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

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Palmetto GBA	A and B and HHH MAC	11201 - MAC A	J - M	South Carolina
Palmetto GBA	A and B and HHH MAC	11202 - MAC B	J - M	South Carolina
Palmetto GBA	A and B and HHH MAC	11301 - MAC A	J - M	Virginia
Palmetto GBA	A and B and HHH MAC	11302 - MAC B	J - M	Virginia
Palmetto GBA	A and B and HHH MAC	11401 - MAC A	J - M	West Virginia
Palmetto GBA	A and B and HHH MAC	11402 - MAC B	J - M	West Virginia
Palmetto GBA	A and B and HHH MAC	11501 - MAC A	J - M	North Carolina
Palmetto GBA	A and B and HHH MAC	11502 - MAC B	J - M	North Carolina

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LCD Information

Document Information

LCD ID
L36143

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

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

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

Revision Effective Date
For services performed on or after 09/29/2016

Revision Ending Date
N/A

Retirement Date
N/A

Notice Period Start Date
N/A

Notice Period End Date
N/A

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 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 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).

Palmetto GBA expects participating laboratories to:

- Demonstrate compliance with Palmetto GBA’s Analytical Performance Specifications for Comprehensive Genomic Profiling criteria (M00100, v1) in one of two ways:
    - Submit AV validation data directly to Palmetto GBA, or
    - Submit AV validation data to Palmetto GBA approved registry that will report compliance to Palmetto GBA.
- Collect CGP test and patient specific information in the MolDX approved registry that meets the following characteristics:
    - National in scope and open to any lab, (commercial or academic), and any provider location (academic, community);
    - Independent of the participating laboratory (commercial or academic);
    - Governed by a well-designed protocol listed on clinicaltrials.gov with national cross-institution leadership, patient consent, Institutional Review Board (IRB) approval, end points, and regular reporting;
    - Requires and verifies that CGP testing is essentially equivalent to MolDX Analytical Performance Specifications for Comprehensive Genomic Profiling AND has demonstrable plans to maintain compliance to both MolDX and other

published standards;

- Will collect detailed genomic information as detailed by the registy– including raw (FASTQ or BAM) data and variant call data in connection with clinical outcomes and report these to the registry in a timely fashion;
- Will compare CGP identified mutations in the EGFR, ROS1 and ALK regions to companion diagnostic tools (where exist) on a subset of patients to determine concordance;
- Organization overseeing the registry or essential partners to that organization cannot have a history of data siloing (e.g. not sharing data with competitors) or history of requiring physician-groups purchase or lease any propriety software;
- Registry organization has to have shown a strong commitment and effort to work with national organizations committed to data sharing (i.e. Genetics Data Commons, NCI, Vice President Biden's Moonshot initiative, etc.);
- Registry will allow open, non-commercial research access to the database (with appropriate curation), and will allow equal access to commercial groups;
- Non-profit registry organization is preferred;

- Registry to report to Palmetto GBA every six months the following:
  - Number of patients enrolled in registry
  - Biomarker prevalence in registry patients
  - Treatments and time to progression in patients with a given biomarker per line of therapy for at least 2-3 lines of therapy
  - Overall survival of patients by biomarker status and treatment profile
  - Concordance analysis of biomarker testing results between CGP and a FDA approved companion diagnostic test (where one exists for a given biomarker)
- Registry will assure publication of test results and clinical findings on a regular basis

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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:

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Description Group 1 ICD-10 Codes that Support Medical Necessity radio button
Search Group 1 ICD-10 Codes that Support Medical Necessity Submit button SEARCH GROUP **Search Group 1**
ICD-10 Codes that Support Medical Necessity Clear button CLEAR SEARCH

ICD-10 CODE	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
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

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ICD-10 Codes that DO NOT Support Medical Necessity

Additional ICD-10 Information

N/A

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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 J11 MAC upon request.

Sources of Information and Basis for Decision
References

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
09/29/2016	R5	Expanded coverage to include smokers with NSCLC and added clarified the CDD registry criteria. Under "**Sources of Information and Basis for Decision"**, added reference #16 and #17.	• Other
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	• 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)
11/27/2015	R3	added "-CDD" after the word MolDX in the title	• Other (added "-CDD" after the word MolDX in the title)
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.	• Other (Bill type and/or revenue code removal)
10/01/2015	R1	Added Bill Type codes, ICD-10 codes and references that were left off ICD-10 version in error.	• Typographical Error

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Associated Documents

Attachments

N/A

Related Local Coverage Documents

N/A

Related National Coverage Documents

N/A

Public Version(s)

Updated on 09/23/2016 with effective dates 09/29/2016 - N/A
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
Updated on 06/03/2015 with effective dates 10/01/2015 - 11/26/2015
Updated on 05/18/2015 with effective dates 10/01/2015 - N/A
Updated on 05/14/2015 with effective dates 10/01/2015 - N/A

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Keywords

N/A

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