HIGHMARK Delaware
HEALTH OPTIONS

CLINICAL MEDICAL POLICY	
Policy Name:	Molecular Tumor Markers for Non-Small Cell Lung Cancer (NSCLC)
Policy Number:	MP-061-MD-DE
Responsible Department(s):	Medical Management
Provider Notice Date:	08/15/2019; 10/15/2018; 10/01/2017
Issue Date:	09/16/2019; 11/15/2018; 11/01/2017
Effective Date:	09/16/2019; 11/15/2018; 11/01/2017
Annual Approval Date:	07/16/2020
Revision Date:	07/16/2019; 09/11/2018
Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 11

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 (tyrosine kinase inhibitors). 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 NCSLC 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®).

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 know 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.
    - Plasma cell-free /circulating tumor DNA testing (‘liquid biopsy’)

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

Procedure Codes

CPT Codes	Description
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
81235	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)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 & 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by southern blot analysis)
81405	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)
81406	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)
81479	Unlisted molecular pathology procedure
84999	Unlisted chemistry procedure
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider

Noncovered Procedure Codes

CPT Codes	Description
86152	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood)
86153	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood), physician interpretation and report, when required

Diagnosis Codes

ICD-10 Codes	Description
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.11	Malignant neoplasm of upper lobe, right main bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or 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

C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung

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

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 (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP 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).

In September 2017, the NCCN guidelines on NSCLC made 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.

Update 2019

The 2018 NCCN guidelines for non-small cell lung cancer recommend that all patients with adenocarcinoma be tested for EGRF mutations, routine ALK gene arrangements, ROS1, BRAF, and PD-1. For 2019, NCCN revised the recommendation for PD-l1 IHC testing to category 1 from 2A in patients with metastatic NSCLC and advises consideration for other genetic alterations such as NTRK gene fusions, RET rearrangements, MET genetic alterations and ERBB2(HER2) mutations in order to identify rare oncogenic driver alterations for which effective therapy may be available.

In 2018, the CAP, IASLC and AMP 2013 guidelines were reviewed and reaffirmed by all three organizations. Additional recommendations were developed for NSCLC patients and include:

- Testing for ROS1 mutations is new and strongly recommended for all lung cancer patients regardless of clinical characteristics.
- Multiplexed genetic sequencing panels (e.g., NGS testing) are preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1, however, single gene assays are still acceptable. In addition to small mutations, NGS assays have the capability to detect fusions/rearrangements and copy number changes in the examined genes. NGS also enables the use of small specimens (e.g., fine needle aspirates) that are standard of care and help avoid the risks to the patient associated with obtaining surgical biopsies.
- When NGS is performed, several other genes are also recommended – BRAF, ERBB2, MET, RET, and KRAS. However, these genes are not essential when only single gene tests are performed. Note: BRAF had late-breaking early evidence, which we expect to mature to a stronger recommendation for inclusion as a single gene assay, as well, in the near future.
- Testing in relapse is required for EGFR (T790M), but not for ALK, as the differential sensitivities of second-line ALK inhibitors in the setting of specific acquired mutations in ALK have not yet sufficiently matured and are still investigational.
- Testing for EGFR T790M in relapse may be done by biopsy or cell-free circulating DNA. However, cell-free DNA is not appropriate for initial diagnosis at this time, unless a tissue or cytology sample cannot be obtained.
- Previous recommendations, otherwise, were largely reinforced, with some strengthening of evidence that has led to strengthening of the original recommendations. Most notable changes:
    - Inclusion of IHC for ALK as an alternative to FISH;

        - Inclusion of any cytology sample with adequate cancer content, as opposed to recommending cell blocks.
    - Opinion is expressed that samples should also be set aside for assays to predict response to immunotherapy (e.g., PD-L1 IHC), but no specific recommendations about how to predict this treatment response were made, and will be the subject of an upcoming guideline.

Driver mutations (somatic genome alterations) are the most useful biomarkers for predicting the efficacy of target therapy in advance NSCLC (Sequest and Neal, 2019). In NSCLC, matching a specific targeted drug to an identified drive mutation has resulted in improved therapeutic efficacy. Therefore, the need for driver mutations has become a part of the standard diagnostic work-up for NSCLC. Guidelines from the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association of Molecular Pathologists (AMP) recommend analysis of either the primary tumor or of a metastasis for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) for all patients whose tumor contains an element of adenocarcinoma, regardless of the clinical characteristics of the patient (Lindeman et al., 2013).

The majority of molecular diagnostics have been performed on solid tumor tissue biopsies. However, there are limitations to solid tumor biopsies including their limited availability, repeatability and high failure rates. Recent information identified as gaining popularity are the less invasive blood-based tests called 'liquid biopsies' for guiding therapeutic decisions in patients with lung cancer. This form of biopsy is based on cell-free ctDNA, and/or circulating tumor cells are present in the blood of patients with lung cancer. There are two FDA-approved tests: the cobas EGFR Mutation Test v2 which is blood-based companion diagnostic test for Tarceva (erlotinib). While the use of ctDNA is showing promise, there is lack of standardized methods for detection, processing, analysis, and statistic interpretation (Qin et al., 2018).

POLICY SOURCE(S)

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Policy History

Date	Activity
06/16/2017	Initial policy developed
09/26/2017	Updated operational guidelines
09/27/2017	QI/UM Committee approval
11/01/2017	Provider effective date
09/11/2018	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.
09/11/2018	QI/UM Committee review Approval
11/15/2018	Provider effective date
07/16/2019	Annual Review: Under Related Medical Policies on page 1, removed MP-071-MD-DE and replaced with MP-074-MD-PA; Under the Reference section all hyperlinks were deleted; added procedure code 0022U; Updated the Summary of Literature and references; added noncovered service for liquid biopsy, procedure codes 86152 & 86153, updated Operational Guidelines.
07/16/2019	QI/UM Committee review Approval
09/16/2019	Provider effective date