Medical Policy

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

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Policy Number: 563
BCBSA Reference Number: 2.04.45
NCD/LCD: N/A

Related Policies
- Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies, #790
- Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy), #797

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

EGFR TESTING
Except as noted below, analysis of 2 types of somatic variants within the epidermal growth factor receptor (EGFR) gene—small deletions in exon 19 and a point variant in exon 21 (L858R)—may be considered MEDICALLY NECESSARY to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva®; gefitinib [Iressa®], or afatinib [Gilotrif®]), in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

Analysis of the T790M variants in the gene for the EGFR is considered MEDICALLY NECESSARY as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR tyrosine kinase inhibitor therapy.

Analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a point mutation variant in exon 21 (L858R)—is considered INVESTIGATIONAL for patients with advanced non-small-cell lung cancer (NSCLC).

Analysis of other EGFR variants within exons 18 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®; Pfizer, New York City, NY], or ceritinib [Zykadia™], alectinib [Alecensa®]), or
brigatinib [Alunbrig™]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

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.

**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.

*The 2017 guidelines from the National Comprehensive Cancer Network recommend that EGFR mutation 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.

**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.

**OTHER GENES**

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

**Prior Authorization Information**

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
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<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>Medicare HMO BlueSM</td>
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</tr>
<tr>
<td>Medicare PPO BlueSM</td>
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</table>

**CPT Codes / HCPCS Codes / ICD Codes**

_Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member._

_Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable._
The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>81235</td>
<td>EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)</td>
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<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
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<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
</tbody>
</table>

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
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<tr>
<td>0022U</td>
<td>Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider</td>
</tr>
</tbody>
</table>

According to the policy statement above, the following CPT codes are considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81275</td>
<td>KRAS Kirsten rat sarcoma viral oncogene homolog (eg, carcinoma) gene analysis variants in exon 2 (eg, codons 12 and 13)</td>
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<tr>
<td>81276</td>
<td>KRAS (kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)</td>
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<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
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<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
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**Description**

**NON-SMALL-CELL LUNG CANCER**

Treatment options for non-small-cell lung cancer (NSCLC) depend on disease stage and include various combinations of surgery, radiotherapy, systemic therapy, and best supportive care. Unfortunately, in up to 85% of cases, the 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 a 1-year survival of 30% to 45%.² 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. *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
**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.\(^4\)

**TARGETED THERAPIES**

Three orally administered EGFR-selective, small-molecule TKIs have been identified for treating NSCLC: gefitinib (Iressa®; AstraZeneca, Cambridge, England), erlotinib (Tarceva®; OSI Pharmaceuticals, Melville NY) and afatinib (Gilotrif™; Boehringer Ingelheim, Ingelheim, Germany). Gefitinib, erlotinib, and afatinib currently are approved by the U.S. Food and Drug Administration (FDA) for NSCLC.

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. Ceritinib is a potent ALK inhibitor that is approved for ALK-positive patients who 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 FDA for treatment of unresectable or metastatic melanoma with BRAF\(^{V600}\) variants. The combination of dabrafenib and trametinib was approved for treatment of metastatic NSCLC in 2017.

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.

Proposed targeted therapies for the remaining genetic alterations in NSCLC addressed are trastuzumab and afatinib for HER2 variants, crizotinib for MET amplification and cabozantinib for RET rearrangements.

**Summary**

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 a specific variant.

For individuals who have advanced-stage 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) with chemotherapy. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and progression-free survival, with a reduction in toxicity and improvement in quality of life. 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 overall survival, disease-specific survival, test accuracy and validity, quality of life, 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 amplifications, 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. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, quality of life, 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 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. In two randomized controlled trials of advanced KRAS-variant positive disease, MEK inhibitors did not improve progression-free survival compared with docetaxel. Studies for HER2, RET, and MET variant testing have reported response rates and progression-free survival 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.

**Policy History**

<table>
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<tr>
<td>3/2017</td>
<td>BCBSA National medical policy review. Added testing for T790M mutation in patients who have progressed on or after EGFR-TKI therapy to medically necessary statement. Effective 3/1/2017.</td>
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<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
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<tr>
<td>7/2014</td>
<td>BCBSA National medical policy review. Medically necessary indications updated to include afatinib. Effective 7/1/2014.</td>
</tr>
<tr>
<td>2/2013</td>
<td>New references from BCBSA National medical policy.</td>
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</table>

**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
References


