CLINICAL MEDICAL POLICY	
Policy Name:	Molecular Tumor Markers for Non-Small Cell Lung Cancer (NSCLC)
Policy Number:	MP-061-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	09/01/2024; 09/01/2023; 09/01/2022; 08/20/2021; 09/21/2020; 09/16/2019; 09/15/2018
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Next Annual Review:	06/2025
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Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 13

Policy History

Date	Activity
10/01/2024	Provider Effective date
08/07/2024	PARP Approval
07/17/2024	QI/UM Committee review
07/17/2024	Annual Review: No changes to clinical criteria. Updated the following CPT code Description language: 81404, 81405, and 81406 per AMA guidance. Updated 'Summary of Literature' and 'Reference Sources' sections.
10/01/2023	Provider Effective date
08/07/2023	PARP Approval
07/19/2023	QI/UM Committee review
07/19/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
10/01/2022	Provider Effective date
08/08/2022	PARP Approval
07/20/2022	QI/UM Committee review
07/20/2022	Annual Review: No changes to clinical criteria. Added TAG determination information. Updated 'Summary of Literature' and 'Reference Sources' sections.
09/20/2021	Provider Effective Date
08/10/2021	PARP Approval

06/16/2021	Annual Review: Added criteria for NTRK 1/2/3, METex14 skipping, RET rearrangement, liquid biopsy testing. Updated medical necessity statements. Added noted regarding review of additional NCCN criteria. Added procedure codes 0239U and 0242U, and removed procedure codes 86152 and 86153. Added CPT codes 88374, and 88377. Updated summary of literature and references.
06/16/2021	QI/UM Committee review
10/19/2020	Provider Effective date
08/11/2020	PARP approval
06/17/2020	QI/UM Committee review
06/17/2020	Annual Review; Clinical criteria unchanged, updated references, and summary of literature, added diagnosis codes C33, C34.00, C34.10, C34.30, C34.80, C34.90, C38.4, C45.0.
09/16/2019	Provider effective date
07/10/2019	PARP Approval
06/20/2019	QI/UM Committee review
06/20/2019	Annual Review: Under Related Medical Policies on page 1, removed MP-071-MD-PA 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.
06/16/2017	Initial policy developed

Disclaimer

Highmark Wholecare℠ 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 Wholecare℠ 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.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

Definitions

Prior Authorization Review Panel (PARP) – A panel of representatives from within the Pennsylvania Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

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. Highmark Wholecare utilizes the following NSCLC testing medical necessity criteria :
   A. EGFR testing may be considered medically necessary in individuals with nonsquamous NSCLC or in NSCLC NOS to predict treatment benefit from EGFR tyrosine kinase inhibitor (TKI) therapy. The presence of this mutation is predictive of treatment benefit from EGFR therapy.
   B. ALK gene fusion testing may be considered medically necessary 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 may be considered medically necessary for the selection of individuals who are candidates for TKI 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 rearrangement testing may be considered medically necessary for individuals with advanced or metastatic NSCLC to determinate the treatment of first-line therapy with ceritinib, crizotinib, or entrectinib, or subsequent therapy with lorlatinib or entrectinib.
   E. PD-L1 expression level testing may be considered medically necessary in determining treatment with 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®).
   H. NTRK 1/2/3 may be considered medically necessary in individuals with advanced or metastatic NSCLC to aid in determining first line therapy with larotrectinib or entrectinib.
   I. Testing for METex14 skipping mutations may be considered medically necessary in individuals with advanced or metastatic NSCLC in conjunction with treatment using capmatinib.
   J. Testing for RET rearrangements may be considered medically necessary in individuals with advanced or metastatic NSCLC to aid in determining treatment with selpercatinib(preferred), pralsetinib (preferred), cabonzantinib (category 2b), or vendetanib (category 2B).
   K. Liquid biopsies or cell-free/circulating tumor DNA testing may be considered medically necessary when ANY ONE of the following criteria are met:
      - The individual is not medically fit for invasive biopsy, OR
      - NSCLC has been pathologically confirmed, but there is insufficient material available for molecular testing; OR
      - The individual's tumor is progressing after at least one round of chemotherapy.
   L. Highmark Wholecare™ considers molecular testing medically necessary for advanced NSCLC when the tumor is wild-type (e.g., no mutation detected) EGFR, ALK, BRAF, METex14 skipping, RET, or ROS1 or with unknown status, and the individual has failed first-line systemic chemotherapy.

