FEP Medical Policy Manual

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

Effective Policy Date: January 1, 2020

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 and associated tests

Molecular Analysis for Targeted Therapy 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 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.

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**EGFR Gene**

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

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

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

**ALK Gene**

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

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

**BRAF Gene**

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

**ROS1 Gene**

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

**KRAS Gene**

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

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

**HER2 Gene**

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

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

**MET Gene**

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

**NTRK Gene Fusions**

Neurotrophic tyrosine receptor kinase (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.

**Tumor Mutational Burden**

Tumor mutational burden is an emerging biomarker of outcomes with immunotherapy in multiple tumor types, including lung cancer.

**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.

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**BRAF V600E Testing**

Analysis of the BRAF V600E variant may be considered medically necessary to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar] and trametinib [Mekinist]), in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

**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).

**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 in NSCLC.

**NTRK Gene Fusion Testing**

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

**Other Genes**

Analysis of genetic alterations in the genes HER2, RET, and MET for targeted therapy in patients with NSCLC is considered investigational.

**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 2019 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.”

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## 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.

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

## FDA REGULATORY STATUS

### Targeted Therapies

Four orally administered EGFR-selective, small-molecule TKIs have been identified for treating NSCLC: gefitinib (Iressa; AstraZeneca), erlotinib (Tarceva; OSI Pharmaceuticals), afatinib (Gilotrif; Boehringer Ingelheim), and osimertinib (Tagrisso; AstraZeneca). Gefitinib, erlotinib, afatinib, and osimertinib currently are approved by the U.S. Food and Drug Administration (FDA) for NSCLC when EGFR status is confirmed through a companion diagnostic test.

Crizotinib is an oral small-molecule TKI that is FDA-approved for patients with locally advanced or metastatic NSCLC who are positive for the ALK or ROS1 gene rearrangements confirmed through a companion diagnostic test. Ceritinib is a potent ALK inhibitor that is approved for ALK-positive patients whose cancer has progressed while taking crizotinib or who could not tolerate crizotinib. Alectinib is a selective ALK inhibitor with high central nervous system penetration that is active against several secondary resistance variants to crizotinib. Brigatinib is also an ALK inhibitor that may be able to overcome a broad range of the resistance mechanisms in patients who have progressed on or are intolerant to crizotinib.

BRAF or MEK inhibition with TKIs (eg, vemurafenib/dabrafenib or trametinib) was originally approved by the FDA for treatment of unresectable or metastatic melanoma with BRAF V600 variants confirmed through a companion diagnostic test. The combination of dabrafenib and trametinib was approved for the treatment of metastatic NSCLC in 2017 for patients with confirmed BRAF V600 variants.

For the treatment of KRAS-mutated NSCLC, EGFR TKIs and anti-EGFR monoclonal antibodies have been investigated as treatment options. Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Cetuximab may be used in combination with chemotherapy in patients with advanced or recurrent NSCLC as first-line and maintenance therapy. Panitumumab is not used in NSCLC.

Larotrectinib was approved in 2018 for the treatment of patients with solid tumors harboring an NTRK gene fusion. There is currently no FDA approved companion diagnostic test for larotrectinib. The clinical review states, "The clinical review team and CDRH agreed that it is in the best interest of U.S. patients to approve larotrectinib before one or more companion diagnostic assays are ready for a PMA submission. Loxo Oncology has agreed to a post-marketing commitment to work with diagnostic developers to develop an analytically and clinically validated companion diagnostic test for the selection of patients with NTRK fusion-positive solid tumors for whom larotrectinib is safe and effective."

Nivolumab in combination with ipilimumab has been investigated as a treatment option for patients with NSCLC with tumor mutational burden \( \geq 10 \) mutations per megabase. There is no FDA companion diagnostic test for tumor mutational burden.

Targeted therapies currently under investigation and not FDA-approved for the remaining genetic alterations in NSCLC are trastuzumab and afatinib for HER2 variants, crizotinib for MET amplification, and cabozantinib for RET rearrangements.

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Regulatory Status

Table 1 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved diagnostic tests.8,9,10,11,12,13,14,15,16,17,18.

Table 1. FDA-Approved Targeted Treatment for NSCLC and Companion Diagnostic Tests

