MEDICAL POLICY

POLICY TITLE	MOLECULAR ANALYSIS FOR TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER
POLICY NUMBER	MP- 2.241

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I. POLICY

EGFR Testing

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**.

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 (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. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

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 non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

NTRK 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

Testing for genetic alterations in the genes *HER2*, *RET*, and *MET* for targeted therapy in patients with NSCLC is considered **investigational.** There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

Tumor Mutational Burden

Tumor mutational burden testing is a biomarker of outcomes with immunotherapy in multiple tumor types, including lung cancer. This procedure is considered **investigational.** There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

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."

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual 2.04.45 Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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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. 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%. 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. 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

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.

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 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 confirmed through a companion diagnostic test. The combination of dabrafenib and trametinib was approved for 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.

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.

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 postmarketing 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 iplimumab has been investigated as a treatment option for patients with NSCLC with tumor mutational burden>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 HER2variants, crizotinib for MET amplification, and cabozantinib for RET rearrangements.

REGULATORY STATUS

Table 1 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved diagnostic tests.

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

Treatment	Indication	FDA Approval of Companion Diagnostic Test
Afatinib (Gilotrif)	• 2013: First line for patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitutions • 2016: Second line for patients with metastatic squamous NSCLC • 2018: First line for patients with nonresistant *EGFR* variants other than exon 19 or exon 21 NSCLC	• 2013: therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen) • 2017: FoundationOne CDx™ (Foundation Medicine)
Alectinib (Alecensa)	• 2015: Second line for patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib	2017: FoundationOne CDx™ (Foundation Medicine)

	• 2017: First line for patients with *ALK*-positive NSCLC who have not received prior systemic therapy for metastatic disease	
Brigatinib (Alunbrig)	• 2017: Second line for patients with metastatic *ALK*-positive NSCLC who have progressed on or are intolerant of crizotinib	Test not specified in FDA approval
Ceritinib (Zykadia)	• 2014: Second line for patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib • 2017: First line for patients with *ALK*-positive metastatic NSCLC	• 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine)
Crizotinib (Xalkori)	• 2011: First line for patients with *ALK*-positive metastatic NSCLC	• 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) • 2017: FoundationOne CDx™ (Foundation Medicine)
Crizotinib (Xalkori)	• 2016: Patients with *ROS1*-positive metastatic NSCLC	• 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)
Dacomitinib (Vizimpro)	• 2018: First line for patients with metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 (L858R) substitutions	Test not specified in FDA approval
Dabrafenib (Tafinlar) plus trametinib (Mekinist)	• 2017: Used in combination for treatment of patients with metastatic NSCLC with *BRAF* V600E variant	• 2017: Oncomine™ Dx Target Test • 2017: FoundationOne CDx™ (Foundation Medicine)
Erlotinib (Tarceva)	• 2013: First line for patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitutions • 2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy	• 2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2016: cobas® EGFR Mutation Test v2 (tissue

	• 2004: Second line for patients with locally advanced or metastatic NSCLC	or blood test) (Roche Diagnostics) • 2017: FoundationOne CDx™ (Foundation Medicine)
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: therascreen® 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)
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)
Larotrectinib (Vitrakvi)	• 2018: Adult and pediatric patients with solid tumors that: o have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, o are metastatic or where surgical resection is likely to result in severe morbidity, and o have no satisfactory alternative treatments or that have progressed following treatment.	Test not specified in FDA approval

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.

