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

Iowa Medicaid Program	Prior Authorization	**Effective Date**	12/01/2015
Revision Number	6	**Last Reviewed**	4/18/2025
Reviewed By	Medicaid Medical Director	**Next Review**	4/17/2026
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.

Some clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with the presence of an EGFR mutation; however, these features should not be utilized in selecting patients for testing (per NCCN guidelines p. 100)

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

Initial testing for 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 individual is a candidate for targeted therapy that may be prescribed based on the panel test results.

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.

CPT	Description
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).

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

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Multiple Cancers, Including Cancer Syndromes – Gene Panel ACG: A-0790 (AC) Milliman Care Guidelines 27th Ed. Copyright 2023.

Oncology Companion Diagnostic Testing – FoundationOne CDx ACG: A-1055 (AC) Milliman Care Guidelines. Copyright 2023.

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

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Table of Pharmacogenetic Associations. US Food and Drug Administration. Content current as of : 10/26/2022. Accessed November 14, 2024

Biomarker Tests and Cancer Treatment. American Cancer Society. Copyright 2024.

Biomarkers for Oncology. Local Coverage Determination. CMS. LCD ID L35396. For services performed on or after 12/13/2020.

Oncology Companion Diagnostic Testing – FoundationOne CDx. ACG: A-1055 (AC) Milliman Care Guidelines. 27th Ed. Copyright 2023. Accessed 12/12/2024.

Lilenbaum RC. Overview of the initial treatment of advanced non-small cell lung cancer. UpToDate. Topic last updated: June 21, 2024. Accessed November 14, 2024.

Neal JW. Personalized, genotype-directed therapy for advanced non-sall cell lung cancer. UpToDate. Topic last updated: October 4, 2024. Accessed November 11, 2024.
Targeted Cancer Therapies. National Cancer Institute. National Institute of Health. Updated: April 27, 2022.

Iowa Code 514c.36 Biomarker Testing- coverage legislation. Signed July 1, 2024.

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
[mm/dd/yyyy]	CAC		[#]
Signature			

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]	CAC		[#]
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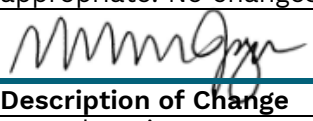
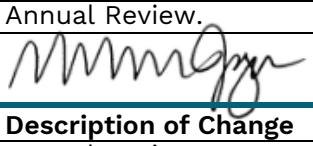
Change Date	Changed By	Description of Change	Version
04/18/2025	CAC	Annual Review. Updated Guidelines, Criteria, Coding and References sections.	6
Signature William (Bill) Jagiello, DO			

Change Date	Changed By	Description of Change	Version
04/19/2024	CAC	Review of literature to include additional CPT codes, as appropriate. No changes.	5
Signature William (Bill) Jagiello, DO			

Change Date	Changed By	Description of Change	Version
01/19/2024	CAC	Annual Review.	4
Signature William (Bill) Jagiello, DO			

Change Date	Changed By	Description of Change	Version
10/20/2023	CAC	Annual Review.	3
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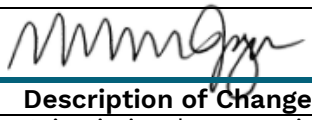
Change Date	Changed By	Description of Change	Version
07/21/2023	CAC	Annual review.	2
Signature William (Bill) Jagiello, DO			

Change Date	Changed By	Description of Change	Version
07/15/2022	CAC	Criteria implementation.	1
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CAC = Medicaid Clinical Advisory Committee