

# Local Coverage Determination (LCD): MoIDX-CDD: NSCLC, Comprehensive Genomic Profile Testing (L36143)

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## Contractor Information

<b>Contractor Name</b>	<b>Contract Type</b>	<b>Contract Number</b>	<b>Jurisdiction</b>	<b>State(s)</b>
<a href="#">Palmetto GBA</a>	A and B and HHH	MAC 11201 - MAC A	J - M	South Carolina
<a href="#">Palmetto GBA</a>	A and B and HHH	MAC 11202 - MAC B	J - M	South Carolina
<a href="#">Palmetto GBA</a>	A and B and HHH	MAC 11301 - MAC A	J - M	Virginia
<a href="#">Palmetto GBA</a>	A and B and HHH	MAC 11302 - MAC B	J - M	Virginia
<a href="#">Palmetto GBA</a>	A and B and HHH	MAC 11401 - MAC A	J - M	West Virginia
<a href="#">Palmetto GBA</a>	A and B and HHH	MAC 11402 - MAC B	J - M	West Virginia
<a href="#">Palmetto GBA</a>	A and B and HHH	MAC 11501 - MAC A	J - M	North Carolina
<a href="#">Palmetto GBA</a>	A and B and HHH	MAC 11502 - MAC B	J - M	North Carolina

[Back to Top](#)

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## LCD Information

### Document Information

LCD ID  
L36143

Original Effective Date  
For services performed on or after 10/01/2015

LCD Title  
MoIDX-CDD: NSCLC, Comprehensive Genomic Profile Testing

Revision Effective Date  
For services performed on or after 12/22/2016

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CMS National Coverage Policy Title XVIII of the Social Security Act, §1862(a)(1)(A) allows coverage and payment for only those services that are considered to be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member

Title XVIII of the Social Security Act, §1862(a)(1)(D) items and services related to research and experimentation

Title XVIII of the Social Security Act, §1833(e), prohibits Medicare payment for any claim which lack the necessary information to process the claim.

42 CFR 410.32(a) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions

42CFR411.15(k)(1) Particular services excluded from coverage

CMS On-Line Manual, Publication 100-08, Medicare Program Integrity Manual, Chapter 3, §3.4.1.3, diagnosis code requirements

Coverage Guidance

### **Coverage Indications, Limitations, and/or Medical Necessity**

This policy provides coverage for comprehensive somatic genomic profiling on tumor tissue-only (hereafter called CGP) for patients with metastatic non-small cell lung cancer (NSCLC) who are lifetime non-smokers, former light smokers or smokers who have not been tested for genomic alterations or who have tested negative for epidermal growth factor receptor (EGFR) mutations, EML4-ALK rearrangements, or ROS1 rearrangements. Alterations detected by CGP, if positive, may allow individuals to be treated with targeted and/or immunotherapy for which they were previously ineligible. At the current time, CGP for germline (i.e. inheritable) mutations is not a Medicare benefit.

### **Background**

It is estimated that more than 220,000 new cases of lung cancer will be diagnosed in the United States (US) this year. This represents roughly 13% of all new cancer diagnoses, and 27% of cancer deaths. Sadly, the estimated 5-year survival rate for all lung cancer patients is 17%, and only 4% for patients with metastatic disease.

The pathophysiological development of lung cancer is complicated, with several known genomic alterations found individually or in combination in many patients. These alterations may be due to toxic exposure or underlying genetic factors, and not all alterations have the same impact on disease development or prognosis. Some alterations appear to be integral to the transformation and ongoing growth of the tumor (driver mutations). Among the best studied in this class are point alterations and indels in EGFR and EML4-ALK translocations. EGFR mutated NSCLC is found in up to 15% of all lung cancers in the US. These mutations convey a more favorable prognosis and allow treatment with oral EGFR inhibitors such as erlotinib, gefitinib, or afatinib. Similarly, translocations of ALK and EML4 or other less common fusion partners occur in approximately 4% of all NSCLC patients and permit treatment with oral ALK-targeted inhibitors such as crizotinib and ceritinib.

The majority of NSCLC cases are diagnosed in patients with a smoking history. Across the spectrum of smoking history, lung cancers of different types develop albeit in varying proportions. Sequencing of tumor specimens in never-smokers has shown a higher mutation frequency of EGFR than in smokers, with some non-smoking ethnic groups such as Asian women having a much higher mutation frequency than their Caucasian counterparts. Similar results have been shown in patients in whom ALK translocations are detected. For example, in one study involving never-smokers or light smokers with adenocarcinoma of the lung, 22% of patients' tumors harbored an ALK. When EGFR mutation carriers were excluded, 33% of patients' tumors had an ALK translocation.

