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

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

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.**

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 (see policy 2.04.143).

BENEFIT APPLICATION

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.[7,8,]

Table 2. Targeted Treatments and Immunotherapy 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)
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: First line for patients with ALK-positive NSCLC who have not received prior systemic therapy for metastatic disease	• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: Ventana ALK (D5F3) CDx Assay

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: 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)

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
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 alternativetherapy.
			• No companiion 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)
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

5.21.13	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. • Treatment of 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 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 neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, ◦ are metastatic or where surgical resection is likely to result in severe morbidity, and ◦ have 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 anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer whose disease has progressed on ◦ crizotinib and at least one 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 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, incombination with ipilimumab and 2 cycles of platinum-doubletchemotherapy.
		  ◦ patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomictumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.
			• PD-L1 IHC 28-8 PharmDx

5.21.69	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 • 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	• 2015: cobas EGFR Mutation Test v2 (blood test) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx
5.21.50	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
5.21.162	Pralsetinib (Gavreto)	• 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

5.21.14	Vemurafenib (Zelboraf)	• Patients with unresectable or metastatic NSCLC with BRAF V600E variant	• 2017: Oncomine™ Dx Target Test • 2017: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • FoundationOne CDx™ (Foundation Medicine)
5.21.38	Trametinib (Mekinist)	• Patients with unresectable or metastatic NSCLC with BRAF V600E variant	• FoundationOne CDx™ (Foundation Medicine) • Oncomine™ Dx Target Test

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; NSCLC: non-small-cell lung cancer; PCR: polymerase chain reaction.

RATIONALE

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.[124.] 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.[125.] 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).[126,] 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.[127,] 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.[125,] 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.[126,] *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[5]:

- *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[5]:

- *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[5.]:

- *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[5.]:

- *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."[5.] 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.[5.]

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.[5.]

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.[5.]

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.

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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.

Date	Action	Description
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.