IV. RATIONALE

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Summary of Evidence

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for EGFR variants and ALK rearrangements, the evidence includes phase 3 studies comparing TKIs (eg, afatinib, erlotinib, gefitinib, osimertinib) with chemotherapy. The relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and PFS, with a reduction in toxicity and improvement in theQOL. 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 KRASpost 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 haveshown that KRASvariants in patients with NSCLC confer a high level of resistance to TKIs; data are insufficient to assess any additional benefit to testing for KRASvariants 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 twoRCTs of advanced KRAS-variant positive disease, MEK inhibitors did not improve PFS compared with docetaxel. Studies for HER2,RET, and METvariant 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 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 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 TMB testing, the evidence includes an 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.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered for KRAS testing for NSCLC when used to predict treatment non-response to anti-EGFR therapy:

CPT Codes®								
81275	81276	88363						

Investigational; therefore, not covered when used to test for genetic alterations in the genes RET, MET, HER2, and TMB for targeted therapy in patients with NSCLC:

CPT Codes®								
81404	81405	81479	0022U	0037U				

Covered when medically necessary:

CPT Codes®								
81191	81192	81193	81194	81210	81235	81401	88342	88365

ICD-10-CM Diagnosis Codes	Description
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
D38.1	Neoplasm of uncertain behavior of trachea, bronchus and lung

IX. REFERENCES

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1. *Fathi AT, Brahmer JR. Chemotherapy for advanced stage non-small cell lung cancer. Semin Thorac Cardiovasc Surg. Fall 2008;20(3):210-216. PMID 19038730.*

2. *Martoni A, Marino A, Sperandi F, et al. Multicentre randomised phase III study comparing the same dose and schedule of cisplatin plus the same schedule of vinorelbine or gemcitabine in advanced non-small cell lung cancer. Eur J Cancer. Jan 2005;41(1):81-92. PMID 15617993.*
3. *Rudd RM, Gower NH, Spiro SG, et al. Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. J Clin Oncol. Jan 1 2005;23(1):142-153. PMID 15625369.*
4. *Thunnissen E, van der Oord K, den Bakker M. Prognostic and predictive biomarkers in lung cancer. A review. Virchows Arch. Mar 2014;464(3):347-358. PMID 24420742.*
5. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 7.2019. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 10, 2020.*
6. *Hellmann MD, Ciuleanu TE, Pluzanski A et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N. Engl. J. Med., 2018 Apr 17;378(22). PMID 29658845.*
7. *Food and Drug Administration (FDA). NDA Multidisciplinary Review and Evaluation NDA 210861 and NDA 211710 VITRAKVI (larotrectinib), 2018. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210861Orig1s000_211710Orig1s000MultidisciplineR.pdf. Accessed September 10, 2020.*
8. *OSI Pharmaceuticals. Tarceva (erlotinib) tablets for oral use prescribing information. 2019; http://www.tarceva.com. Accessed September 10, 2020.*
9. *Boehringer Ingelheim Pharmaceuticals, Inc. GilotrifTM (afatinib) tablets for oral use prescribing information. 2018; http://www.gilotrif.com/. Accessed September 10, 2020.*
10. *Food and Drug Administration (FDA). FDA approves first blood test to detect gene mutation associated with non- small cell lung cancer. 2016; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm504488.htm. Accessed September 10, 2020.*
11. *Ventana. VENTANA ALK (D5F3) CDx Assay - P140025. 2015; https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140025c.pdf. Accessed September 10, 2020.*
12. *Food and Drug Administration (FDA). FDA approves osimertinib for first-line treatment of metastatic NSCLC with most common EFGR mutations. 2018; https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm605113.htm. Accessed October 4, 2019.*
13. *Food and Drug Administration (FDA). FDA approves new pill to treat certain patients with non-small cell lung cancer. 2015; http://www.ahdbonline.com/web-exclusives/2019-fda-approves-new-pill-to-treat-certain-patients-with-non-small-cell-lung-cancer. Accessed September 10, 2020.*

