DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options provides coverage under the medical surgical benefits of the Company's Medicaid products for medically necessary molecular tumor markers for non-small cell lung cancer.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person’s unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.
DEFINITIONS

Genetic Testing – A form of testing that is utilized to determine the absence or presence of a specific gene, set of genes, genetic mutations or duplications. Results can be used to diagnose a disease, predict course of disease, identify appropriate targeted cancer therapies, and screen for specific health conditions.

Anaplastic Lymphoma Kinase (ALK) – A tyrosine kinase that is aberrantly active in NSCLC because of a chromosomal rearrangement which leads to a fusion gene and expression of a protein with constitutive tyrosine kinase activity. This is a predictive biomarker.

Epidermal Growth Factor Receptor (EGFR) – A receptor tyrosine kinase frequently overexpressed and activated in NSCLC. Largely confined to never-smokers. EGFR is a predictive biomarker.

Non-Small Cell Lung Cancer (NSCLC) – Any type of epithelial lung cancer other than small cell lung cancer. The most common types of NCSLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. There are several other types which occur less frequently.

Kristen Rat Sarcoma Viral Oncogene Homolog (KRAS) – A protein involved in the EGFR-related signal transmission. The KRAS gene, which encodes RAS proteins, can harbor oncogenic mutations that can result in rendering a tumor resistant to therapies that target the EGFR receptor. KRAS mutations are prognostic biomarkers.

Mesenchymal-Epithelial Transition Mitogen (MET) – A MET amplification is one of the critical events for acquired resistance in EGFR-mutated adenocarcinomas refractory to EGFR-TKIs. MET is a predictive biomarker.

Programmed Cell Death (PD) – A transmembrane protein expressed on T cells, B cells, and NK cells. It is an inhibitory molecule that binds to PD-ligand 1 (PD-L1).

Programmed Cell Death Ligand 1 (PD-L1) – A transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. This test is also known as cluster of differentiation 274. PD-L1 is a predictive biomarker.

Proteomic Testing – The study of the structure and function of proteins to predict response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in individuals with NSCLC with wild type or unknown EGFR variant status. It is used specifically in a select number of individuals who should not receive EGFR TKIs in the second- or third-line setting.

Reactive Oxygen Species 1 (ROS1) – A receptor of the insulin family and chromosomal rearrangements that result in fusion genes. Patients with ROS1 fusions are typically never-smokers with adenocarcinoma. This is a predictive biomarker.

PROCEDURES

1. The following molecular tumor markers or mutation analyses are considered medically necessary for the prediction of sensitivity and/or resistance to chemotherapy receptive to NSCLC. All patients must have been diagnosed with NSCLC and have undergone the subsequent molecular tumor marker or mutation testing.
A. EGFR testing in individuals with nonsquamous NSCLC or in NSCLC NOS to predict treatment benefit from EGFR tyrosine kinase inhibitor therapy. The presence of this mutation is predictive of treatment benefit from EGFR therapy.

B. ALK gene fusion testing in individuals with nonsquamous NSCLC or in NSCLC NOS for prediction of response to crizotinib therapy. The current standard method for detecting ALK in NSCLC is fluorescence in situ hybridization (FISH). It is a predictive biomarker.

C. KRAS gene sequencing for the selection of individuals who are candidates for tyrosine kinase inhibitor therapy. KRAS mutations are predictive of lack of benefit from platinum/Vinorelbine chemotherapy or EGFR TKI therapy. KRAS is a prognostic biomarker. However, it is predictive of lack of therapeutic efficacy with EGFR-TKI medications.

D. ROS1 rearrangements are predictive biomarkers that have been identified in a small subset of patients with NSCLC. The presence of the ROS1 rearrangements predicts successful treatment with Crizotinib.

E. PD-L1 expression level testing provides information regarding the effectiveness of anti-PD-1 therapy.

F. Testing for the BRAF V600E variant may be considered medically necessary to select patients with advanced or metastatic (stage III or IV) NSCLC for treatment with BRAF- or MEK-inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]).

G. The Oncomine™ Dx Target test may be considered medically necessary to select patients with advanced or metastatic (stage III or IV) NSCLC for treatment with gefitinib GT56 | 2 (Iressa®), crizotinib (Xalcori®), or a combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®).

Note: Per the National Comprehensive Cancer Network (NCCN), EGFR testing and ALK testing are not routinely recommended in patients with squamous cell carcinoma.

Highmark Health Options considers proteomic testing medically necessary for advanced NSCLC when the tumor is wild-type (e.g., no mutation detected) EGFR or with unknown EGFR status, and the patient has failed first-line systemic chemotherapy. In addition, the test results will be used to determine whether or not to proceed with second-line therapy such as Tarceva® (erlotinib) therapy.

2. Contraindications
   There are no known contraindications for molecular tumor testing.

3. When the molecular tumor markers are not covered
   Molecular tumor testing is not covered for conditions other than those listed above because the scientific evidence has not been established. Therefore services are considered not medically necessary.

4. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

5. Place of Service
   The place of service for molecular tumor markers for NSCLC is outpatient.

6. Genetic Counseling
Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for genetic mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient.

Genetic testing for mutations requires documentation of medical necessity from one of the following providers who has evaluated the patient and intends to see the person after testing has been performed for counseling:

- Board Eligible or Board Certified Genetic Counselor
- Advanced Genetics Nurse
- Genetic Clinical Nurse
- Advanced Practice Nurse in Genetics
- Board Eligible or Board Certified Clinical Geneticist
- A physician with experience in cancer genetics
- A physician specializing medical oncology

GOVERNING BODIES APPROVAL

The EGFR Mutation Analysis has been commercially available in the United States since September 2005. Genzyme Genetics, which performs the assay with plasma samples, is regulated and certified under the CLIA of 1988 and is considered qualified to perform high-complexity clinical testing. The FDA does not require formal approval before the selling of these diagnostic tests.

In November 2015, the FDA granted approval to the cobas EGFR Mutation Test v2. The cobas EGFR Mutation Test v2 is a real-time PCR test for the qualitative detection of defined mutations of the EGFR gene in DNA derived from formalin-fixed paraffin-embedded tumor tissue from NSCLC patients. In 2013, this test was initially approved for selecting patients with NSCLC when Tarceva was indicated. The new version of the test expands the use to aid in identifying patients with NSCLC whose tumors are defined EGFR mutation and for whom safety and efficacy of a drug have been established.

The molecular biomarker tests can be offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

Additional information is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm.

CODING REQUIREMENTS

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<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>81235</td>
<td>EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<td>81275</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 &amp; 13)</td>
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<td>81276</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)</td>
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<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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<td>81404</td>
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<td>Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
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<td>Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array for neoplasia)</td>
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### Diagnosis Codes

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<tr>
<th>ICD-10 Codes</th>
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<tr>
<td>C34.01</td>
<td>Malignant neoplasm of right main bronchus</td>
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<tr>
<td>C34.02</td>
<td>Malignant neoplasm of left main bronchus</td>
</tr>
<tr>
<td>C34.11</td>
<td>Malignant neoplasm of upper lobe, right main bronchus or lung</td>
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<tr>
<td>C34.12</td>
<td>Malignant neoplasm of upper lobe, left bronchus or lung</td>
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<tr>
<td>C34.2</td>
<td>Malignant neoplasm of middle lobe, bronchus or lung</td>
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<tr>
<td>C34.31</td>
<td>Malignant neoplasm of lower lobe, right bronchus or lung</td>
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<tr>
<td>C34.32</td>
<td>Malignant neoplasm of lower lobe, left bronchus or lung</td>
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<tr>
<td>C34.81</td>
<td>Malignant neoplasm of overlapping sites of right bronchus and lung</td>
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<tr>
<td>C34.82</td>
<td>Malignant neoplasm of overlapping sites of left bronchus and lung</td>
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<tr>
<td>C34.91</td>
<td>Malignant neoplasm of unspecified part of right bronchus or lung</td>
</tr>
<tr>
<td>C34.92</td>
<td>Malignant neoplasm of unspecified part of left bronchus or lung</td>
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### REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

### SUMMARY OF LITERATURE

Lung cancer is the third most common type of non-skin cancer in the United States. It is the leading cause of cancer death in men and women. The estimated new cases and deaths from lung cancer (NSCLC and SCLC) in the United States in 2017 are 222,500 new cases (116,990 in men and 105,510 in women) and 155,870 deaths (84,590 in men and 71,280 in women). The five-year survival rate from 1995 to 2001 in patients with lung cancer was 15.7% (National Cancer Institute). Non-small cell lung carcinoma is the most
common type of lung cancer and includes predominately adenocarcinomas and squamous cell carcinomas.

Risk factors for lung cancer include:
- increasing age
- current or history of tobacco use (cigarettes, pipes, and cigars)
- exposure to cancer-causing substances in secondhand smoke
- occupational exposure to asbestos, arsenic, chromium, beryllium, nickel and other agents
- radiation exposure (radiation therapy to the breast or chest, radon exposure in the home or workplace, medical imaging tests, atomic bomb radiation)
- living in an area with air pollution
- family history of lung cancer
- human immunodeficiency virus infection
- beta carotene supplements in heavy smokers

Lung cancer screening includes chest x-ray, low-dose helical CT scans, and sputum cytology.

According to the NCCN Guidelines (6.2017), predictive biomarkers are indicative of patient survival independent of the treatment received. These biomarkers are an indicator of the innate tumor aggressiveness and include ALK fusion oncogene, ROS1, and PD-L1 ligand. Emerging biomarkers include HER2, BRAF V600E mutations, RET gene arrangements, and high-level MET amplifications or MET exon 14 skipping mutations.

