MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**MOLECULAR ANALYSIS for TARGETED THERAPY OF NON-SMALL CELL LUNG CANCER**
Policy Number	**2.02.35**
Category	**Laboratory Tests**
Effective Date	**12/20/07**
Revised Date	**12/18/08, 12/17/09, 02/17/11, 12/15/11, 12/20/12, 12/19/13, 02/19/15, 08/18/16, 11/16/17, 02/21/19**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

I. Based on our criteria and peer-reviewed literature, epidermal growth factor receptor (EGFR) gene mutational analysis is considered **medically appropriate** as a technique to predict treatment response to tyrosine kinase inhibitor (TKI) drugs.

II. Based on our criteria and peer-reviewed literature, epidermal growth factor receptor (EGFR) T790M gene mutational analysis is considered **medically appropriate** after tumor re-biopsy in patients with non-small cell lung cancer (NSCLC), (e.g., adenocarcinoma and large cell carcinoma) who have developed acquired resistance and disease progression on or after TKI-therapy.

III. Based on our criteria and peer-reviewed literature, anaplastic lymphoma kinase (ALK) gene mutational analysis is considered **medically appropriate** as a technique to predict treatment response to anaplastic lymphoma kinase inhibitor (ALK) drugs

IV. Based on our criteria and peer-reviewed literature, ROS-1, BRAFV600E, MET gene mutational analysis, high-level MET gene mutational analysis, RET rearrangements, and HER2 gene mutation testing is considered **medically appropriate** as a technique to predict treatment response to drug therapy.

V. Based on our criteria and peer-reviewed literature, programmed death receptor 1 (PD-1) or its ligand (PDL-1) expression analysis is considered **medically appropriate** as a technique to predict treatment response to drug therapy.

VI. Based on our criteria and peer-reviewed literature, analysis of somatic mutations of the KRAS gene is considered **medically appropriate** as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors.

VII. Based on our criteria and peer-reviewed literature, testing for genetic alterations for targeted therapy in any other genes in patients with NSCLC, are considered **investigational**.

Refer to Corporate Medical Policy #2.02.41 regarding KRAS Mutation Analysis in Metastatic Colorectal Cancer.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

POLICY GUIDELINES

The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Epidermal growth factor receptor (EGFR), a receptor tyrosine kinase (TK), is frequently over expressed and activated in non-small cell lung cancer (NSCLC). Two EGFR tyrosine kinase inhibitor (TKI) drugs, erlotinib and gefitinib, have been approved by the FDA as a second or third line therapy for advanced NSCLC. Erlotinib (Tarceva) received approval from the FDA in November 2004 as salvage therapy for advanced NSCLC, based on results of a phase III clinical trial that demonstrated a modest survival benefit, 6.7 months median survival compared to 4.7 months in the placebo group. Gefitinib (Iressa) was approved by the FDA in 2003 through the agency's accelerated approval process, based on the initially promising results of phase II trials. The labeled indication was limited to patients with NSCLC who had failed two or more prior chemotherapy regimens. However, in December 2004, results of phase III trials became available, suggesting that gefitinib was not associated with a survival benefit. In the press release, the FDA noted that in phase III trials patients treated with erlotinib did have a very modest, but statistically significant improvement in survival, implying that this was the preferred agent. In May 2005, the FDA revised the labeling of gefitinib to further limit its use to patients who were currently benefiting from the drug, or who had benefited in the past. However, based on a phase IV, open-label, single arm study to assess efficacy and safety and tolerability of first-line gefitinib in Caucasian patients with stage IIIA/B/IV EGFR mutation-positive NSCLC, NCCN guidelines (2016) has recommended erlotinib and gefitinib as first-line therapy in patients with advanced, recurrent, or metastatic non-squamous NSCLC who have known active sensitizing EGFR mutations.

Subgroup analyses of clinical trials of both of these drugs suggested that factors predicting response were female sex, never having smoked, Asian descent, or bronchioalveolar cancer (as opposed to other NSCLC histologies). Several studies subsequently reported that these characteristics are associated with somatic mutations in the EGFR gene TK ATP-binding domain, suggesting that mutational analysis potentially could be used to predict sensitivity to these targeted therapies. EGFR gene mutation analysis is now commercially available through Genzyme Genetics.