14. *Food and Drug Administration (FDA). Highlights of Prescribing Information: Mekinist. 2014; https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204114s001lbl.pdf. Accessed September 10, 2020.*
15. *Food and Drug Administration (FDA). Highlights of Prescribing Information: Tafinlar. 2014; https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202806s002lbl.pdf. Accessed September 10, 2020.*
16. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): OncomineTM Dx Target Test. 2017; https://www.accessdata.fda.gov/cdrh_docs/pdf16/p160045b.pdf. Accessed September 10, 2020.*
17. *Food and Drug Administration (FDA). FDA approves crizotinib capsules. 2016; http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm490391.htm. Accessed September 10, 2020.*
18. *Fang W, Zhang J, Liang W, et al. Efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors for Chinese patients with squamous cell carcinoma of lung harboring EGFR mutation. J Thorac Dis. Oct 2013;5(5):585-592. PMID 24255770.*
19. *Mitsudomi T, Kosaka T, Yatabe Y. Biological and clinical implications of EGFR mutations in lung cancer. Int J Clin Oncol. Jun 2006;11(3):190-198. PMID 16850125.*
20. *Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol. Sep 1 2005;23(25):5900-5909. PMID 16043828.*
21. *Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. Sep 3 2009;361(10):958-967. PMID 19692684.*
22. *Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR- TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. Apr 15 2013;19(8):2240-2247. PMID 23470965.*
23. *Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. Mar 23 2011;3(75):75ra26. PMID 21430269.*
24. *Mujoomdar M, Moulton K, Spry C. Epidermal Growth Factor Receptor Mutation Analysis in Advanced Non-Small Cell Lung Cancer: A Review of the Clinical Effectiveness and Guidelines. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2010 August.*
25. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): therascreen EGFR RGQ PCR Kit. 2013; https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120022b.pdf. Accessed September 10, 2020.*
26. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): cobas EGFR Mutation Test. 2013; https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120019b.pdf. Accessed September 10, 2020.*

27. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): cobas EGFR Mutation Test v2. 2015; https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120019S007b.pdf. Accessed September 10, 2020.*
28. *Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol. Nov 2013;31(11):1023-1031. PMID 24142049.*
29. *Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst. May 1 2013;105(9):595-605. PMID 23594426.*
30. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Epidermal growth factor receptor (EGFR) mutations and tyrosine kinase inhibitor therapy in advanced non-small-cell lung cancer. TEC Assessments. 2007;Volume 22:Tab 6.*
31. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Epidermal growth factor receptor (EGFR) mutations and tyrosine kinase inhibitor therapy in advanced non-small-cell lung cancer. TEC Assessments. 2010;Volume 25:Tab 6.*
32. *Guetz GD, Landre T, Uzzan B, et al. Is there a survival benefit of first-line epidermal growth factor receptor tyrosine-kinase inhibitor monotherapy versus chemotherapy in patients with advanced non-small-cell lung cancer?: a meta-analysis. Target Oncol. Feb 2016;11(1):41-47. PMID 26092590.*
33. *Kato T, De Marinis F, Spicer J, et al. The impact of first-line tyrosine kinase inhibitors (TKIs) on overall survival in patients with advanced non-small cell lung cancer (NSCLC) and activating epidermal growth factor receptor (EGFR) mutations: meta-analysis of major randomized trials by mutation type. Value Health. Nov 2015;18(7):A436. PMID 26532455.*
34. *Kuan FC, Kuo LT, Chen MC, et al. Overall survival benefits of first-line EGFR tyrosine kinase inhibitors in EGFR- mutated non-small-cell lung cancers: a systematic review and meta-analysis. Br J Cancer. Nov 17 2015;113(10):1519-1528. PMID 26461059.*
35. *Greenhalgh J, Dwan K, Boland A, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev. May 25 2016(5):CD010383. PMID 27223332.*
36. *Normando SR, Cruz FM, Del Giglio A. Cumulative meta-analysis of epidermal growth factor receptor-tyrosine kinase inhibitors as first-line therapy in metastatic non-small-cell lung cancer. Anticancer Drugs. Oct 2015;26(9):995-1003. PMID 26237501.*
37. *An N, Zhang Y, Niu H, et al. EGFR-TKIs versus taxanes agents in therapy for nonsmall-cell lung cancer patients: A PRISMA-compliant systematic review with meta-analysis and meta-regression. Medicine (Baltimore). Dec 2016;95(50):e5601. PMID 27977598.*
38. *Petrelli F, Borgonovo K, Cabiddu M, et al. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR- mutated non-small cell-lung cancer: a meta-analysis of 13 randomized trials. Clin Lung Cancer. Nov 5 2012;13(2):107-114. PMID 22056888.*
39. *Wu YL, Zhou C, Liam CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase*

III, randomized, open-label, ENSURE study. Ann Oncol. Sep 2015;26(9):1883-1889. PMID 26105600.