   Note: Additional indications from the National Comprehensive Cancer Network (NCCN) guidelines may be considered at the time of review.

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

3. When the molecular tumor markers are not considered medically necessary
    - Molecular tumor testing is considered not medically necessary for conditions other than those listed above because the scientific evidence has not been established. Any requests for molecular tumor testing approval that does not meet the guidelines listed above will require a review by a Medical Director on a case-by-case basis.
    - Plasma cell-free/circulating tumor DNA testing ('liquid biopsy') is considered not medically necessary for conditions other than those listed above because the scientific evidence has not been established.

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

5. Place of Service
   The proper 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 genetic provider (not employed by a genetic testing lab) prior to genetic testing for mutations. This service is necessary in order to inform patient about the benefits and limitations of specific genetic tests. Genetic testing for mutations requires documentation of medical necessity from at least one of the following providers who has evaluated the patient, and intends to see the patient after testing has been performed:
    - 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 of appropriate expertise or other obstetrical provider specializing in the care for the indication(s) for genetic testing

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.

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).

The use of the molecular tumor marking testing outside of listed FDA guidelines will require approval from a Medical Director on a case-by-case basis.

CMS

The Centers for Medicare and Medicaid Services (CMS) has published the following guidance:

- Local Coverage Determination (LCD) Biomarkers for Oncology (L35396)

The Pennsylvania Department of Human Services Technology Assessment Group (TAG) workgroup meets quarterly to discuss issues revolving around new technologies and technologies or services that were previously considered to be a program exception. During this meeting, decisions are made as to whether or not certain technologies will be covered and how they will be covered. TAG's decisions are as follow:

- Option #1: Approved - Will be added to the Fee Schedule
- Option #2: Approved as Medically Effective - Will require Program Exception
- Option #3: Approved with (or denied due to) Limited/Minimal Evidence of Effectiveness - Will require Program Exception
- Option #4: Denied - Experimental/Investigational

As of October 2014, the TAG workgroup assigned EGFR testing an Option # 1, specifically for CPT code 81235.

Summary of Literature

There is an estimated 1.8 million new cases of NSCLC worldwide diagnosed every year (Harris, 2017). 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). From 2015 to 2019, death rates decreased by about 5% per year in men and by 4% per year in women. Non-small cell lung carcinoma is the most common type of lung cancer and includes predominately adenocarcinomas and squamous cell carcinomas (NCI, 2022).

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

There has been great progress in lung cancer screening, minimally invasive techniques for diagnosis and treatment, advancements in radiation therapy, new targeted therapies, and new immunotherapies. According to the NCCN, patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer; 5-year survival rates range for 15% to 50%, depending on the biomarker (NCCN, 2023).

Several biomarkers have emerged as predictive markers for NSCLC. A predictive biomarker is indicative of therapeutic efficacy, because there is an interaction between the biomarker and therapy on patient outcome. The NCCN NSCLC Panel recommends testing for certain molecular and immune biomarkers in all appropriate patients with metastatic NSCLC to assess whether patients are eligible for targeted therapies or immunotherapies based on data showing improvement in overall survival for patients receiving targeted therapies or immunotherapies compared with traditional chemotherapy regimens. Predictive molecular biomarkers include ALK rearrangements, BRAF p.V600E point mutations, EGFR mutations, Kirsten RAt Sarcoma virus (KRAS) mutations, mesenchymal-epithelial transition factor exon 14 (METex14) skipping mutations, neurotrophic tyrosine receptor kinase 1/2/3 (NTRK1/2/3) gene fusions, rearranged during transfection (RET) rearrangements, and ROS proto-oncogene 1 (ROS1) gene rearrangements; PD-L1 expression is the predictive immune biomarker (NCCN, 2024).