<table>
<thead>
<tr>
<th>FEP Pharmacy Policy</th>
<th>Treatment</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.21.39</td>
<td>Afatinib (Gilotrif)</td>
<td>• 2013: First line for patients with metastatic NSCLC whose tumors have <em>EGFR</em> exon 19 deletions or exon 21 (L858R) substitutions</td>
<td>• 2013: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen)</td>
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<td></td>
<td></td>
<td>• 2016: Second line for patients with metastatic squamous NSCLC</td>
<td>• 2017: FoundationOne CDx™ (Foundation Medicine)</td>
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<td>• 2018: First line for patients with nonresistant <em>EGFR</em> variants other than exon 19 or exon 21 NSCLC</td>
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<td>5.21.75</td>
<td>Alectinib (Alecensa)</td>
<td>• 2015: Second line for patients with <em>ALK</em>-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
<td>2017: FoundationOne CDx™ (Foundation Medicine)</td>
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<tr>
<td></td>
<td></td>
<td>• 2017: First line for patients with <em>ALK</em>-positive NSCLC who have not received prior systemic therapy for metastatic disease</td>
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<tr>
<td>5.21.92</td>
<td>Brigatinib (Alunbrig)</td>
<td>• 2017: Second line for patients with metastatic <em>ALK</em>-positive NSCLC who have progressed on or are intolerant of crizotinib</td>
<td>Test not specified in FDA approval</td>
</tr>
<tr>
<td>5.21.46</td>
<td>Ceritinib (Zykadia)</td>
<td>• 2014: Second line for patients with <em>ALK</em>-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
<td>• 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems)</td>
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<tr>
<td></td>
<td></td>
<td>• 2017: First line for patients with <em>ALK</em>-positive metastatic NSCLC</td>
<td>• 2017: FoundationOne CDx™ (Foundation Medicine)</td>
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<td>5.21.12</td>
<td>Crizotinib (Xalkori)</td>
<td>• 2011: First line for patients with ALK-positive metastatic NSCLC</td>
<td>• 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories)</td>
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<tr>
<td>5.21.12</td>
<td>Crizotinib (Xalkori)</td>
<td>• 2016: Patients with ROS1-positive metastatic NSCLC</td>
<td>• 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)</td>
</tr>
<tr>
<td>5.21.117</td>
<td>Dacomitinib (Vizimpro)</td>
<td>• 2018: First line for patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitutions</td>
<td>Test not specified in FDA approval</td>
</tr>
<tr>
<td>5.21.37</td>
<td>Dabrafenib (Tafinlar) plus trametinib (Mekinist)</td>
<td>• 2017: Used in combination for treatment of patients with metastatic NSCLC with BRAF V600E variant</td>
<td>• 2017: Oncomine™ Dx Target Test</td>
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<tr>
<td>5.21.82</td>
<td>Erlotinib (Tarceva)</td>
<td>• 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions</td>
<td>• 2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics)</td>
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<td></td>
<td></td>
<td>• 2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy</td>
<td>• 2016: cobas® EGFR Mutation Test v2 (tissue or blood test) (Roche Diagnostics)</td>
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<tr>
<td></td>
<td></td>
<td>• 2004: Second line for patients with locally advanced or metastatic NSCLC</td>
<td>• 2017: FoundationOne CDx™ (Foundation Medicine)</td>
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</table>
| 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: thesrascreen® 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) |
| 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 | • 2015: cobas® EGFR Mutation Test v2 (blood test)  
• 2017: FoundationOne CDx™ (Foundation Medicine) |
| 5.21.120            | Lorlatinib (Lorbrena) | Second line for patients with *ALK*-positive metastatic NSCLC (see FEP pharmacy policy for criteria) | Test not specified in FDA approval |
| 5.21.134            | Entrectinib (Rozlytrek) | Patients with *ROS1*-positive metastatic NSCLC | Test not specified in FDA approval |
| 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) |

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<td>5.21.38</td>
<td>Trametinib (Mekinist)</td>
<td>Patients with unresectable or metastatic NSCLC with <em>BRAF</em> V600E variant</td>
<td>FoundationOne CDx™ (Foundation Medicine)</td>
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<td>Oncomine™ Dx Target Test</td>
</tr>
<tr>
<td>5.21.50</td>
<td>Pembrolizumab (Keytruda)</td>
<td>First-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations in combination with pemetrexed and platinum chemotherapy</td>
<td>EGFR and ALK: test not specified in FDA approval of Keytruda</td>
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<td>Note: policy 2.04.45 does not address PD-L1 testing</td>
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<tr>
<td>5.21.53</td>
<td>Nivolumab (Opdivo)</td>
<td>Metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on a FDA-approved therapy for these aberrations prior to receiving Opdivo</td>
<td>Test not specified in FDA approval</td>
</tr>
<tr>
<td>5.21.80</td>
<td>Atezolizumab (Tecentriq)</td>
<td>First-line treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations in combination with bevacizumab, paclitaxel, and carboplatin</td>
<td>EGFR and ALK: test not specified in FDA approval of Tecentriq</td>
</tr>
<tr>
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<td></td>
<td>Metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on a FDA-approved therapy for these aberrations prior to receiving Tecentriq</td>
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ALK: anaplastic lymphoma kinase; *EGFR*: epidermal growth factor receptor; FDA: Food and Drug Administration; FISH: fluorescence in situ hybridization; NSCLC: non-small-cell lung cancer; PCR: polymerase chain reaction.