40. *Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. Mar 2012;13(3):239-246. PMID 22285168.*
41. *Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. Aug 2011;12(8):735-742. PMID 21783417.*
42. *Zhou C, Wu YL, Chen G, et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol. Sep 2015;26(9):1877-1883. PMID 26141208.*
43. *Ahn MJ, Park BB, Ahn JS, et al. Are there any ethnic differences in molecular predictors of erlotinib efficacy in advanced non-small cell lung cancer? Clin Cancer Res. Jun 15 2008;14(12):3860-3866. PMID 18559606.*
44. *Amann JM, Lee JW, Roder H, et al. Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 3503. J Thorac Oncol. Feb 2010;5(2):169-178. PMID 20035238.*
45. *Felip E, Rojo F, Reck M, et al. A phase II pharmacodynamic study of erlotinib in patients with advanced non- small cell lung cancer previously treated with platinum-based chemotherapy. Clin Cancer Res. Jun 15 2008;14(12):3867-3874. PMID 18559607.*
46. *Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol. Mar 20 2008;26(9):1472-1478. PMID 18349398.*
47. *Schneider CP, Heigener D, Schott-von-Romer K, et al. Epidermal growth factor receptor-related tumor markers and clinical outcomes with erlotinib in non-small cell lung cancer: an analysis of patients from German centers in the TRUST study. J Thorac Oncol. Dec 2008;3(12):1446-1453. PMID 19057271.*
48. *Giaccone G, Gallegos Ruiz M, Le Chevalier T, et al. Erlotinib for frontline treatment of advanced non-small cell lung cancer: a phase II study. Clin Cancer Res. Oct 15 2006;12(20 Pt 1):6049-6055. PMID 17062680.*
49. *Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. J Clin Oncol. Mar 1 2007;25(7):760-766. PMID 17228019.*
50. *Zhu CQ, da Cunha Santos G, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol. Sep 10 2008;26(26):4268- 4275. PMID 18626007.*
51. *Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer*

patients: results of an online tumor registry of clinical trials. Clin Cancer Res. Aug 15 2009;15(16):5267-5273. PMID 19671843.

52. *Sun JM, Won YW, Kim ST, et al. The different efficacy of gefitinib or erlotinib according to epidermal growth factor receptor exon 19 and exon 21 mutations in Korean non-small cell lung cancer patients. J Cancer Res Clin Oncol. Jun 16 2011;137(4):687-694. PMID 20552223.*
53. *Yoshioka H, Hotta K, Kiura K, et al. A phase II trial of erlotinib monotherapy in pretreated patients with advanced non-small cell lung cancer who do not possess active EGFR mutations: Okayama Lung Cancer Study Group trial 0705. J Thorac Oncol. Jan 2010;5(1):99-104. PMID 19898258.*
54. *Sim EH, Yang IA, Wood-Baker R, et al. Gefitinib for advanced non-small cell lung cancer. Cochrane Database Syst Rev. Jan 16 2018;1:CD006847. PMID 29336009.*
55. *Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. Sep 03 2009;361(10):947-957. PMID 19692680.*
56. *Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. Feb 2010;11(2):121-128. PMID 20022809.*
57. *Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. Jun 24 2010;362(25):2380-2388. PMID 20573926.*
58. *Han B, Jin B, Chu T, et al. Combination of chemotherapy and gefitinib as first-line treatment for patients with advanced lung adenocarcinoma and sensitive EGFR mutations: A randomized controlled trial. Int J Cancer. Sep 15 2017;141(6):1249-1256. PMID 28560853.*
59. *Wu YL, Saijo N, Thongprasert S, et al. Efficacy according to blind independent central review: Post-hoc analyses from the phase III, randomized, multicenter, IPASS study of first-line gefitinib versus carboplatin/paclitaxel in Asian patients with EGFR mutation-positive advanced NSCLC. Lung Cancer. Feb 2017;104:119-125. PMID 28212993.*
60. *Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol. Jan 2013;24(1):54-59. PMID 22967997.*
61. *Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. Sep 20 2013;31(27):3327-3334. PMID 23816960.*
62. *Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol. Sep 20 2013;31(27):3342-3350. PMID 23816967.*
63. *Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR*

mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. Feb 2014;15(2):213-222. PMID 24439929.

