Prior Authorization Review Panel
MCO Policy Submission

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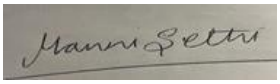
Plan: AmeriHealth Caritas Pennsylvania	**Submission Date**: 8/1/2024
Policy Number: ccp.1218	**Effective Date:** 4/2016 **Revision Date:** July 1, 2024
Policy Name: Molecular analysis for targeted therapy of non-small cell lung cancer	
Type of Submission – Check all that apply: **New Policy** **X Revised Policy*** **Annual Review – No Revisions** **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Molecular analysis for targeted therapy of non-small cell lung cancer

Clinical Policy ID: CCP.1218

Recent review date: 7/2024

Next review date: 11/2025

Policy contains: Anaplastic lymphoma kinase; epidermal growth factor receptor; non-small cell lung cancer; receptor tyronese kinase 1 mutations; targeted therapy.

AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania on a case by case basis when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania clinical policies are not guarantees of payment.

Coverage policy

Molecular analysis for targeted therapy for non-small cell lung cancer is clinically proven and, therefore, may be medically necessary according to the National Comprehensive Cancer Network (2024) guidelines and FDA-approved labeling (U.S. Food and Drug Administration, 2023b). Testing should be performed in a Clinical Improvements Laboratory Amendments-approved lab or via an FDA-approved companion diagnostic test.

Molecular analysis for advanced or metastatic non-small cell lung cancer is clinically proven and, therefore, may be medically necessary when it will influence treatment planning for the following indications (Kerr, 2014; Leighl, 2014; Lindeman, 2013, 2018; National Comprehensive Cancer Network, 2024; U.S. Food and Drug Administration, 2023a):

- EGFR Gene Mutations: Small deletions in exon 19, exon 20 sequencing, and a point mutation in exon 21 (L858R) to predict response to afatinib, dacomitinib, erlotinib, gefitinib, ramucirumab, bevacizumab, Osimertinib, or osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous).
- EGFR T790M Mutation: To predict response to osimertinib.
- EGFR Exon 20 Insertion Mutation: To predict response to amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous).

- EGFR S768I, L861Q, and/or G719X: To predict response to amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous) as subsequent therapy.
- ALK Gene Rearrangements: To predict response to alectinib, brigatinib, ceritinib, crizotinib, or lorlatinib.
- BRAF V600E Mutation: To predict response to dabrafenib and trametinib or encorafenib/binimetinib**.**
- ROS1 Gene Mutations: To predict response to ceritinib, crizotinib, entrectinib, lorlatinib or repotrectinib**.**
- PD-L1 Expression: To predict response to pembrolizumab, atezolizumab, cemiplimab-rwlc, or nivolumab.
- RET Fusion-Positive: To predict response to pralsetinib, selpercatinib, cabozantinib, or vandetanib.
- MET Exon 14 Skipping: To predict response to capmatinib, crizotinib, or tepotinib.
- High-Level MET Amplification: To predict response to crizotinib.
- ERBB2 Mutation: To predict response to ado-trastuzumab or fam-trastuzumab.
- Tumor Mutation Burden: To predict response to pembrolizumab.
- NTRK Gene Fusion: To predict response to entrectinib or larotrectinib.
- KRAS Mutations: To predict efficacy of anti-EGFR tyrosine kinase inhibitors and to determine the need for further molecular testing.

For medication medical necessity determinations, refer to the applicable state-approved pharmacy policy.

Limitations

Other molecular analyses related to targeted therapy for lung cancer are investigational/not clinically proven and, therefore, not medically necessary, including (National Comprehensive Cancer Network, 2024):

- Epidermal growth factor receptor gene mutations to predict an improved response to necitumumab, in combination with platinum chemotherapy in members with advanced squamous cell lung cancer, as evidence supporting a net benefit of adding necitumumab to chemotherapy has not been demonstrated.
- Other somatic rearrangement mutations of the anaplastic lymphoma kinase gene.
- Programmed death ligand 1 testing to predict the efficacy of anti-epidermal growth factor receptor monoclonal antibody therapy with single-agent nivolumab, durvalumab, or atezolizumab for members with metastatic non-small cell lung cancer.
- Plasma cell-free or circulating tumor deoxyribonucleic acid testing in lieu of tissue diagnosis, with three exceptions:
    - If the member is medically unfit for invasive tissue sampling.
    - If there is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be performed if an oncogenic driver is not identified.
    - If a companion diagnostic test has been validated using plasma samples (See Appendix).

