Local Coverage Determination (LCD):
MolDX: Next-Generation Sequencing for Solid Tumors (L38119)

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Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
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Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
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Noridian Healthcare Solutions, LLC	A and B MAC	01911 - MAC A	J - E	American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands

LCD Information

Document Information

LCD ID **Original Effective Date**

L38119

For services performed on or after 05/17/2020

LCD Title
MolDX: Next-Generation Sequencing for Solid Tumors

Revision Effective Date
N/A

Proposed LCD in Comment Period
N/A

Revision Ending Date
N/A

Source Proposed LCD
DL38119

Retirement Date
N/A

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Notice Period Start Date
04/02/2020

Notice Period End Date
05/16/2020

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CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

CMS Internet-Only Manual, Pub 100-03, Medicare National Coverage Determinations Manual, Chapter 1, Part 2, §90.2 Next-Generation Sequencing (NGS) for Patients with Advanced Cancer.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This policy describes and clarifies coverage for Lab-Developed Tests (LDTs), FDA-cleared, and FDA-approved clinical laboratory tests utilizing Next-Generation Sequencing (NGS) in cancer as allowable under the National Coverage Determination (NCD) 90.2, under section D describing Medicare Administrative Contractor (MAC) discretion for coverage. This policy's scope is specific for solid tumor testing, and is exclusive of hematologic malignancies, circulating tumor DNA testing (ctDNA), and other cancer-related uses of NGS, such as germline testing in/for patients with cancer.

Summary of Evidence

Summary of Evidence

NGS testing in solid tumors is becoming a routine component of the diagnostic process[1]; the results can uncover the genomic mechanisms of cancer that have predictive, diagnostic, and prognostic utility to the patient and are used to better their management[2]. Understanding the mechanisms of disease and targeting treatment based on those aberrant processes (i.e., targeted therapies for biomarkers) has improved patient outcomes in many tumor types and is the basis of Precision Medicine[3]. Capturing mutations and other relevant genetic/genomic information is standard of care for determining clinical care for many tumor types, including the most common, such as melanoma, lung, colorectal, and breast carcinoma[4-7]. NGS adds the ability to capture abundant genomic data both efficiently, and relatively cheaply, and its use is showing to improve patient outcomes although studies in this regard are ongoing[8]. The established CMS National Coverage policy NCD 90.2 confirms these tests to be both reasonable and necessary in Medicare beneficiaries.

Professional Society Clinical Practice Guidelines

Guidelines for validating clinical NGS tests for use in cancer have been published in a joint effort by the Association for Molecular Pathology and the College of American Pathologists [9]. Guidelines for employing bioinformatics pipelines for NGS testing have also been published by these groups[10], as well as guidelines for interpreting somatic variants in these panels (these same groups in collaboration with the American Society of Clinical Oncology)[11].

Guidelines from several societies currently suggest or prefer the use of NGS over other methods for lung cancer[12, 13] and colorectal cancer[14, 15].

Additionally, societal guidelines recommend genetic testing for other tumor types that can be identified by NGS, such as melanoma, thyroid, brain, and ovarian cancers, among others[7, 16-20].

Test Description

NGS is not a specific test but a sequencing methodology utilized to capture genomic information. Unlike Sanger sequencing (the prior standard technology) that typically provides sequence information for a single DNA strand/molecule, NGS allows for massively parallel sequencing of millions of DNA molecules concurrently[21, 22]. This allows for capturing many relevant genomic targets simultaneously, usually by utilizing capture technologies such as by PCR amplification or hybrid capture. As such, NGS tests for use in cancer are often comprised of gene panels whose content is either relevant to a specific tumor type or condition, or a larger panel of genes that can be used for multiple tumor types.

NGS tests can vary significantly for many reasons. While NGS defines a broad methodology for massively parallel sequencing, different technologies that have different strengths, weaknesses, and technical limitations or liabilities are available[23]. The most common sequencing platforms in clinical use today are from Illumina and Thermo Fisher. While both sequence by synthesis similar to Sanger sequencing, these platforms utilize different chemistries, signal amplification, and detection methods. Gene panels can include only the portions of genes that contain the most critical clinically-relevant information, or be comprehensive, containing entire exonic gene regions (coding regions), introns (non-coding regions), and even sequence RNA for detecting gene fusions. Downstream from the pre-analytic processes mentioned above, the bioinformatics used to process and assess the resultant sequencing reads and identify variants/mutations can yield different results based on the software used and what variant types of variants the test is attempting to detect. These software tools must take the resultant sequencing file (generally starting with the FASTQ format), align all possible sequences with a reference genome (BAM/SAM), and identify variants from the reference (typically a VCF file)[10]. Once such variants are identified, they must be assessed for validity and subsequently for their clinical relevance. The types of genomic information reported can vary, as tests can uncover a myriad of genomic alterations such as single nucleotide variants (SNVs), Insertions/Deletions (INDELs), Copy Number Alterations (CNAs; these can be simply amplifications at a single locus or chromosomal gains and losses), and gene fusions/translocations. The resultant information can also be used to calculate additional relevant information, such as Tumor Mutation Burden (TMB), or the presence of microsatellite instability (MSI). All of these variant classes have demonstrated clinical utility. As such, NGS testing in cancer comprises a large heterogeneous group of assays that are substantially different from each other. Additionally, NGS testing is highly complex and requires expertise from handling the specimen, to running complex equipment, to understanding the required bioinformatics, to interpreting the findings and creating an actionable medical report.

