Clinical Policy Title: Molecular analysis for targeted therapy of non-small cell lung cancer

Clinical Policy Number: 05.01.04

Effective Date: April 1, 2016
Initial Review Date: January 20, 2016
Most Recent Review Date: February 15, 2017
Next Review Date: February 2018

Related policies:

CP# 05.02.11 Advanced non-small cell lung cancer with TKI and PD-1 drugs
CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.14 Gene expression profile testing for breast cancer
CP# 02.01.20 Genetic testing for Alzheimer’s disease
CP# 11.04.02 Genetic testing for autism spectrum disorders
CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 02.01.07 Genetic testing for cystic fibrosis
CP# 00.01.03 Genetic testing for cytochrome p450 Polymorphisms (CYP2C19)
CP# 02.01.23 Genetic testing for Duchenne (CPT 81161)
CP# 05.01.03 Genetic testing for G1691A Polymorphisms Factor V Leiden
CP# 02.01.19 Genetic testing for hereditary cancer susceptibility
CP# 02.01.21 Genetic testing for hereditary cardiomyopathy
CP# 04.01.02 Genetic testing for Long QT syndrome (LQTS)
CP# 02.01.04 Genetic testing for primary autosomal recessive microcephaly
CP# 02.01.09 Genetic testing for rare diseases
CP# 13.01.01 Genetic testing for prostate cancer prognosis
CP# 09.01.09 Genetic testing in neurology
CP# 02.01.18 Genetic testing in sensorineural hearing loss

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evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

**Coverage policy**

AmeriHealth Caritas Pennsylvania considers the use of molecular analysis for targeted therapy of advanced non-small cell lung cancer (NSCLC) to be clinically proven and, therefore, medically necessary, under certain conditions.

Analysis of two types of somatic mutations 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 an improved response to afatinib (Gilotrif®), erlotinib (Tarceva®), or gefitinib (Iressa®) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

Analysis of EGFR mutations that are positive for the T790M gene may be considered necessary to predict an improved response to osimertinib (Tagrisso®) as a first-line treatment or after progression with platinum chemotherapy, afatinib, erlotinib, or gefitinib.

Analysis of mutations within the EGFR gene may be medically necessary to predict an improved response to necitumumab (Portrazza®) in patients with advanced squamous cell lung cancer, in combination with platinum chemotherapy.

Analysis of somatic rearrangement mutations of the anaplastic lymphoma kinase (ALK) gene may be considered medically necessary to predict treatment response to alectinib (Alcensa®), ceritinib (Zykadia®), and crizotinib (Xalkon®) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.

Analysis of mutations within the ROS1 gene may be considered medically necessary to predict treatment response to crizotinib (Xalkon®) in patients with advanced lung adenocarcinoma.

**Limitations:**

Other molecular analyses related to targeted therapy for lung cancer are considered investigational, including:

1. Small deletions in exon 19 and a point mutation in exon 21 (L858R), which are types of somatic mutations within the EGFR gene, for patients with advanced squamous cell NSCLC. EGFR testing would be considered for advanced squamous cell NSCLC if mutation-directed therapy is being considered.

2. Other EGFR mutations within exons 18 – 24 or other applications related to NSCLC.
3. Other somatic rearrangement mutations of the ALK gene.

4. Somatic mutations of the Kirsten rat sarcoma (KRAS) gene to predict the efficacy of anti-EGFR monoclonal antibody cetuximab in NSCLC.

5. Genetic alterations in the genes ROT, MET, BRAF, and HER2 for targeted therapy in patients with NSCLC.

All other uses of genetic testing for lung cancer are considered investigational and, therefore, medically unnecessary.

**Alternative covered services:**

None.

**Background**

Lung cancer is one of the most commonly diagnosed cancers. In 2016, an estimated 224,390 Americans were diagnosed with the disease. Lung cancer has historically had high mortality rates; an estimated 158,080 Americans died from the disease, the most of any cancer type. The five-year survival rate from the disease has remained low, rising only from 12.2 percent to 18.7 percent between 1975 – 77 and 2006 – 12 (Howlander, 2016).

Part of the difficulty in treating lung cancer is that 57 percent of new cases are metastasized (“distant”) to other parts of the body at the time of diagnosis. For these patients, chemotherapy is the only recommended treatment option, and the five-year survival rate for these patients is just 4.3 percent, according to the National Cancer Institute (Howlander, 2016). Improved treatments for advanced lung cancer are needed.