Next-generation sequencing tests for tumor profiling (e.g., Caris Molecular Intelligence® Tumor Profiling, Caris Life Sciences, Irving, Texas) that are not listed in the Appendix are investigational and, therefore, not medically necessary, as their clinical utility has not been established for predicting response to the targeted therapies approved for use in members with advanced or metastatic non-small cell lung cancer.

Molecular testing in members with non-small cell lung cancer is investigational/not clinically proven and, therefore, not medically necessary for determining clinical trial eligibility.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Lung cancer is one of the most commonly diagnosed cancers. Lung cancer has had historically high mortality. The five-year relative survival rate from 2012 to 2018 is 22.9% (National Cancer Institute, 2022). The majority (55%) of new cases present with advanced, metastasized disease at initial diagnosis. For these patients, chemotherapy has traditionally been the only recommended treatment option. Poor survival rates for patients with lung cancer (especially those with advanced disease), difficulties tolerating chemotherapy regimens, and improved knowledge of oncogenetics has led to development and approval of a series of drugs that target the genetic anomalies of cancerous cells and are better tolerated.

Somatic mutations in epidermal growth factor receptor genes occur in an estimated 10-20% of lung cancers among Caucasians, and over 50% among Asians (Harrison, 2020). Unlike traditional chemotherapy, several tyrosine kinase inhibitors (afatinib, dacomitinib, erlotinib, and gefitinib) can target these somatic mutations in people with advanced non-small cell lung cancer, in particular, adenocarcinoma, which accounts for 40% of all lung cancers, with fewer side effects.

The U.S. Food and Drug Administration (2023a) approved gefitinib in 2003 as a second-line treatment for non-small cell lung cancer after platinum chemotherapy; it was taken off the market by the manufacturer two years later and returned as an approved first-line therapy in 2015. Erlotinib was the other early first-generation treatment, approved in 2004, while dacomitinib was approved in 2018. Afatinib is a second-generation treatment approved in 2013. Osimertinib was approved as a third-generation therapy in November 2015, after therapeutic failure of first- and second-generation targeted therapies due to cancer mutation; two-thirds of these patients tested positive for the *T790M* mutation, to which osimertinib is sensitive.

The anaplastic lymphoma kinase gene exists in about 5% of non-small cell lung cancers (Arbor, 2017). Targeted therapies for those patients with somatic rearrangements of the anaplastic lymphoma kinase gene are lorlatinib, alectinib, brigatinib, ceritinib, or crizotinib. The U.S. Food and Drug Administration approved these drugs in May 2021, December 2015, April 2017, April 2014, and November 2013, respectively. Crizotinib was also approved in March 2016 for patients with non-small cell lung cancer and the presence of a *ROS* proto-oncogene 1 mutation, which has been observed in 1% of non-small cell lung cancers. On June 22, 2017, the U.S. Food and Drug Administration approved the combined therapy of dabrafemib and trametinib for patients with non-small cell lung cancer and presence of a *V600E* mutation of the proto-oncogene B-*raf* gene. On August 15, 2019, the Administration approved entrectinib for ROS1-positive patients with advanced non-small cell lung cancer (U.S. Food and Drug Administration, 2023a).

Squamous cell lung cancer accounts for the minority of the non-small cell lung cancer population. Only one targeted therapy drug (necitumumab), approved in November 2015, is available for people with squamous cell lung cancer and the epidermal growth factor receptor mutation. Currently, there are no approved targeted therapies for small cell lung cancer, as trials to identify such treatments continue.

The Kirsten rat sarcoma oncogene is the most common mutation in non-small cell lung cancer, occurring in 20 to 40% of lung adenocarcinoma cases (Adderly, 2019). In May 2021, the Food and Drug Administration approved sotorasib as a targeted treatment for patients with a G12C mutation of the Kirsten rat sarcoma oncogene (Nakajima, 2022).

Classifying molecular arrangements of patients with advanced lung cancer with biomarkers indicative of therapeutic efficacy provides actionable information that predicts those who will likely have extended progression-free survival and fewer side effects. The U.S. Food and Drug Administration (2023a) continues to approve new targeted therapies and immunotherapies and companion molecular diagnostic tests used for determining treatment eligibility (See Appendix).