Epidermal growth factor receptor has become the leading target for molecular-based therapy in NSCLC. EGFR is overexpressed in 40% to 80% of NSCLC tumor specimens and has been associated with advanced stage, poor prognosis, and/or resistance to therapy (Hayes, 2006).

EGFR is a receptor tyrosine kinase (TK) frequently overexpressed and activated in NSCLC. Research has shown that the therapeutic interdiction of the EGFR pathway could be used to halt tumor growth in solid tumors that express EGFR. Based on this research, two main classes of anti-EGFR agents were developed for use in multiple types of cancer. These two agents are small molecule TKIs and monoclonal antibodies (MAbs) that block the interaction of EGFR ligand.

In NSCLC, the prevalence of EGFR mutation varies by population. The highest prevalence is in non-smoking, Asian women with adenocarcinoma, reported at 30% to 50%. The prevalence is approximately 10% in the Caucasian population.

In October 2014, ASCO endorsed a guideline from the College of American Pathologists (CAP), the International Society for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) on molecular testing of patients with lung cancer. The guidelines focus on EGFR and ALK testing, and when and how to do the testing.

Since the identification of mutations in lung cancer, molecularly targeted therapy has been developed to improve survival in subsets of patients with metastatic disease. Subsets of adenocarcinoma are identify by EGFR, MAPK, and PI3K that define mechanisms of drug sensitivity and primary or acquired resistance to kinase inhibitors. Some other genetic abnormalities of potential relevance to treatment options include
translocations involving anaplastic lymphoma kinase (ALK) tyrosine kinase receptor and mesenchymal epithelial transition factor (MET).

In 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology jointly issued guidelines with the following recommendations:

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

In 2015, NCCN guidelines for NSCLC recommended proteomic testing for patients with NSCLC with wild-type EGFR or with unknown status. Per the guidelines, a patient with a “poor” classification should not be offered erlotinib as a second-line therapy. The NCCN guidelines identified the Gregorc, et al. study (2014) that reported serum protein test status is predictive of differential benefit in overall survival for erlotinib versus chemotherapy as the second-line setting. Those patients in the study that were classified as likely to have a “poor outcome” had better outcomes on chemotherapy than on erlotinib.

The FDA has approved the ThermoFisher Oncomine DX Target Test for NSCLC in June 2017 (Harris, 2017). Oncomine DX Target Test is the only FDA approved companion test that detects ROS1 fusions and that detects BRAF V600E, but it does not detect ALK fusions (CMS, 2018). It can simultaneously identify the three gene variants that are a key to targeted therapy selection: BRAF and ROS1, and EGFR. The targeted therapies are dabrafenib (Tafinlar) in combination with trametinib (Mekinist), crizotinib (Xalkori), and gefitinib (Iressa), respectively. These three drugs are FDA approved therapies for NSCLC patients with the above gene variants (CMS, 2018). The FDA approval was based on the results from a three-cohort, multicenter, and nonrandomized clinical trial of patients with stage IV NSCLC (Harris, 2017). Of the 1.8 million worldwide total of new NSCLC cases diagnosed per year, about 36,000 patients; or 1-3 percent of that total are positive for the BRAFV600 mutation (Harris, 2017).

In September 2017, the NCCN guidelines on NSCLC make the following recommendations (category 2A) regarding **BRAF** testing:

- **BRAF testing** is recommended for the same patients with metastatic non-squamous cell carcinoma for whom **EGFR** testing is recommended. BRAF testing can be considered for metastatic squamous cell NSCLC.
- **NCCN** recommends that BRAF testing be performed as part of a broader profiling test that also assesses **EGFR, ALK, and ROS1**, at minimum.
- Dabrafenib/trametinib or doublet chemotherapy regimens (e.g. carboplatin/pemetrexed for non-squamous NSCLC) are recommended for those with the **BRAF V600E** variant.

“Patients with **BRAF V600E** mutation—positive metastatic NSCLC have responded less favorably to standard chemotherapy, suggesting that there is a critical need for a targeted therapy,” Bruno Strigini,
CEO, Novartis Oncology, said in a press release (Harris, 2017). The literature does appear to show clinical validity for all tests and utility for the companion testing.

**POLICY SOURCE(S)**


Policy History

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<tr>
<th>Date</th>
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<tr>
<td>06/16/2017</td>
<td>Initial policy developed</td>
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<tr>
<td>09/26/2017</td>
<td>Updated operational guidelines</td>
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<tr>
<td>09/27/2017</td>
<td>QI/UM Committee approval</td>
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<td>11/01/2017</td>
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<tr>
<td>09/11/2018</td>
<td>Annual Review Revisions: Added criteria to Procedures section 1 (1.F. and 1.G.); Added data on BRAFV600 mutation to summary of literature; Updated formatting; Removed the word ‘Covered’ from Covered Procedure Codes and Covered Diagnosis Codes in the Attachments list; Added CPT code 81210 for BRAFV600 mutation testing; Removed CPT codes 88342, 88363, AND 88365; added new references. Removed hyperlinks from all references.</td>
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