Per NCCN guidelines for non-small cell lung cancer (2017), anaplastic lymphoma kinase (ALK) occurs most commonly in a unique subgroup of NSCLC patients who share many of the clinical features of NSCLC patients likely to harbor EGFR mutations. However, for the most part, ALK translocations and EGFR mutations are mutually exclusive. The current standard method for detecting ALK NSCLCL is fluorescence in situ hybridization (FISH), although other methods are currently being evaluated, including polymerase chain reaction (PCR) and immunohistochemistry (IHC). The appropriate antibody and detection method for ALK protein expression can be used for rapid prescreening of ALK-re-arranged lung adenocarcinomas and selection of cases that will subsequently be confirmed by FISH testing. Crizotinib and ceritinib are oral ALK inhibitors that are approved by the FDA for patients with metastatic NSCLC who have the ALK gene rearrangement (i.e., ALK positive).

The Kirsten rat sarcoma viral oncogene homolog (KRAS) gene (which encodes RAS proteins) can harbor oncogenic mutations that result in a constitutively activated protein, independent of signaling from the EGF receptor, possibly rendering a tumor resistant to therapies that target the EGF receptor. 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. For the treatment of KRAS-mutated NSCLC, EGFR TKIs and anti-EGFR monoclonal antibodies have been investigated as possible 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.

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 (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.

Other, potentially targetable oncogenic mutations have been characterized in lung adenocarcinomas, including in the genes MET amplification is one of the critical events for acquired resistance in EGFR-mutated adenocarcinomas refractory to EGFR-TKIs. 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) 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.

PD-1 is a checkpoint protein on T-cells in the immune system and when bound to PD-L1, blocks the recognition of T-cells that the cancer cells are foreign invaders of the body. Some cancer cells will express PD-L1 in greater amounts, which will cause slowing of the immune attack by the T-cells or cause avoidance of the immune attack. Check-point protein inhibitors such as pembrolizumab, block binding of PD-1 with PD-L1 and potentially enhance immune response against cancer cells.

RATIONALE

A 2010 BlueCross BlueShield TEC Assessment found “while to date there have been no prospective, randomized clinical trials specifically looking at how EGFR therapy affects patient outcomes, there is strong evidence that response to erlotinib can be predicted based on EGFR mutation status. In evaluating patients with NSCLC, a serious disease with poor overall prognosis, use of EGFR mutation testing appears to be a valuable tool in assisting physicians to make optimal treatment choices and improve their ability to identify patients likely to benefit or not benefit from erlotinib treatment”. Based on the available evidence, use of tumor cell EGFR mutation analysis to predict response to erlotinib (Tarceva®) meets TEC criteria.

Evidence compiled from nonconcurrent-prospective studies and one-arm prospective enrichment studies is sufficient to conclude that a gain-of-function somatic mutation in the tumor-cell EGFR gene tyrosine kinase domain identifies a population subset (patients with mutation-positive tumors) with advanced NSCLC who exhibit improved objective radiologic response, progression-free survival, and overall survival when treated with erlotinib compared to the same treatment in patients with wild-type tumors or to standard chemotherapy in patients with EGFR-positive tumors.

Data are strongest for demonstrating differences in objective radiologic response, is less consistent, but strong, for progression-free survival, and is less consistent, but strong, for overall survival. There is growing consensus that both objective radiologic response and progression-free survival are reasonable endpoints to use for assessment of treatment response. There is a published meta-analysis suggesting objective radiologic response is strongly associated with median overall survival in patients with NSCLC treated with TKIs. There is also a growing discussion that overall survival may be a compromised endpoint for NSCLC due to the face NSCLC is a particularly aggressive disease with an increasing number of treatment choices, many specifically available for cross-over use in patients demonstrating resistance to earlier therapies. These cross-over therapies are likely to make evaluation of overall survival a challenging, and perhaps impossible, study endpoint.

Recent prospective and retrospective studies have shown convincing evidence that EGFR mutations can identify disease likely to respond to erlotinib. There is growing evidence that this information affects the net health outcome by identifying patients who are likely to exhibit good outcomes with this treatment with minimal toxicity. Recent reports suggest EGFR mutations also identify patients more likely to respond to erlotinib than to alternative drug choices.

There is also growing information demonstrating that EGFR status can help physicians identify wild-type tumors in patients who are unlikely to respond to erlotinib. In these patients alternative treatment choices should be considered. It is therefore prudent for physicians to evaluate patients with wild-type tumors carefully, considering the unique patient specific variables and preferences at hand, to discuss these with the patient, and to use this information to make patient informed, collaborative personalized treatment choices.

