Molecular Analysis for Targeted Therapy for Non-Small Cell Lung Cancer (NSCLC)

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Description of Procedure or Service

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, 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.

Epidermal Growth Factor Receptor (EGFR) Gene

The 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 TKIs). These targeted therapies dampen signal transduction through pathways downstream to the EGF receptor, 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 which leads to a fusion gene and expression of a protein with constitutive tyrosine kinase 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.
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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.

**Human Epidermal Growth Factor Receptor 2 (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 use in treating NSCLC: gefitinib (Iressa®, AstraZeneca), erlotinib (Tarceva®, OSI Pharmaceuticals), and afatinib (Gilotrif™, Boehringer Ingelheim). Gefitinib, erlotinib and afatinib are approved by the U.S. Food and Drug Administration (FDA) for NSCLC. Although gefitinib was originally FDA approved, a 2004 phase 3 trial suggested that gefitinib was not associated with a survival benefit. In May 2005, FDA revised gefitinib labeling further limiting its use to patients who had previously benefited 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.
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Crizotinib is an oral small-molecule TKI which 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 whose cancer 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 that are addressed in this policy 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.

Regulatory Status

Erlotinib received initial FDA approval in 2004 for second-line treatment of patients with advanced NSCLC. In 2013, erlotinib indications were expanded to include first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. In 2016, FDA approved cobas® EGFR Mutation Test v2, a blood-based genetic test to detect epidermal growth factor receptor (EGFR) mutations in patients with NSCLC. Afatinib was FDA-approved in July 2013 for first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or L858R mutations. A companion diagnostic test, the therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit, was coapproved for this indication.

Both cobas® and therascreen® are polymerase chain reaction (PCR) assays. FDA-approved product labels for both erlotinib and afatinib indicate that EGFR mutations must be “detected by an FDA-approved test” but do not specify which test must be used.

On August 26, 2011, based on 2 multicenter, single-arm trials, FDA granted accelerated approval to crizotinib (XALKORI Capsules, Pfizer) for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test. FDA approved the Vysis ALK Break Apart fluorescence in situ hybridization (FISH) Probe Kit (Abbott Molecular) concurrently with the crizotinib approval. This companion diagnostic test is designed to detect rearrangements of the ALK gene in NSCLC and captures all ALK gene rearrangements. On November 20, 2013, crizotinib received full approval. In July 2015, an additional test, the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems), was approved by FDA for the qualitative detection of ALK in patients with NSCLC. If the test indicates the presence of ALK, the patient may be considered for treatment with crizotinib.

In July 2015, FDA approved gefitinib as a first-line treatment for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 substitution mutations detected by an FDA-approved test. The FDA news release on gefitinib approval mentioned the companion diagnostic test therascreen® EGFR RGQ PCR.

In November 2015, osimertinib was granted accelerated approval by FDA for the treatment of patients with NSCLC with a specific EGFR mutation (T790M) who have not responded to previous EGFR-blocking therapy.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
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BCBSNC will provide coverage for molecular analysis for targeted therapy for non-small cell lung cancer when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Molecular Analysis for Targeted Therapy for Non-Small Cell Lung Cancer (NSCLC) is covered

Analysis of two types of somatic mutation within the 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 (for example, erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®] in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines).

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 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 (see Policy Guidelines section).

When Molecular Analysis for Targeted Therapy for Non-Small Cell Lung Cancer (NSCLC) is not covered

Analysis of two types of somatic mutation within the EGFR gene, small deletions in exon 19 and a point mutation in exon 21 (L858R), is considered investigational for patients with advanced NSCLC of squamous cell-type.

Analysis for other EGFR mutations within exons18-24, or other applications related to NSCLC, is considered investigational.

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

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

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

Policy Guidelines

These tests are intended for use in patients with advanced 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 gene are considered good candidates for treatment with erlotinib or
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afatinib. Patients found to be wild type are unlikely to respond to erlotinib or afatinib; other treatment options should be considered.

2016 guidelines from the National Comprehensive Cancer Network guidelines for the treatment of NSCLC recommend the following for EGFR:

- EGFR mutation testing is recommended (as a category 1) in patients with non-squamous NSCLC (i.e., 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 mutations.

When EGFR mutation is discovered prior to first-line chemotherapy: erlotinib (category 1), afatinib (category 1), or gefitinib (category 1) are recommended.

When EGFR mutation is discovered during first-line chemotherapy: interrupt or continue chemotherapy, then follow with erlotinib, afatinib, or gefitinib.

If progression occurs following first-line treatment: osimertinib, local therapy or continuing with erlotinib, afatinib, or gefitinib are recommended (depending on symptoms, location of metastases, and number of lesions).

Erlotinib should not be given as first-line therapy to patients negative for EGFR mutations or with unknown EGFR status.