Currently, a variety of different techniques are used to test for these genomic alterations in tumor specimens including three FDA cleared/approved CDx tests for NSCLC to determine if a patient is a candidate for targeted therapy. For EGFR, there is the Cobas ® EGFR Mutation Test for erlotinib and Therascreen EGFR RCQ PCR Kit for

Printed on 1/26/2017. Page 2 of 7

afatinib. For ALK, there is the Vysis ALK Break Apart FISH Probe Kit for crizotinib. These tests look at specific regions in the target gene to determine if the genomic alteration of interest is present.

In addition to these FDA-approved CDx test, there are a variety of laboratory-developed tests (LDTs) that are used to identify EGFR mutations and ALK translocations. These include bidirectional Sanger sequencing, direct DNA sequencing, hybridization sequencing, pyrosequencing and sequencing by denaturation to name a few. Some of these LDTs provide more extensive genetic analysis than their FDA-approved counterparts, but there are few head-to-head comparison studies demonstrating greater diagnostic accuracy or clinical utility of the various approaches.

For various reasons, CDx or LDT sequencing techniques may miss deleterious EGFR mutations and ALK translocations. For example, alterations may occur outside the sequenced region or involve complex alterations (e.g. insertions or deletions (indels), copy number alterations, or translocations) that are not detectable by the specific test. Newer techniques such as massively parallel sequencing, also known as next generation sequencing (NGS), offer the possibility of not only increased analytical sensitivity but also the ability to detect a broader range of genomic alterations than existing CDx and LDT techniques.

In a recent study by Drilon, NSCLC patients who tested negative for alterations in various target genes (including EGFR and ALK) were studied using CGP. Despite robust non-NGS (and CGP) testing using multiple techniques, CGP testing identified EGFR mutations in 7% more patients than had been identified by prior combined methodologies, and 6% more ALK translocations than by previous FISH analysis. Although some of the EGFR mutated malignancies found by NGS are less likely to respond to available EGFR tyrosine kinase inhibitors (TKIs) (e.g. exon 20 insertions), others such as complex double mutations and exon 18 mutations (which are typically undetectable with so-called "hotspot" panels), are likely to benefit from targeted therapy. CGP analysis was equally compelling for ALK translocations. In two patients, where FISH analysis was clearly negative, translocations were identified using CGP. These patients would likely benefit from treatment with crizotinib.

Although the study population is small, the significant number of potentially actionable genomic alterations that were missed by non-NGS methodologies is compelling, and demonstrates that CGP can identify a group of non-small cell lung cancer patients who are likely to benefit from targeted therapy. Since this pilot study, additional studies have indeed confirmed non-CGP approaches miss an estimated 17% and 30% of EGFR mutations and ALK translocations, respectively.

### **Comprehensive Genomic Profiling (CGP) Test Description:**

CGP analysis is defined as a single test using tumor tissue only (i.e., not matched tumor and normal) that does not distinguish between somatic and germline alterations and can detect the following classes of alterations:

1. Base pair substitutions (including single nucleotide variants (SNVs))
2. Insertions and deletions (Indels; up to 70 bp)
3. Copy number variations (CNVs; including both amplifications (ploidy < 4 with copy number = 8) and homozygous deletions (ploidy < 4 with copy number = 0))
4. Translocations

Other non-NGS testing platforms may be considered if they can similarly detect all four classes of alterations with comparable test performance as CGP.

### **MolDX CGP Analysis Coverage**

CGP analysis is covered only when the following conditions are met:

- Patient has been diagnosed with advanced (Stage IIIB or IV) NSCLC; **and**
- Patient has not been tested for genomic alterations **OR** previously tested negative for EGFR mutations, ALK rearrangements, or ROS1 rearrangements through non-CGP methods; **and**
- Testing is performed by a lab that satisfies Palmetto GBA's Analytical Performance Specifications for Comprehensive Genomic Profiling (M00118, v1). Requires submission of specifications by MolDX or entity approved by MolDX.