Recent developments have identified several drugs (afatinib, erlotinib, and gefitinib) that can target therapy to persons with somatic mutations in EGFR genes (which traditional chemotherapy does not do) for advanced NSCLC, in particular adenocarcinoma (which accounts for 40 percent of all lung cancers). These drugs are much better tolerated by lung cancer patients compared to platinum chemotherapy and have been approved by the U.S. Food and Drug Administration (FDA) as first- and second-line treatments. Classifying molecular arrangements helps predict which patients with advanced lung adenocarcinoma will likely have extended progression-free survival (PFS) and fewer side effects to these targeted therapies than traditional chemotherapy, but not overall survival (OS) to date. In particular, small deletions in exon 19 and a point mutation in exon 21 (L858R) predict an improved response to afatinib or erlotinib.
These therapies were developed after discovering the EGFR mutation exists in about 15 percent of lung cancer patients. Gefitinib was one of two first-generation treatments approved by the FDA in 2003 as a second-line treatment for NSCLC (after platinum chemotherapy); it was taken off the market by the manufacturer two years later, and returned as a first-line therapy as approved by the FDA in 2015. Erlotinib was the other first-generation treatment, approved by the FDA in 2013. Afatinib is a second-generation treatment for persons with EGFR mutations, approved in 2013.

Osimertinib is a third-generation therapy that was FDA approved in November 2015. This therapy was developed as first- and second-generation targeted therapies stopped working after a cancer mutates; two-thirds of these patients tested positive for the T790M mutation.

Targeted therapy for those patients with somatic rearrangements of the ALK gene will likely have improved outcomes when treated with alectinib, ceritinib, or crizotinib. These drugs were approved by the FDA in December 2015, April 2014, and November 2013, respectively. The ALK gene exists in about 5 percent of NSCLC patients.

One of these drugs (crizotinib) was also approved by the FDA in March 2016 for NSCLC patients with the ROS1 mutation, which has been observed in 1 percent of lung cancer patients.

Squamous cell lung cancer accounts for the minority of the NSCLC population. Only one targeted therapy drug (necitumumab), approved by the FDA in November 2015, is available for persons with the EGFR mutation.

Currently, there are no targeted therapies for small cell lung cancer approved by the FDA, as trials to identify such treatments continue.

The KRAS mutation is the most common mutation in NSCLC, occurring in 25 percent of cases. However, despite numerous trials using animals, no effective targeted therapy for this mutation has yet been identified.

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on December 29, 2016. Search terms were “lung cancer,” “metastatic,” “molecular arrangements,” “ROS1,” “ALK,” and “EFGR.”
We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

The poor survival rates for patients with lung cancer (especially those with metastases), difficulties tolerating chemotherapy regimens and improved knowledge of genetic abnormalities in lung cancer patients has led to development and approval of a series of drugs that target cancerous cells.

The 2013 guideline from the College of American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology (AMP) recommends specific procedures for testing NSCLC patients for EGFR and ALK status (Lindeman, 2013). This guideline was soon endorsed by the American Society of Clinical Oncology (Leighl, 2014), the European Society for Medical Oncology (Kerr, 2014), and the UK’s National Institute for Health Care and Excellence (NICE, 2013).

The three-group guideline suggests that patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics. Furthermore, the groups recommend lung cancer patients with squamous cell carcinomas, small cell carcinoma, or large cell carcinoma lacking any immunohistochemistry evidence of adenocarcinoma should not be tested for EGFR and ALK mutations.

The groups also indicated that testing should be conducted for Stage IV patients at time of diagnosis, and for those suitable for therapy at time for progression who were not previously tested. The guideline leaves the decision to test NSCLC patients with Stage I, II, or III disease to the individual oncology team, in conjunction with laboratory managers. Fresh, frozen, or alcohol-fixed specimens for polymerase chain reaction-based EGFR mutations should be used. Laboratories, including a pathologist, should use an ALK fluorescence in situ hybridization (FISH) assay with dual-labeled break-apart probes for ALK mutation testing.

The standard for mutation testing in advanced lung cancer is tissue samples from biopsy, which costs up to $1,000 and takes two weeks for results to be known (Adamson, 2013). However, immunohistochemistry, a low-cost and rapid technique from blood samples, can be used instead. Studies show that this approach is accurate for ALK and ROS1 mutations; however, mutant-specific antibodies against EGFR demonstrate a good specificity but a low-to-fair sensitivity, and caution should
be taken in detecting this mutation (Rossi, 2016). However, other meta-analyses agree that immunohistochemistry provides accurate results for EGFR testing (Chen, 2014; Dahabreh, 2010).

The Lux-trial program of the Boehringer Ingelheim pharmaceutical company (Ingelheim am Rhein, Germany) comprises more than 10 trials worldwide, including lung (LUX-Lung) and other cancers. Begun in the mid-2000s, the program incorporates a Lux-Lung component, focusing on targeted therapies for lung cancer. The initial results of Lux-Lung 1 were released in December 2010, and subsequent results followed in 2014, 2015, and 2016.

The FDA action to approve erlotinib as targeted therapy for EGFR mutations for advanced NSCLC was based on clinical trials, principally a study of erlotinib vs. platinum-based doublet chemotherapy (n = 174). Results showed consistently greater outcomes for the erlotinib group. Median progression-free survival (PFS) was 10.4 months vs. 5.2 months; median OS was 22.9 months vs. 19.5 months, which was not significant; and the objective response rate (ORR) was 65 percent for the erlotinib arm vs. 16 percent for the chemotherapy arm (Khozin, 2014).