- **ALK Gene Rearrangements** - Patients with ALK rearrangements are resistant to EGFR TKIs but have similar clinical characteristics to those with EGFR mutations, such as adenocarcinoma histology and being light or never smokers. The NCCN NSCLC Panel recommends testing for ALK rearrangements in patients with metastatic nonsquamous NSCLC based on data showing the efficacy of alectinib, brigatinib, ceritinib, crizotinib, or lorlatinib for ALK rearrangements and on the FDA approvals.
- **BRAF V600E Mutations –** This mutation occurs in 1% to 2% of patients with lung adenocarcinoma; it is the most common of the BRAF point mutations when considered across all tumor types. . Patients with BRAF p.V600E mutations are typically current or former smokers, whereas those with EGFR mutations or ALK rearrangements are typically nonsmokers. Testing for BRAF mutations is recommended in patients with metastatic nonsquamous NSCLC. Testing may be considered in patients with metastatic NSCLC squamous cell carcinoma because BRAF mutations also occur in squamous cell NSCLC, although at a lower rate than nonsquamous NSCLC. The NCCN NSCLC Panel recommends testing for BRAF mutations in patients with metastatic nonsquamous NSCLC based on data showing the efficacy of dabrafenib plus trametinib for patients with BRAF p.V600E mutations and on the FDA approval.
- **EGFR Mutations** - The NCCN NSCLC Panel recommends testing for EGFR mutations, including common and uncommon mutations, in eligible patients with metastatic NSCLC based on clinical

trial data. Molecular testing for EGFR mutations is also recommended for eligible patients with resectable stage IB to IIIA NSCLC to determine whether adjuvant therapy with osimertinib is an option. The NCCN Panel recommends that molecular testing be considered in all patients with metastatic NSCLC squamous cell carcinoma because these patients may also have actionable biomarkers, such as EGFR mutations, although at a lower incidence than those with metastatic NSCLC adenocarcinoma. The NCCN NSCLC Panel also recommends testing for EGFR mutations (category 1) and other biomarkers in patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of afatinib, dacomitinib, erlotinib, gefitinib, or osimertinib and on FDA approvals.

- **KRAS Mutations -** Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have KRAS mutations; KRAS is the most common mutation in this population. The NCCN NSCLC Panel recommends testing for KRAS mutations in eligible patients with metastatic NSCLC based on data showing the efficacy of sotorasib as a subsequent therapy option for patients with KRAS p.G12C mutations and on the FDA approval for sotorasib.
- **MET Genomic Alterations** - C-MET, the hepatocyte growth factor (HGF) receptor, is a tyrosine kinase receptor that is involved in cell survival and proliferation; oncogenic driver genomic alterations in MET include METex14 skipping mutations, MET gene copy number (GCN) gain or amplification, and MET protein overexpression. METex14 skipping mutations are more frequent in older women who are nonsmokers. The NCCN NSCLC Panel recommends testing for METex14 skipping mutations in eligible patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with METex14 skipping mutations and on the FDA approvals for capmatinib and tepotinib. The panel also decided that crizotinib or systemic therapy options (such as carboplatin plus [pemetrexed or paclitaxel]) are useful in certain circumstances.
- **NTRK1/2/3 Gene Fusions** - NTRK gene fusions encode tropomyosin receptor kinase (TRK) fusion proteins (eg, TRKA, TRKB, TRKC) that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma. It is estimated that NTRK1/2/3 fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers such as EGFR, ALK, or ROS1. The NCCN NSCLC Panel recommends NTRK1/2/3 gene fusion testing in patients with metastatic NSCLC based on clinical trial data showing the efficacy of larotrectinib and entrectinib for patients with NTRK gene fusion–positive disease and on FDA approvals; however, clinical data are limited in NSCLC to support this recommendation.
- **RET Rearrangements** - RET is a tyrosine kinase receptor that affects cell proliferation and differentiation. RET rearrangements occur in about 1% to 2% of patients with NSCLC and are more frequent in patients with adenocarcinoma histology. The NCCN NSCLC Panel recommends testing for RET rearrangements in eligible patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with RET rearrangements and on the FDA approvals for selpercatinib and pralsetinib. The NCCN Panel decided that selpercatinib or pralsetinib are preferred monotherapy options for patients with RET rearrangement-positive metastatic NSCLC; cabozantinib is useful in certain circumstances.
- **ROS1 Rearrangements** - It is estimated that ROS1 gene rearrangements occur in about 1% to 2% of patients with NSCLC. The NCCN NSCLC Panel recommends ROS1 testing in patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of crizotinib, ceritinib, and entrectinib for patients with ROS1 rearrangements. ROS1 testing can be considered in patients with metastatic squamous cell NSCLC because ROS1 rearrangements also occur in metastatic squamous cell NSCLC, although at a lower rate than nonsquamous NSCLC. The NCCN NSCLC Panel recommends crizotinib, entrectinib, or ceritinib as first-line monotherapy options for patients with ROS1-positive metastatic NSCLC based on clinical trial data.