64. *Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. Lancet Oncol. May 2012;13(5):539-548. PMID 22452895.*
65. *Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small- cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol. May 2012;13(5):528-538. PMID 22452896.*
66. *Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small- cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol. Sep 20 2013;31(27):3335-3341. PMID 23816963.*
67. *Food and Drug Administration (FDA). TAGRISSOTM (osimertinib) Highlights of Prescribing Information. 2015; http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208065s000lbl.pdf. Accessed September 10, 2020.*
68. *Yang J, Ramalingam SS, Janne PA, et al. LBA2_PR: Osimertinib (AZD9291) in pre-treated pts with T790M- positive advanced NSCLC: updated Phase 1 (P1) and pooled Phase 2 (P2) results. J Thorac Oncol. Apr 2016;11(4 Suppl):S152-153. PMID 27198353.*
69. *Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small- cell lung cancer. J Clin Oncol. Aug 28 2018:JCO2018783118. PMID 30153097.*
70. *Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. Feb 16 2017;376(7):629-640. PMID 27959700.*
71. *Lin JZ, Ma SK, Wu SX, et al. A network meta-analysis of nonsmall-cell lung cancer patients with an activating EGFR mutation: Should osimertinib be the first-line treatment? Medicine (Baltimore). Jul 2018;97(30):e11569. PMID 30045282.*
72. *Zhang W, Wei Y, Yu D, et al. Gefitinib provides similar effectiveness and improved safety than erlotinib for advanced non-small cell lung cancer: A meta-analysis. Medicine (Baltimore). Apr 2018;97(16):e0460. PMID 29668619.*
73. *De Mello RA, Escriu C, Castelo-Branco P, et al. Comparative outcome assessment of epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of advanced non-small-cell lung cancer: a network meta- analysis. Oncotarget. Feb 20 2018;9(14):11805-11815. PMID 29545937.*
74. *Crequit P, Chaimani A, Yavchitz A, et al. Comparative efficacy and safety of second-line treatments for advanced non-small cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analysis. BMC Med. Oct 30 2017;15(1):193. PMID 29082855.*
75. *Wu D, Duan C, Wu F, et al. Which treatment is preferred for advanced non-small-cell lung cancer with wild-type epidermal growth factor receptor in second-line therapy? A meta-*

analysis comparing immune checkpoint inhibitor, tyrosine kinase inhibitor and chemotherapy. Oncotarget. Sep 12 2017;8(39):66491-66503. PMID 29029530.

76. *Yang Z, Hackshaw A, Feng Q, et al. Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: A meta-analysis. Int J Cancer. Jun 15 2017;140(12):2805-2819. PMID 28295308.*
77. *Zhang Y, Zhang Z, Huang X, et al. Therapeutic efficacy comparison of 5 major EGFR-TKIs in advanced EGFR- positive non-small-cell lung cancer: a network meta-analysis based on head-to-head trials. Clin Lung Cancer. Sep 2017;18(5):e333-e340. PMID 28462807.*
78. *Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. Jan 11 2018;378(2):113-125. PMID 29151359.*
79. *Urata Y, Katakami N, Morita S, et al. Randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L. J Clin Oncol. Sep 20 2016;34(27):3248- 3257. PMID 27022112.*
80. *Yang JJ, Zhou Q, Yan HH, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non- small cell lung cancer with EGFR mutations. Br J Cancer. Feb 28 2017;116(5):568-574. PMID 28103612.*
81. *Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation- positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. May 2016;17(5):577-589. PMID 27083334.*
82. *Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. Clin Cancer Res. Apr 15 2011;17(8):2081-2086. PMID 21288922.*
83. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Vysis ALK Break Apart FISH Probe Kit. 2011; https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110012b.pdf. Accessed September 10, 2020.*
84. *Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Ventana ALK (D5F3) CDx Assay. 2015; https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140025B.pdf. Accessed September 10, 2020.*
85. *Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. Dec 4 2014;371(23):2167-2177. PMID 25470694.*
86. *Shaw AT, Kim TM, Crino L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. Jul 2017;18(7):874-886. PMID 28602779.*
87. *Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK- rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. Mar 04 2017;389(10072):917-929. PMID 28126333.*
88. *Ou SH, Ahn JS, De Petris L, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. J Clin Oncol. Mar 01 2016;34(7):661-668. PMID 26598747.*

89. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol. Feb 2016;17(2):234-242. PMID 26708155.

90. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. Jul 01 2017;390(10089):29-39. PMID 28501140.

91. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. Aug 31 2017;377(9):829-838. PMID 28586279.

92. Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase- positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Ann Oncol. Sep 12 2018. PMID 30215676.

93. Gettinger SN, Bazhenova LA, Langer CJ, et al. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet Oncol. Dec 2016;17(12):1683-1696. PMID 27836716.

94. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase- positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol. Aug 01 2017;35(22):2490-2498. PMID 28475456.

95. Camidge DR, Kim DW, Tiseo M, et al. Exploratory analysis of brigatinib activity in patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer and brain metastases in two clinical trials. J Clin Oncol. Sep 10 2018;36(26):2693-2701. PMID 29768119.

96. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small- cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol. May 2016;17(5):642-650. PMID 27080216.

97. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol. Jul 2016;17(7):984-993. PMID 27283860.

98. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. Oct 2017;18(10):1307-1316. PMID 28919011.

99. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med. Aug 20 2015;373(8):726-736. PMID 26287849.

100. Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol. Oct 2012;7(10):e23-24. PMID 22743296.

101. Peters S, Michielin O, Zimmermann S. Dramatic response induced by vemurafenib in a BRAF V600E-mutated lung adenocarcinoma. J Clin Oncol. Jul 10 2013;31(20):e341-344. PMID 23733758.

102. Robinson SD, O'Shaughnessy JA, Cowey CL, et al. BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib. Lung Cancer. Aug 2014;85(2):326-330. PMID 24888229.

103. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. Nov 20 2014;371(21):1963-1971. PMID 25264305.

104.Lim SM, Kim HR, Lee JS, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. J Clin Oncol. Aug 10 2017;35(23):2613-2618. PMID 28520527.

105.Mazieres J, Zalcman G, Crino L, et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. J Clin Oncol. Mar 20 2015;33(9):992-999. PMID 25667280.

106.Kim HR, Lim SM, Kim HJ, et al. The frequency and impact of ROS1 rearrangement on clinical outcomes in never smokers with lung adenocarcinoma. Ann Oncol. Sep 2013;24(9):2364-2370. PMID 23788756.

107.Mao C, Qiu LX, Liao RY, et al. KRAS mutations and resistance to EGFR-TKIs treatment in patients with non- small cell lung cancer: a meta-analysis of 22 studies. Lung Cancer. Sep 2010;69(3):272-278. PMID 20022659.

108.Linardou H, Dahabreh IJ, Kanaloupiti D, et al. Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. Lancet Oncol. Oct 2008;9(10):962-972. PMID 18804418.

109.Papadimitrakopoulou V, Lee JJ, Wistuba, II, et al. The BATTLE-2 Study: a biomarker-integrated targeted therapy study in previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol. Aug 01 2016. PMID 27480147.

110.Rulli E, Marabese M, Torri V, et al. Value of KRAS as prognostic or predictive marker in NSCLC: results from the TAILOR trial. Ann Oncol. Oct 2015;26(10):2079-2084. PMID 26209642.