The 2017 National Comprehensive Cancer Network (NCCN) Guidelines recommend consideration of erlotinib, with or without chemotherapy in first-line therapy for advanced or metastatic NSCLC in patients with known activated EGFR mutation or gene amplification. EGFR mutations were predictive of a better response in patients receiving erlotinib (53% in patients with mutations versus 18% in those without mutations). KRAS mutations are associated with intrinsic

TKI resistance and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy. Overlapping EGFR and KRAS mutations occur in less than 1% of patients with lung cancer. Other TKIs such as, Afatinib and Osimertinib have been recommended by NCCN in patients with EGFR mutations and metastatic NSCLC. Afatinib has been recommended and FDA approved for first-line therapy in patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations. Afatinib may also be continued in patients who have progressed if patients do not have multiple systemic lesions. Afatinib is not recommended as subsequent therapy. Osimertinib is an oral TKI that inhibits both EGFR sensitizing mutations and T790M mutations. Osimertinib has been approved by the FDA for patients with metastatic EGFR T790M mutation-positive NSCLC, who have progressed on or after EGFR TKI therapy. The NCCN panel recommends osimertinib as subsequent therapy for patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on erlotinib, gefitinib, or afatinib therapy. Alectinib is recommended and has been approved by the FDA for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Patients who do not tolerate crizotinib may be switched to alectinib or certinib. ROS1 gene rearrangements occur more frequently in younger women with adenocarcinoma who are never smokers and in those who are negative for EGFR mutations, KRAS mutations, and ALK gene rearrangements (also known as triple negative). Crizotinib is very effective for patients with ROS1 rearrangement with response rates of about 70% including complete responses. The FDA has approved crizotinib for patients with ROS1 rearrangements.

Other genetic alterations such as, BRAF V600E and HER2 mutations, MET amplification, and RET rearrangements have been associated with emerging targeted therapies. Targeted agents are available for patients with NSCLC who have these other genetic alterations, although they are FDA approved for other indications. The NCCN Panel strongly endorses broader molecular profiling (also known as precision medicine) to identify rare driver mutations to ensure that patients receive the most appropriate treatment; patients may be eligible for clinical trials for some of these targeted agents.

As a primary immunosuppressive driver, PD-L1 overexpression may be an important facilitator for tumor growth and metastasis. PD-L1 has been detected in up to 50% of human cancers, making the PD-L1 pathway a focus of cancer research. NCCN recommends IHC testing for PD-L1 expression before first-line treatment in patients with metastatic NSCLC with negative or unknown test results for EGFRT mutations, ALK rearrangements, and ROS1 rearrangements. Although it is not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether patients are candidates for pembrolizumab. PD-L1 expression is continuously variable and dynamic; thus, a cutoff value for a positive result is artificial. Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses. The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.

The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) guideline on molecular testing for the selection of patients with lung cancer for epidermal growth factor receptor (EGFR) recommend EGFR molecular testing in patients with lung adenocarcinoma and mixed lung cancers with an adenocarcinoma component regardless of clinical characteristics (e.g., younger age, smoking status) for EGFR-targeted TKI therapy. EGFR mutation testing should be ordered at the time of diagnosis for patients who present with advanced-stage disease who are suitable for therapy, or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested, or testing tumors at time of diagnosis for stage I, II, or III disease so that molecular information is available to an oncologist at the time of recurrence for a subset of patients who subsequently experience recurrence, although this decision is deferred to local laboratories and oncology teams. KRAS mutation testing is not recommended as a sole determinant of EGFR-targeted therapy.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13
81479	Unlisted molecular pathology procedure
0022U (E/I)	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 (Oncomine™ Dx Target Test (100090) – Thermo Fisher Scientific)

HCPCS Codes

Code	Description
None	

ICD10 Codes

Code	Description
C34.10-C34.12	Malignant neoplasm of upper lobe, bronchus or lung (code range)
C34.30-C34.32	Malignant neoplasm of lower lobe, bronchus or lung (code range)
C34.80-C34.82	Malignant neoplasm of overlapping sites of bronchus and lung (code range)
C34.90-C34.92	Malignant neoplasm of unspecified part of bronchus or lung (code range)

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*Key Article

KEY WORDS

EGFR, Epidermal Growth Factor Receptor Mutation Analysis, afatinib, erlotinib, gefitinib, NSCLC.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Genomic Sequence Analysis Panels in the Treatment of Non-Small Cell Lung Cancer. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36376&ContrId=298&ver=3&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active%7cFuture&bc=AggAAAIAAAAAAA%3d%3d&.

There is a Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&bc=AAAAAAAAACAA&&utm_campaign=FoundationOne%20CDx&utm_source=hs_email&utm_medium=email&utm_content=61525882&_hsenc=p2ANqtz-_RlYQJUaVsqZ4Mg0L3KyI-D3c8sEtU-RkxTdCGIMf5qy6Qq-SAqTqlVvcS_hLXWFSG6cDEeCAAQLqbistIEakGsrAl5A&_hsmi=61525882