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 GENE**
Except as noted below, analysis of 2 types of somatic mutation within the epidermal growth factor receptor (EGFR) gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—may be considered **MEDICALLY NECESSARY** to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) 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 for the T790M mutation 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-TKI therapy.

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

Analysis for other EGFR mutations within exons 18 to 24, or other applications related to NSCLC, is **INVESTIGATIONAL**.

**ALK GENE**
Analysis of somatic rearrangement mutations of the ALK gene may be considered **MEDICALLY NECESSARY** to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori®] or ceritinib
[Zykadia®] in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

Analysis of somatic rearrangement mutations of the ALK gene is considered INVESTIGATIONAL in all other clinical situations.

**KRAS GENE**

Analysis of somatic mutations of the KRAS gene is considered INVESTIGATIONAL as a technique to predict treatment nonresponse to anti-EGFR therapy with TKIs and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC.

**OTHER GENES**

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

These tests are intended for use in patients with advanced non-small-cell lung cancer (NSCLC). 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 gene are considered good candidates for treatment with erlotinib or afatinib. Patients found to be wild type are unlikely to respond to erlotinib or afatinib; other treatment options should be considered.

**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>
<th>Commercial Managed Care (HMO and POS)</th>
<th>No</th>
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<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
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<tr>
<td>Medicare HMO Blue℠</td>
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<tr>
<td>Medicare PPO Blue℠</td>
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**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:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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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>
</tr>
<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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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>
</tr>
<tr>
<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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<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>
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Description

Treatment options for non-small-cell lung cancer (NSCLC) depend on disease stage and include various combinations of surgery, radiotherapy, chemotherapy, and best supportive care. Unfortunately, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30% to 45%. More recently, 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 EGFR mutations and ALK rearrangements in clinical decision making for the treatment of NSCLC is routine. The use of testing for other mutations to direct targeted therapy is not well-established and continues to evolve.

EGFR GENE

Epidermal growth factor receptor (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.

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

The prevalence of EGFR mutations in NSCLC varies by population, with the highest prevalence in nonsmoking Asian women with adenocarcinoma, in whom EGFR mutations have been reported to be up to 30% to 50%. The reported prevalence in the white population is approximately 10%.
ALK GENE
Anaplastic lymphoma kinase (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.

KRAS GENE
The KRAS gene (which encodes RAS proteins) can harbor oncogenic mutations that result in a constitutively activated protein, independent of signaling from the EGFR, possibly rendering a tumor resistant to therapies that target the EGFR. Mutations 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.

ROS 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.

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 in 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.

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 approximately 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the mutations in NSCLC are non-V600E mutations. Most BRAF mutations occur more frequently in smokers.

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 mutations are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.

TARGETED THERAPIES
Three orally administered EGFR-selective, small-molecule TKIs have been identified for treating NSCLC: gefitinib (Iressa®; AstraZeneca), erlotinib (Tarceva®; OSI Pharmaceuticals), and afatinib (Gilotrif™; Boehringer Ingelheim). Gefitinib, erlotinib, and afatinib currently are approved by the U.S. Food and Drug Administration (FDA) for NSCLC. Although gefitinib was originally approved by FDA, a 2004 phase 3 trial suggested that the drug was not associated with a survival benefit. In May 2005, FDA revised gefitinib labeling further limiting its use to patients who had previously benefitted or were currently benefiting from the drug; no new patients were to be given gefitinib. However, in July 2015, FDA approved gefitinib as first-line treatment for metastatic NSCLC in patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

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 gene rearrangement. 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.
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 generally used in NSCLC. Proposed targeted therapies for the remaining genetic alterations in NSCLC addressed herein are trastuzumab and afatinib for HER2 mutations, crizotinib for MET amplification, and ROS1 rearrangement, vemurafenib and dabrafenib for BRAF mutations, 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 generally 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 mutation.

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for EGFR mutations and 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, symptoms, change in disease status, morbid events, quality of life, medication use, and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy in terms of tumor response rate and progression-free survival (PFS), 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 KRAS, HER2, or BRAF mutations, ROS or RET rearrangements, or MET amplifications, the evidence includes for KRAS post hoc analyses of phase 3 trials, phase 2 trials, a large prospective study, retrospective single-arm studies, and 2 meta-analyses; for the other mutations, the evidence includes a phase 2 trial with preliminary data on 3 patients, and retrospective analyses of very small case series and case reports. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and treatment-related morbidity. Studies have shown that KRAS mutations in patients with NSCLC confer a high level of resistance to TKIs; data are insufficient to assess any association between KRAS mutation status and survival in these patients, and the impact of testing for these mutations on clinical management is unknown. In 2 randomized trials with post hoc analyses of KRAS mutation status and use of anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab with chemotherapy, KRAS mutations did not identify patients who would benefit from anti-EGFR antibodies, because outcomes with cetuximab were similar regardless of KRAS mutation status. Studies for ROS, RET, MET, HER2, and BRAF mutation 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.

Policy History

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<th>Date</th>
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<td>3/2017</td>
<td>BCBSA National medical policy review. Added testing for T790M mutation</td>
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<tr>
<td></td>
<td>in patients who have progressed on or after EGFR-TKI therapy to</td>
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<tr>
<td>7/2016</td>
<td>BCBSA National medical policy review. Gefitinib added to list of FDA-</td>
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<tr>
<td></td>
<td>approved TKIs for NSCLC. 7/1/2016</td>
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<tr>
<td>6/2016</td>
<td>BCBSA National medical policy review. Correction only: 2015 FDA</td>
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<tr>
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<td>approval of gefitinib added. 6/1/2016</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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**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
- Medical Technology Assessment Guidelines

**References**