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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 receptor tyrosine kinase gene (ALK) rearrangements, the evidence includes phase 3 studies comparing tyrosine kinase inhibitors (TKIs) (e.g., afatinib, erlotinib, gefitinib, osimertinib) with chemotherapy. The 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 the 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. The 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. 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, RET rearrangements, or MET amplification, the evidence includes for KRAS post hoc analyses trials, observational studies, and meta-analyses; for the other variants, the evidence includes a phase 2 trial with preliminary data and retrospective analyses of very small case series and case reports. The relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. 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 testing for KRAS variants to select for EGFR TKIs beyond EGFR testing. In two 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. In two RCTs of advanced KRAS-variant positive disease, MEK inhibitors did not improve progression free survival (PFS) compared with docetaxel. Studies for HER2, RET, and MET 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 the effects of the technology on health outcomes.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive neurotrophic tyrosine receptor kinase (NTRK) gene fusion testing, the evidence includes prospective observational studies. The 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 (TRK) fusion-positive solid tumors, 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. 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 tumor mutational burden (TMB) testing, the evidence includes a randomized controlled trial (RCT) and retrospective observational studies. In a subgroup analysis of an ongoing RCT, 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. The evidence is insufficient to determine the effects of the technology on health outcomes.
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines

EGFR Testing

The NCCN guidelines (v.7.2019) for the treatment of metastatic non-small-cell lung cancer (NSCLC) recommend the following on epidermal growth factor receptor (EGFR) testing:

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

- When an EGFR variant is discovered prior to first-line chemotherapy, erlotinib (category 1), afatinib (category 1), dacomitinib (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.7.2019) state the following on anaplastic lymphoma kinase (ALK) rearrangement testing:

- ALK-rearrangement testing is recommended (category 1) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.

- If ALK-positive status is discovered before first-line chemotherapy, alectinib (category 1; preferred), brigatinib (category 1), crizotinib (category 1), or ceritinib (category 1) is recommended.

- If ALK rearrangement is discovered during first-line chemotherapy, interrupt or complete planned chemotherapy and start alectinib (preferred), brigatinib, crizotinib or ceritinib.

- If there is progression on first-line therapy, continue alectinib, crizotinib, or ceritinib, switch to ceritinib, alectinib, lorlatinib, or brigatinib, or consider local therapies are recommended (depending on symptoms, the location of metastases, and the number of lesions).

- In patients with SCC, ALK-rearrangement testing should be considered in never-smokers; when histology is assessed using small biopsy specimens (rather than surgically resected samples); or when histology is mixed adenosquamous (category 2A).

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

ROS1 Testing

The NCCN guidelines (v.7.2019) state the following on ROS1-rearrangement testing:

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**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), entrectinib (preferred) or ceritinib is recommended.

**BRAF Testing**

The NCCN guidelines (v.6.2018) 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.

**KRAS Gene**

The NCCN guidelines (v.7.2019) 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.

**NTRK Gene Fusions**

The NCCN guidelines (v.7.2019) state the following on **NTRK** gene fusion testing:\(^5\):

The Panel added a recommendation for NTRK gene fusion testing in patients with metastatic NSCLC based on clinical data and the approval of larotrectinib for patients with NTRK gene fusion-positive disease. 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 FDA approvals.

**Tumor Mutational Burden**

The NCCN guidelines (v.7.2019) state the following on tumor mutational burden testing:\(^5\):

Tumor mutational burden is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure tumor mutational burden.

**Other Genes**

The NCCN guidelines (v.6.2018) do not give specific recommendations for testing for genetic alterations in the genes **HER2**, **RET**, or **MET** in NSCLC. However, the guidelines state that the following emerging targeted agents are available for patients with one of these specific genetic alterations:\(^128\):

High-level **MET** amplification or **MET** exon 14 skipping mutation: crizotinib (category 2A)

**HER2** variants: ado-trastuzumab emtansine (category 2B)

**RET** rearrangements: cabozantinib or vandetanib (category 2A).

**College of American Pathologists et al**

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

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

American Society of Clinical Oncology

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

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

The ASCO (2017) also updated its evidence-based recommendations on systemic therapy for patients with stage IV NSCLC. Table 2 summarizes the recommendations and associated quality and strength of evidence.

Table 2. Recommendations on Systemic Therapy for Stage IV NSCLC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>QOE</th>
<th>SOR</th>
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</thead>
<tbody>
<tr>
<td>First-line therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitizing EGFR variants: afatinib, erlotinib, or gefitinib</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>ALK rearrangements: crizotinib</td>
<td>Intermediat e</td>
<td>Moderat e</td>
</tr>
<tr>
<td>ROS1 rearrangement: crizotinib</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>Second-line therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitizing EGFR variants and T790M resistance variant: osimertinib</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>ROS1 rearrangement who have not received prior crizotinib: crizotinib</td>
<td>Low</td>
<td>Moderat e</td>
</tr>
<tr>
<td>BRAF variants who have received prior immune checkpoint therapy: dabrafenib alone or in combination with trametinib</td>
<td>Insufficient</td>
<td>Moderat e</td>
</tr>
</tbody>
</table>

American College of Chest Physicians Guidelines

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

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.

REFERENCES


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This Policy was approved by the FEP® Pharmacy and Medical Policy Committee according to the history below:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2018</td>
<td>New policy</td>
<td>Analysis of somatic variants in exons 18 through 21 (e.g., 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 (e.g., 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 (e.g., 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 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 in NSCLC. Analysis of genetic alterations in the genes HER2, RET, and MET for targeted therapy in patients with NSCLC is considered investigational.</td>
</tr>
<tr>
<td>December 2019</td>
<td>Replace policy</td>
<td>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.</td>
</tr>
</tbody>
</table>

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