111.Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. Jul 14 2005;353(2):123-132. PMID 16014882.

112.Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med. Jan 2005;2(1):e17. PMID 15696205.

113.Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. Sep 1 2005;23(25):5892-5899. PMID 16043829.

114.Fiala O, Pesek M, Finek J, et al. Gene mutations in squamous cell NSCLC: insignificance of EGFR, KRAS and PIK3CA mutations in prediction of EGFR-TKI treatment efficacy. Anticancer Res. Apr 2013;33(4):1705-1711. PMID 23564819.

115.Guan JL, Zhong WZ, An SJ, et al. KRAS mutation in patients with lung cancer: a predictor for poor prognosis but not for EGFR-TKIs or chemotherapy. Ann Surg Oncol. Apr 2013;20(4):1381-1388. PMID 23208128.

116.Boldrini L, Ali G, Gisfredi S, et al. Epidermal growth factor receptor and K-RAS mutations in 411 lung adenocarcinoma: a population-based prospective study. Oncol Rep. Oct 2009;22(4):683-691. PMID 19724844.

117.Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol. Feb 20 2010;28(6):911-917. PMID 20100966.

118.Khambata-Ford S, Harbison CT, Hart LL, et al. Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. J Clin Oncol. Feb 20 2010;28(6):918-927. PMID 20100958.

119.Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet. May 2 2009;373(9674):1525-1531. PMID 19410716.

120.O'Byrne KJ, Gatzemeier U, Bondarenko I, et al. Molecular biomarkers in non-small-cell lung cancer: a retrospective analysis of data from the phase 3 FLEX study. Lancet Oncol. Aug 2011;12(8):795-805. PMID 21782507.

121.Janne PA, van den Heuvel MM, Barlesi F, et al. Selumetinib plus docetaxel compared with docetaxel alone and progression-free survival in patients with KRAS-mutant advanced non-small cell lung cancer: the SELECT-1 Randomized Clinical Trial. JAMA. May 09 2017;317(18):1844-1853. PMID 28492898.

122.Blumenschein GR, Jr., Smit EF, Planchard D, et al. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC)dagger. Ann Oncol. May 2015;26(5):894-901. PMID 25722381.

123.Mok T, Ladrera G, Srimuninnimit V, et al. Tumor marker analyses from the phase III, placebo-controlled, FASTACT-2 study of intercalated erlotinib with gemcitabine/platinum in the first-line treatment of advanced non- small-cell lung cancer. Lung Cancer. Aug 2016;98:1-8. PMID 27393499.

124.Shen H, Du G, Liu Z, et al. Assessment and prognostic analysis of EGFR mutations or/and HER2 overexpression in Uygur's Non-small Cell Lung Cancer. Int J Clin Exp Med. Dec 2015;8(12):22300-22309. PMID 26885207.

125.Mazires J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. Jun 1 2013;31(16):1997-2003. PMID 23610105.

126.Yoh K, Seto T, Satouchi M, et al. Vandetanib in patients with previously treated RET-rearranged advanced non- small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. Lancet Respir Med. Jan 2017;5(1):42- 50. PMID 27825616.

127.Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov. Jun 2013;3(6):630-635. PMID 23533264.

128.Sadiq AA, Salgia R. MET as a possible target for non-small-cell lung cancer. J Clin Oncol. Mar 10 2013;31(8):1089-1096. PMID 23401458.

129.Rizvi H, Sanchez-Vega F, La K et al. Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing. J. Clin. Oncol., 2018 Jan 18;36(7). PMID 29337640.

130.Singal G, Miller PG, Agarwala V et al. Association of Patient Characteristics and Tumor Genomics With Clinical Outcomes Among Patients With Non-Small Cell Lung Cancer Using a Clinicogenomic Database. JAMA, 2019 Apr 10;321(14). PMID 30964529.