This contractor recognizes that evidence for clinical utility for CGP in advanced NSCLC patients is limited at the current time. However, this contractor believes the clinical studies currently in progress will identify a number of patients who will test positive for an actionable *EGFR*, *ALK* or *ROS1* mutations or identify mutations despite prior negative test results in patients who will benefit from targeted therapy. In addition, CGP testing is likely to identify patients who will need referral/genetic counseling for hereditary cancer risk assessment when an *APC*, *MYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *POLE*, *POLD1*, *BMP1A*, *PTEN* or *STK11* alteration is identified in the test panel. The identification of other pathogenic genes, although not meeting Medicare's reasonable and necessary criteria for coverage, will likely direct patients into clinical trials. Continued coverage for CGP test for NSCLC will be dependent on annual review of publications and/or presentations of clinical utility data demonstrating CGP for NSCLC improves patient outcomes and/or directs or changes selection of therapies to improve patient outcomes.

[Back to Top](#)

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## Coding Information

### Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

### Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

### CPT/HCPCS Codes

**Group 1 Paragraph:** N/A

### Group 1 Codes:

- 81445 TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 5-50 GENES (EG, 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
- 81455 TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN OR HEMATOLYMPHOID NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 51 OR GREATER GENES (EG, 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
- 81479 UNLISTED MOLECULAR PATHOLOGY PROCEDURE

### ICD-10 Codes that Support Medical Necessity

**Group 1 Paragraph:** N/A

### Group 1 Codes:

ICD-10 Codes	Description
C33	Malignant neoplasm of 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

ICD-10 Codes	Description
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right 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 of unspecified bronchus and 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

ICD-10 Codes that DO NOT Support Medical Necessity N/A

ICD-10 Additional Information

[Back to Top](#)

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## General Information

Associated Information

### **Documentation Requirements**

The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. (See "Coverage Indications, Limitations, and/or Medical Necessity") This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available to the JM MAC upon request.

Sources of Information and Basis for Decision

### **References**

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[Back to Top](#)

## Revision History Information

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
12/22/2016	R6	Policy revision; removed registry requirements.	<ul style="list-style-type: none"> <li>Other (Policy revision; removed registry requirements.)</li> </ul>
09/29/2016	R5	Expanded coverage to include smokers with NSCLC and added clarified the CDD registry criteria. Under " <b>Sources of Information and Basis for Decision</b> ", added reference #16 and #17.	<ul style="list-style-type: none"> <li>Other (Expanded coverage to include smokers with NSCLC and added clarified the CDD registry criteria. Under "<b>Sources of Information and Basis for Decision</b>", added reference #16 and #17.)</li> </ul>
11/27/2015	R4	Added annual review date, 10/1/2015, to Annual Review Date field Corrected typographical error from the equal (=) symbol to the less than or equal to (≤) symbol for light smokers	<ul style="list-style-type: none"> <li>Other (Added annual review date, 10/1/2015, to Annual Review Date field Corrected typographical error from the equal (=) symbol to the less than or equal to (≤) symbol for light smokers)</li> </ul>
11/27/2015	R3	added "-CDD" after the word MolDX in the title	<ul style="list-style-type: none"> <li>Other (added "-CDD" after the word MolDX in the title)</li> </ul>
10/01/2015	R2	Per CMS Internet-Only Manual, Pub 100-08, Medicare Program Integrity Manual, Chapter 13, §13.1.3 LCDs consist of only "reasonable and necessary" information. All bill type and revenue codes have been removed.	<ul style="list-style-type: none"> <li>Other (Bill type and/or revenue code removal)</li> </ul>
10/01/2015	R1	Added Bill Type codes, ICD-10 codes and references that were left off ICD-10 version in error.	<ul style="list-style-type: none"> <li>Typographical Error</li> </ul>

[Back to Top](#)

## Associated Documents

Attachments N/A

Related Local Coverage Documents N/A

Related National Coverage Documents N/A

Public Version(s) Updated on 12/16/2016 with effective dates 12/22/2016 - N/A [Updated on 09/23/2016 with effective dates 09/29/2016 - 12/21/2016](#) [Updated on 04/14/2016 with effective dates 11/27/2015 - 09/28/2016](#) [Updated on 11/20/2015 with effective dates 11/27/2015 - N/A](#) Some older versions have been archived. Please visit the [MCD Archive Site](#) to retrieve them. [Back to Top](#)

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## **Keywords**

N/A Read the [LCD Disclaimer](#) [Back to Top](#)