- **PD-L1 Expression Levels** - Human ICI antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells. NCCN NSCLC Panel recommends IHC testing for PD-L1 expression (category 1) ideally before first-line treatment (if clinically feasible) in all patients with metastatic NSCLC to assess whether the ICI regimens are an option based on clinical data showing the efficacy of these regimens. Although it is not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether patients are candidates for PD-1 or PD-L1 inhibitors.
  (NCCN, 2023).

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);
- 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.

Additional CAP, IASLC & AMP 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 CAP, the IASLC, and the AMP recommend analysis of either the primary tumor or of a metastasis for EGFR and 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).

The American Society of Clinical Oncology (ASCO) gave the following new and revised recommendations in their 2017 update. Regarding first-line treatment for patients with non-squamous cell carcinoma or squamous cell carcinoma (without positive markers, eg, EGFR/ALK /ROS1), if the patient has high programmed death ligand 1 (PD-L1) expression, pembrolizumab should be used alone; if the patient has low PD-L1 expression, clinicians should offer standard chemotherapy. All other clinical scenarios follow 2015 recommendations. Regarding second-line treatment in patients who received first-line chemotherapy, without prior immune checkpoint therapy, if NSCLC tumor is positive for PD-L1 expression, clinicians should use single-agent nivolumab, pembrolizumab, or atezolizumab; if tumor has negative or unknown PD-L1 expression, clinicians should use nivolumab or atezolizumab (ASCO, 2017).

Lindeman, et al., largely reaffirmed their 2013 guidelines with updated recommendations to allow testing of cytology samples, require improved assay sensitivity, and recommend against the use of immunohistochemistry for EGFR testing. Key new recommendations include ROS1 testing for all adenocarcinoma patients; the inclusion of additional genes (ERBB2, MET, BRAF, KRAS, and RET) for laboratories that perform next-generation sequencing panels; immunohistochemistry as an alternative to fluorescence in situ hybridization for ALK and/or ROS1 testing; use of 5% sensitivity assays for EGFR T790M mutations in patients with secondary resistance to EGFR inhibitors; and the use of cell-free DNA to "rule in" targetable mutations when tissue is limited or hard to obtain.

Coding Requirements

Procedure Codes

CPT Code	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	KR AS (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 (eg, 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 (eg, 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 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81479	Unlisted molecular pathology procedure
84999	Unlisted chemistry procedure
88374	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure
88377	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; each multiplex probe stain procedure
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 1- 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements

Diagnosis Codes

ICD-10 Code	Description
C33	Malignant neoplasm of the trachea
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 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
C34.30	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 unspecified bronchus of 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
C38.4	Malignant neoplasm of pleura
C45.0	Mesothelioma of pleura

Noncovered Procedure Codes

CPT Code	Description
86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

Reference Sources

National Cancer Institute (NCI) Physician Data Query (PDQ). Lung Cancer Screening. May 13, 2022. Accessed on May 31, 2022.

Pennsylvania Department of Human Services. Technology Assessment Group (TAG) Coverage Decisions. Managed Care Operations Memorandum: MCS #12/2014-014. Genetic Code: EGRF. Decision: Option #1. Accessed on May 31, 2022.

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