131. *Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Arch Pathol Lab Med. Jun 2013;137(6):828-860. PMID 23551194.*

132. *Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Mol Diagn. Mar 2018;20(2):129-159. PMID 29398453.*

133. *Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. Aug 14 2017:JCO2017746065. PMID 28806116.*

134. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.45, Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer. November 2019.*

X. POLICY HISTORY

Top

MP 2.241	**CAC 4/26/11 New Policy.** Adopted BCBSA (medically necessary).
	CAC 6/26/12 Consensus review. No changes, references updated. FEP variation added.
	12/20/2013 Administrative update. 2013 Codes added
	05/20/13 Administrative update. Code review completed.
	8/1/13 Administrative update. Add Medicare variation referencing LCD L33142.
	CAC 11/26/13 Consensus review. No change to policy statements. Added rationale section. References updated**.**
	7/24/14 Administrative update. For the Medicare variation - For Novitas MAC jurisdictions, the LCD has been assigned a new number. Biomarkers for Oncology LCD changed from L33124 to L34796
	CAC 1/27/15 Minor revision. ▪ Policy title revised to "Molecular Analysis for Targeted Therapy for Non-Small Cell Lung Cancer" for this review. ▪ First policy statement revised to state analysis of two 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 erlotinib or afatinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. Previously, afatinib was not included and the medically necessary indication as for non-small cell lung cancer.

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	▪ A new statement was added that testing for ROS, RET, MET, BRAF and HER2 mutations is considered investigational. ▪ Policy MP-2.240 KRAS Mutation Analysis in Non-Small Cell Lung Cancer (NSCLC) merged with this policy. Background, rationale, references, and guidelines updated. FEP variation updated to reflect combining two policies. (MP 2.240 Info added into this policy). Cellular and histologic classification of NSCLC added to policy guidelines. No coding changes.
	11/2/15 Administrative update. LCD number changed from L34796 to L35396 due to Novitas update to ICD-10.
	CAC 3/29/16 Minor revision. Policy updated only to address *ALK* rearrangement testing. Policy statement added that analysis of somatic rearrangement mutations of the *ALK* gene is considered medically necessary to predict treatment response to crizotinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. Policy statement added that testing for *ALK* gene rearrangements is investigational for all other clinical situations. Reference and rationale update. Coding reviewed.
	1/1/17 Administrative update. Product variation section reformatted.
	CAC 3/28/17 Minor revision. Added testing for T790M mutation in patients who have progressed on or after EGFR-TKI therapy to the EGFR Gene medically necessary statement. The medically necessary statement language for the EGFR and ALK Genes were revised to reference the gene inhibitor therapy with examples of therapy types/drugs. FEP variation updated. Policy Guidelines, Description/Background, Rationale and Reference sections updated. Appendix added. Coding Reviewed
	1/1/18 Administrative update. Medicare variations removed from Commercial Policies.
	1/25/18 Minor revision. Policy section updates: • Genetics nomenclature update ‘mutation’ to ‘variant’; • 'Point mutation' replaced with 'single-nucleotide variant' within the EGFR Gene policy statement; • *ROS1* and *BRAF* testing added as medically necessary when criteria are met; and • Genes within the ‘Other Genes’ statement updated. FEP variation removed as policy was archived December 2015. Policy Guidelines, Description/Background, Rationale and Reference sections updated. Coding revised to mirror policy statements.
	12/14/18 Minor review. The policy section on *EGFR* Testing was changed. Testing for additional variants in the *EGFR* gene was added as medically necessary. Policy statements on other variants unchanged.

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	Description/Background and Reference sections updated. Rationale condensed. Coding reviewed.
	11/7/19 Minor review. New indications for NTRK testing and tumor mutational burden (TMB) testing added. Medically necessary statement for NTRK testing and investigational statement for TMB testing. Literature reviewed and references and coding updated. Effective 5/1/2020.
	9/10/2020 Consensus review. No changes made to the policy statement. Policy guidelines, product variation, description, rationale, benefit variation, disclaimer, and references updated. Coding reviewed.
	9/22/2020 Administrative update. New codes 81191, 81192, 81193, 81194 added. Effective 1/1/2021.

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