The FDA’s 2013 decision to add afatinib to the list of targeted therapies for NSCLC relied on a LUX-Lung 3 Phase III Study with 345 patients that showed afatinib patients lived about as long as those on chemotherapy, with fewer side effects. Afatinib had a higher PFS than pemetrexed and cisplatin chemotherapy (11.1 months vs. 6.9 months). Those patients with EGFR mutations had an even higher median PFS, of 13.6 months (Sequist, 2013).

FDA approval of the only third-generation targeted therapy for EGFR mutations (osimertinib) resulted from positive outcomes in trials, specifically higher OSS, lower toxicity rates, and higher PFS — no increase in OS has yet been observed (Janne, 2015; Yang, 2016).

FDA approval of crizotinib to be used as a first-line treatment for NSCLC patients whose malignancies are ALK-positive was based largely on a clinical trial of 343 patients receiving oral crizotinib vs. IV chemotherapy (pemetrexed plus cisplatin or carboplatin). The crizotinib group had a greater ORR than the chemotherapy group (74 percent vs. 45 percent), and a longer median PFS (10.9 months vs. 7.0 months). However, the one-year survival rate was 16 percent for the crizotinib group, which was actually less than the 21 percent survival rate for chemotherapy patients (Solomon, 2014). Similar results were the basis for the subsequent ALK mutations approved by the FDA (alectinib and certinib).

As targeted therapy is now being used both in further clinical trials and in practice, a series of meta-analyses and systematic reviews have been produced, covering dozens of trials. Those reviewing the accuracy of metastatic tests show a strong ability to predict which patients qualify for targeted therapy (Chen, 2014; Qiu, 2015). Other meta-analyses focused on efficacy show targeted therapy that results from molecular analysis in advanced-stage NSCLC patients resulted in longer PFS, greater ORR, and fewer adverse effects (Hotta, 2015; Lee, 2013; Liang, 2014).
However, OS rates have yet to show any superior results from traditional chemotherapy, and survival within five years remains rare. The challenge of refining molecular analysis of genetic material of advanced NSCLC patients to improve efficacy of targeted therapy remains a high priority for future research.

Studies have also addressed which biomarkers can predict effectiveness of targeted therapy against EGFR mutations. One meta-analysis of 61 studies found that the KRAS mutation is superior to the phosphatase and tensin homolog (PTEN) deficiency and PIK3CA mutation for ORR, OS, and PFS (Wang, 2015).

**Policy updates:**

A total of four professional guideline/other references and five peer-reviewed references have been added to this policy. In addition, the policy now includes treatments approved by the FDA in the most recent year (alectinib for ALK mutations, osimertinib for EGFR mutations).

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang (2015)</td>
<td><strong>Key points:</strong></td>
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</tbody>
</table>
| Predictors of outcomes after EGFR-specific targeted therapy for several biomarkers | • Meta-analysis of 61 studies, three predictors of anti-EGFR agents in lung cancer (KRAS mutation, PTEN deficiency, PIK3CA mutation).  
• ORR, OS, and PFS compared.  
• KRAS superior for OSS (0.42), compared to PTEN and PIK3CA (0.82, 1.08).  
• KRAS superior for OS (1.37), compared to PTEN and PIK3CA (0.88, 0.79).  
• KRAS also an effective prognostic marker for PFS (1.33) |
| Hotta (2015)   | **Key points:**                   |
| Survival benefits in patients with targeted therapy for NSCLC | • 18 Phase III trials investigating EGFR and ALK mutations.  
• PFS greater, no difference in OS. |
| Qiu (2015)     | **Key points:**                   |
| Are circulating tumor DNA effective for the detection of EGFR mutation in NSCLC | • 27 trials, 3110 participants.  
• Circulating tumor DNA is a highly specific and effective way to detect EGFR mutations. |
| Chen (2014)    | **Key points:**                   |
| Are immunohistochemical methods adequate to detect EGFR mutations | • 15 trials; looked at efficacy of anti E746-E750 antibody.  
• Immunohistochemistry alone is sufficient for detecting EGFR mutations.  
• Molecular-based analyses needed if anti E746-E750 results are negative. |
| Liang (2014)   | **Key points:**                   |
| Do TKI inhibitors improve outcomes for patients with certain mutations | • 20 Phase II and III controlled trials, 10,834 participants.  
• Increases in PFS and ORR for patients qualifying for targeted therapy.  
• No increase in OS and disease control rates. |
| Lee (2013)     | **Key points:**                   |
Does EGFR inhibitor raise progression free-survival and overall survival (PFS and OS)

- 23 trials, 14,570 participants.
- EGFR/tyrosine-kinase inhibitor (TKI) therapy extends PFS, but not OS.

Dahabreh (2010)

Are certain EGFR mutations predictors of responses to TKI targeted therapy

Key points:

- 59 trials, 3,101 participants eligible for EGFR mutation.
- EGFR mutations accurately predicted response to single-agent TKI therapy.

References

Professional society guidelines/other:


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>81479</td>
<td>Unlisted molecular pathology procedure (ALK)</td>
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