Two types of tests are considered for coverage, “Hot-spot” tests and comprehensive genomic profile tests (CGP). The definition of these terms, in addition to appropriate coding information is located in Coverage Articles associated with this LCD. These tests can detect any combination of the previously described variant types, but in general, Hot-spot tests are limited to SNVs and small INDELs, whereas CGPs can detect those variants in addition to CNAs, larger

INDELs, gene fusions/translocations, and be used to calculate MSI status and TMB.

Analytical Validity and Clinical Utility

Because of the number of variables described above, additional work must be performed to assess if any given test is both reasonable and necessary for Medicare beneficiaries and to ensure that Medicare claims are properly understood and executed. MolDX has instituted a process for completing a Technical Assessment (TA) that ensures that tests are appropriate for their indications and are properly validated according to published guidelines described above (when applicable). Specifically, in order to understand if a test is both reasonable and necessary, it must be delineated if a test has the properly-validated technology, variant types, gene and variant coverage, and bioinformatics capability to deliver a clinically useful result for the Medicare beneficiary, given their diagnosis.

Labs seeking coverage for LDTs, FDA-cleared, or FDA-approved tests that are not nationally covered utilizing NGS in cancer must submit documentation to allow MolDX to complete a TA. Forms to complete the process are available on the MolDX website. Tests that are currently covered by Palmetto GBA are not exempt from this process. Tests that are currently covered and have not undergone a TA by MolDX will be non-covered unless complete documents to perform a TA are submitted in a timely manner described below.

Criteria for Coverage

All the following must be present for coverage eligibility:

- As per NCD 90.2, this test is reasonable and necessary when:
    - the patient has either:
        - Recurrent cancer
        - Relapsed cancer
        - Refractory cancer
        - Metastatic cancer
        - Advanced cancer (stages III or IV)
    - AND has not been previously tested by the same test for the same genetic content
    - AND is seeking further treatment
- The test has satisfactorily completed a TA by MolDX for the stated indications of the test
- The assay performed includes *at least* the minimum genes and genomic positions required for the identification of clinically relevant FDA-approved therapies with a companion diagnostic biomarker as well as other biomarkers known to be necessary for clinical decision making for its intended use that can be reasonably detected by the test. Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in associated documents such as the MolDX TA forms.

Situations in which Test should not be used or coverage is denied:

The test in question will be non-covered if:

- It does not fulfill all the criteria set forth in the NCD90.2 as stated above
- Another CGP test was performed on the same tumor specimen (specimen obtained on the same date of service)
- A Technical Assessment is not completed satisfactorily by MolDX for new tests
- For tests that are currently covered but a TA submission has not been made, providers must submit complete TA materials by February 10th, 2020 or coverage will be denied

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality: Strong/variable depending on biomarker and specific test
Strength: Strong/variable depending on biomarker and specific test
Weight: Strong/variable depending on biomarker and specific test

Given the abundant literature on genetic and genomic testing in cancer diagnosis and care, this contractor feels strongly that NGS methodology for testing is appropriate for use in Medicare Beneficiaries. However, given the variability for what information tests can provide, additional information must be submitted by providers to ensure the contractor A) understands what test is being performed; B) Why it is being performed; C) If the test is both necessary and reasonable for cancer care for its intended use.

General Information

Associated Information

NA

Sources of Information

NA

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Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A57901 - Billing and Coding: MolDX: Next-Generation Sequencing for Solid Tumors
A57904 - Response to Comments: MolDX: Next-Generation Sequencing for Solid Tumors
LCD(s)
DL38119 - MolDX: Next-Generation Sequencing for Solid Tumors

Related National Coverage Documents

N/A

Public Version(s)

Updated on 03/26/2020 with effective dates 05/17/2020 - N/A

Keywords

N/A