Findings

Guidelines:

The 2024 National Comprehensive Cancer Network (NCCN) guidelines and the International Association for the Study of Lung Cancer (IASLC) Atlas of Molecular Testing for Targeted Therapy in Lung Cancer both recommend broad molecular profiling for all patients with advanced non-squamous non-small cell lung cancer (NSCLC) or NSCLC with a non-squamous component (National Comprehensive Cancer Network, 2024; Sholl, 2023). Testing should be performed at the time of diagnosis to guide selection of optimal targeted therapies and improve outcomes. Key actionable biomarkers that should be assessed include Epidermal Growth Factor Receptor (EGFR) mutations, Anaplastic Lymphoma Kinase (ALK) rearrangements, ROS proto-oncogene 1 (ROS1) rearrangements, proto-oncogene B-Raf (BRAF) mutations, mesenchymal to epithelial transition (MET) exon 14 skipping mutations, RET proto-oncogene rearrangements, Neurotrophic Tyrosine Receptor Kinase (NTRK1/2/3) gene fusions, anti-human epidermal growth factor receptor 2 (ERBB2/HER2) mutations, and Kirsten Rat Sarcoma (KRAS) mutations (National Comprehensive Cancer Network, 2024; Sholl, 2023).

Broad next-generation sequencing (NGS) panels that assess both DNA and RNA are preferred over single gene tests. If tumor tissue is insufficient or unavailable for testing, plasma-based cell-free DNA (cfDNA) analysis is recommended as an alternative approach to identify targetable genomic alterations (National Comprehensive Cancer Network, 2024; Sholl, 2023). In addition to guiding treatment decisions in advanced NSCLC, molecular testing is also increasingly being utilized in early-stage disease to inform the use of adjuvant targeted therapies.

Earlier guidelines issued the American Society of Clinical Oncology (Leighl, 2014), the European Society for Medical Oncology (Kerr, 2014), and the U.K. National Institute for Health and Care Excellence (2013) noted that patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics (Lindeman, 2013). Furthermore, the groups recommend patients with squamous cell carcinomas, small cell carcinoma, or large cell carcinoma lacking any immunohistochemistry evidence of adenocarcinoma should not be tested for epidermal growth factor receptor and anaplastic lymphoma kinase mutations.

The groups also indicated that testing should be conducted for stage 4 patients at time of diagnosis, and for those suitable for therapy at time of progression who were not previously tested. The guideline leaves the decision to test non-small cell lung cancer patients with stage 1, 2, or 3 disease to the individual oncology team, in conjunction with laboratory managers. Fresh, frozen, or alcohol-fixed specimens for polymerase chain reaction-based epidermal growth factor receptor mutations should be used. Laboratories, including a pathologist, should use an anaplastic lymphoma kinase fluorescence in situ hybridization assay with dual-labeled break-apart probes for anaplastic lymphoma kinase mutation testing (Lindeman, 2013).

Systematic reviews and meta-analyses have investigated the accuracy and utility of various methods for detecting genetic mutations in advanced lung cancer patients to guide targeted therapy. A systematic review of 38 studies confirmed a limited role for liquid biopsy in detecting clinically relevant mutations, with positive percent agreement between liquid biopsy and tissue-based biopsy ranging from 53.6% to 67.8% (Esagian, 2020). Similarly, a meta-analysis of 19 studies (n = 2,922) comparing biopsies of lung cancer tissues and blood samples to detect epidermal growth factor receptor mutation 19 showed a significantly higher detection rate for biopsies

(odds ratio = 1.47, P < .001) (Biaoxue, 2018). However, a systematic review of seven studies (n = 2,610) showed that tissue biopsy was a good predictor of enhanced survival benefit after treatment with immune checkpoint inhibitors, while liquid biopsy was not (Zhang, 2022).

Meta-analyses have also evaluated the accuracy of specific techniques for detecting mutations. A meta-analysis of 21 studies (n = 1,639) on circulating tumor DNA to detect epidermal growth factor receptor T790M mutation found sensitivity and specificity rates of 0.67 and 0.80, respectively (Passiglia, 2018), while a meta-analysis of 11 studies (n = 872) on droplet digital PCR to identify T790M mutation discovered sensitivity and specificity rates of 70.1% and 86.9%, respectively (Zhang, 2018). Additionally, a meta-analysis of 40 studies (n = 2,805) found blood biopsy accurately (sensitivity 71%, specificity 93%) detects Kirsten rat sarcoma mutations in non-small cell lung cancer patients (Palmieri, 2022).

Immunohistochemistry has been found to be accurate for detecting anaplastic lymphoma kinase and ROS proto-oncogene 1 mutations, but caution should be taken in detecting epidermal growth factor receptor mutation due to low-to-fair sensitivity (Rossi, 2016; Chen, 2014; Dahabreh, 2010). In a study of 100 advanced lung cancer patients with negative or inconclusive results after testing, mutations identified by next-generation sequencing changed treatment in 42.6% of patients (Rozenblum, 2017). An estimated 79% of liquid biopsy samples showed somatic mutations, and combining liquid biopsy with tissue samples raises detection of targetable mutations in advanced lung cancer (Saarenheimo, 2022).

