STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer
LAB-011

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	1/1/2015
Revision Number:	5	**Last Rev Date:**	4/19/2024
Reviewed By:	Medicaid Medical Director	**Next Rev Date:**	4/18/2025
Approved By:	Medicaid Clinical Advisory Committee	**Approved Date:**	7/15/2022

Descriptive Narrative

Over half of patients with non-small cell lung cancer (NSCLC) present with advanced and, therefore, incurable disease. The identification of specific, targetable oncogenic "driver mutations" in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology. The National Comprehensive Cancer Network (NCCN) NSCLC Panel recommends testing 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.

Targeted therapies based on such knowledge have been developed, tested in clinical trials on populations with specific cancer types expressing the associated biomarker, and have received FDA approval.

NCCN guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of mutations. The guidelines do contain recommendations for specific genetic testing for individual cancers, based on situations where there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type.

The clinical validity of the panels as a whole is difficult to determine due to the many different mutations and the large number of potential cancers for which they can be used. Clinical validity would need to be reported for each specific mutation for a particular type of cancer. Since there are hundreds of different mutations included in the panels and dozens of different cancer types, evaluation of the individual clinical validity for each pairing is an area of ongoing research. A major concern with clinical validity is differentiating mutations that drive cancer growth from genetic variants that are not clinically important. It is expected that variants of uncertain significance will be very frequent with use of panels that include several hundred markers.

Tests for individual biomarkers may require prior authorization – see table below. CPT code 81445 contains all the biomarkers recommended in the NCCN guidelines Version 3.2022, except for PD-L1. Expression of this biomarker can be tested using code 88360.

Guidelines

The NCCN NSCLC Guideline panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-19, in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC.

TESTING RESULTS [ll, mm]

EGFR exon 19 deletion or L858R mutation positive	NSCL-20
EGFR S768I, L861Q, and/or G719X mutation positive	NSCL-23
EGFR exon 20 insertion mutation positive	NSCL-24
KRAS G12C mutation positive	NSCL-25
ALK rearrangement positive	NSCL-26
ROS1 rearrangement positive	NSCL-29
BRAF V600E mutation positive	NSCL-31
NTRK1/2/3 gene fusion positive	NSCL-32
METex14 skipping mutation positive	NSCL-33
RET rearrangement positive	NSCL-34
PD-L1 ≥50% and negative for actionable molecular biomarkers above	NSCL-35
PD-L1 ≥1%-49% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

[ll] If there is insufficient tissue to allow testing for all of EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Predictive, Prognostic, and Emerging Biomarkers

Several biomarkers have emerged as predictive and prognostic markers for NSCLC. A predictive biomarker is indicative of therapeutic efficacy because there is an interaction between the biomarker and therapy on patient outcome. A prognostic biomarker is indicative of patient survival independent of the treatment received because the biomarker is an indicator of the innate tumor behavior (KRAS). The 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. Biomarker testing is recommended in eligible patients with stage IV disease, including M1a, M1b, and M1c.

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.

Emerging predictive molecular biomarkers include ERBB2 (also known as HER2) mutations and high-level MET amplification. Targeted agents are available for patients with NSCLC who have ERBB2 mutations and high-level MET amplifications. However, there is less data to support using these agents and they may not be FDA approved for NSCLC; therefore, they are referred to as emerging biomarkers. Recently, the NCCN Panel deleted tumor mutational burden (TMB) as an emerging immune biomarker based on clinical trial data and other issues.

Criteria

Medically Necessary - 81445

Testing for advanced NSCLC using gene panels is considered medically necessary prior to initiating first-line therapy when **BOTH** of the following are met:

1. The panel contains, at minimum, the following genes (mutations, rearrangements, fusions, or amplifications): ALK, BRAF, EGFR, ERBB2 (HER2), KRAS, MET, NTRK, RET, and ROS1; **AND**
2. The entire gene panel contains between 5-50 genes.

Investigational (not covered) – 81455, 0037U

The following gene panels are considered investigational when testing for advanced NSCLC:

1. FoundationOne CDx (0037U), **OR**
2. Panels containing 51 or more genes (81455).

Large gene mutation panels, including (but not limited to) FoundationOne CDx and panels of 51 or more genes are considered investigational. The evidence is insufficient in determining that these multi-gene panels improve net health outcomes to include changes in clinical management.

Tests for individual biomarkers may require prior authorization. CPT code 81445 contains all of the biomarkers recommended in the NCCN guidelines Version 3.2022, except for PD-L1. Expression of this biomarker, PD-L1, can be tested using code 88360.

Coding

The following list of codes is provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS/CPT code is inappropriate.

HCPCS	Description
Covered with Prior Authorization	
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed**,** 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed (NTRK absent) (ROS1 absent).
Covered	
88360	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual.
Not Covered	
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed (NTRK absent) (ROS1 absent).
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden FoundationOne CDx™ (F1CDx); Foundation Medicine, Inc.

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual and as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage

decisions are made. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

EncoderPro Optum360.

Foundation One CDx for the intended use as a Broad Molecular Profiling Tool. Molecular Test Assessment. April 26, 2022. Hayes Review.

Fernandez-Rozadilla C. Simões AR. Lleonart ME.et al. Tumor profiling at the service of cancer therapy. Front Oncol. 2020.10:595613. doi:10.3389/fonc.2020.595613

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) FDA. Content current as of: 03/31/2022. https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

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Billing and Coding: Biomarkers for Oncology. Medicare Coverage Database. A52986. Revised January 30, 2022.

Survey Findings Summary: Understanding Provider Utilization of Cancer Biomarker Testing Across Cancers. Cancer Action Network. American Cancer Society. December 2021.

Wild C. Grössmann N. FoundationOne CDx: Genetic profiling of solid tumours. Rapid Assessment 014. Vienna, Austria: Ludwig Boltzmann Institute for Health Technology Assessment; 2019.

Overman MJ. Morse M. Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors. UpToDate. Last updated January 03, 2022.

Targeted Cancer Therapies. National Cancer Institute. National Institute of Health. Updated: April 27, 2022.

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History

Change Date	Changed By	Description of Change	Version

Signature

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Signature

Change Date	Changed By	Description of Change	Version
4/19/2024	CAC	Review of literature to include additional CPT codes, as appropriate. No changes.	5

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Change Date	Changed By	Description of Change	Version
1/19/2024	CAC	Annual review.	4

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Change Date	Changed By	Description of Change	Version
10/20/2023	CAC	Annual review.	3

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Change Date	Changed By	Description of Change	Version
7/21/2023	CAC	Annual review.	2

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Change Date	Changed By	Description of Change	Version
7/15/2022	CAC	Criteria implementation.	1

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