2014 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology recommend:

- EGFR mutation and ALK rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (e.g., smoking history);
- In the setting of fully excised lung cancer specimens, EGFR and ALK testing is not recommended in lung cancers when an adenocarcinoma component is lacking (such as pure squamous cell lacking any immunohistochemical evidence of adenocarcinomatous differentiation); and
- In the setting of more limited lung cancer specimens (e.g., biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous cell histology. Clinical criteria (e.g., young age, lack of smoking history) may be useful to select a subset of these samples for testing.

Over half of patients with non-small-cell lung cancer (NSCLC) present with advanced and therefore incurable disease, and 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, which may direct targeted therapy depending on the presence of a specific mutation.

In NSCLC, the first successful example of targeted therapy involved mutations in the epidermal growth factor receptor (EGFR) gene, in which lung tumors harboring specific activating mutations in the EGFR kinase domain showed a high sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Phase 3 studies comparing EGFR-TKIs to chemotherapy in patients with EGFR-mutated NSCLC 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.

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,
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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 qualitatively 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 KRAS, ROS, RET, MET, HER2, and BRAF testing, 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 remainder of the mutations, 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, as 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0022U, G0452, 81235, 81275, 81403, 81405, 81406, 81479, 88363, S3713

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director – 3/2011


Medical Director – 2/2013
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Senior Medical Director – 3/2014


Senior Medical Director review 3/2015


United States Food and Drug Administration (FDA), Available at: http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm


Medical Director review 10/2016


Policy Implementation/Update Information

Policy titled, Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with Non Small Cell Lung Cancer (NSCLC)

4/12/11 New policy. Medical Director review 3/23/11. “Except as noted below, analysis of two types of somatic mutation within the 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 erlotinib in patients with advanced NSCLC.” “Analysis of two types of somatic mutation within the EGFR gene small deletions in exon 19 and a point mutation in exon 21 (L858R) is considered investigational for patients with advanced NSCLC of
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9/30/11 Specialty Matched Consultant Advisory Panel review 8/31/2011. No change to policy. (btw)

4/17/12 Reference added. (btw)

9/4/12 Specialty Matched Consultant Advisory Panel review 8/15/2012. No change to policy. Policy Guidelines section updated. (btw)

12/28/12 Added 81235 and G0452 to Billing/Coding section. Removed the following statement with deleted codes: “This laboratory test would likely be coded using a series of nonspecific genetic testing codes. Providers may use a series of the following CPT codes: 83891, 83896, 83898, 83901, 83907, 83912, 88313, 88323, and/or 88381.” (btw)

2/26/13 Updated policy guidelines. Reference added. Senior Medical Director review 2/8/2013. (btw)

9/11/13 Specialty Matched Consultant Advisory Panel review 8/21/2013. No change to policy. (btw)

11/26/13 Added “of nonsquamous cell type” to the When Covered statement. (btw)

4/15/14 Description section updated. Updated the When Covered section from “Analysis of two types of somatic mutation within the 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 erlotinib in patients with advanced NSCLC of nonsquamous cell type.” to “Analysis of two types of somatic mutation within the 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 erlotinib or afatinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).” Policy Guidelines updated to include information regarding afatinib. Senior Medical Director review 3/22/2014. Reference added. (btw)

9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No change to policy statement. (lpr)

Policy re-titled, Molecular Analysis for Targeted Therapy for Non Small Cell Lung Cancer

10/1/15 Policy reitled from “Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with Non-Small Cell Lung Cancer (NSCLC) to “Molecular Analysis for Targeted Therapy for Non-Small Cell Lung Cancer.” Extensive revisions and updates to entire policy. Added KRAS information from previous evidence based guideline. Under “When Not Covered” section added investigational indications: Analysis of somatic mutations of the KRAS gene is considered investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC; Testing for genetic alterations in the genes ROS, RET, MET, BRAF and HER2, for targeted therapy in patients with NSCLC is considered investigational and Analysis of somatic rearrangement mutations of the ALK gene is considered investigational in all other clinical situations. Under “ When Covered” section added medically necessary indication: Analysis of somatic rearrangement mutations of the ALK gene may be
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considered medically necessary to predict treatment response to crizotinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines). Reference added. Specialty Matched Consultant Advisory Panel review 8/26/2015. Notification given 10/1/15 for effective date 12/30/15. (lpr)

12/30/15 KRAS information can now be found in Corporate Medical Policy “KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer.” Removed references to KRAS in this medical policy. No change to policy statement or intent. (lpr)

2/29/16 Reference added. No change to policy statement. (lpr)

11/22/16 Specialty Matched Consultant Advisory Panel review 8/31/16. Extensive updates to Description, Regulatory status and Policy Guidelines sections. Under “When Covered” section: added covered indication for “testing T790M mutation in patients who have progressed on or after EGFR TKI therapy.” References added. Medical Director review 10/2016. (lpr)

10/13/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. CPT 0022U added to Billing/Coding section. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.