Despite the growing body of evidence, a review of 28 clinical practice guidelines for non-small cell lung cancer found that recommendations for molecular testing were addressed in only 11 for the main types of mutations, and fewer for other mutations (Zhang, 2021).

In 2024, the coverage and findings sections of this policy was reorganized and condensed. New guidelines from the National Comprehensive Cancer Network guidelines and the International Association for the Study of Lung Cancer were added to the policy (National Comprehensive Cancer Network, 2024; Sholl, 2023). We also found the following systematic review:

This systematic review and meta-analysis included 86 studies (25 prospective and 61 retrospective) (n = 4,524) patients with oncogene-driven non-small cell lung cancer treated with immunotherapy (Chen, 2024). The pooled objective response rates (ORRs) for single-agent immunotherapy in retrospective studies were 8% for EGFR, 3% for ALK, 28% for KRAS, 24% for BRAF, 23% for MET, 14% for HER2, 7% for RET, and 8% for ROS1 alterations. In prospective studies, the ORRs were 6% for EGFR, 0% for ALK, and 23% for KRAS alterations. Median progression-free survival ranged from 2.31 to 3.24 months across different alterations. Patients with EGFR, ALK, HER2, RET, and ROS1 alterations had poor responses to single-agent immunotherapy, but efficacy significantly improved with combination immunotherapy, particularly for EGFR-mutated NSCLC, which had an ORR of 58% with chemoimmunotherapy plus anti-angiogenic agents. KRAS G12C, BRAF non-V600E, and MET amplification showed better responses to immunotherapy. These findings highlight the variability in response to immunotherapy based on specific genetic alterations in non-small cell lung cancer and emphasize the potential benefits of combination therapies for enhancing patient outcomes (Chen, 2024).

References

On June 7, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “respiratory tract neoplasm” (MeSH), “respiratory tract neoplasms/therapy” (MeSH), and “respiratory tract neoplasms/genetics” (MeSH). We included the best

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Policy updates

1/2016: initial review date and clinical policy effective date: 4/2016

1/2017: Policy references updated.

1/2018: Policy references updated.

1/2019: Policy references updated.

1/2020: Policy references updated and indications added per National Comprehensive Cancer Network guidelines.

7/2020: Clarified medically necessary tumor profiling tests in limitations section.

7/2021: Policy references updated. Coverage and appendix modified.

7/2022: Policy references updated.

7/2023: Policy references updated.

7/2024: Policy references updated.

Appendix 1

Molecular and Biomarker-Directed Therapy for Advanced or Metastatic Lung Cancer (National Comprehensive Cancer Network, 2024).

EGFR Exon 19 Deletion or Exon 21 L858R
First-line therapy
Afatinib
Erlotinib
Dacomitinib
Gefitinib
Osimertinib
Erlotinib + ramucirumab
Erlotinib + bevacizumab (nonsquamous)
Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous)

Subsequent therapy
Osimertinib
Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)

EGFR S768I, L861Q, and/or G719X
First-line therapy
Afatinib
Erlotinib
Dacomitinib
Gefitinib
Osimertinib

Subsequent therapy
Osimertinib
Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)

EGFR Exon 20 Insertion Mutation
First-line therapy
Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)
Subsequent therapy
Amivantamab-vmjw

Commented [VD1]: Mobocertinib was withdrawn from the U.S. market in 2023 and is no longer recommended as a subsequent treatment option per NCCN

KRAS G12C Mutation
Subsequent therapy
Sotorasib
Adagrasib

ALK Rearrangement
First-line therapy
Alectinib
Brigatinib
Ceritinib
Crizotinib
Lorlatinib

Subsequent therapy
Alectinib
Brigatinib
Ceritinib
Lorlatinib

ROS1 Rearrangement
First-line therapy
Ceritinib
Crizotinib
Entrectinib
Repotrectinib

Subsequent therapy
Lorlatinib
Entrectinib
Repotrectinib

BRAF V600E Mutation
First-line therapy
Dabrafenib/trametinib
Dabrafenib
Vemurafenib
Encorafenib/binimetinib

Subsequent therapy
Dabrafenib/trametinib
Encorafenib/binimetinib

NTRK1/2/3 Gene Fusion
First-line/Subsequent therapy
Larotrectinib
Entrectinib

MET Exon 14 Skipping Mutation
First-line therapy/Subsequent therapy
Capmatinib
Crizotinib
Tepotinib

RET Rearrangement
First-line therapy/Subsequent therapy
Selpercatinib
Pralsetinib
Cabozantinib

ERBB2 (HER2) Mutation
Subsequent therapy
Fam-trastuzumab deruxtecan-nxki
Ado-trastuzumab emtansine