LCD - MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L39232)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
Noridian Healthcare Solutions, LLC	A and B MAC	02101 - MAC A	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02102 - MAC B	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02202 - MAC B	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02301 - MAC A	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02302 - MAC B	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02401 - MAC A	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	02402 - MAC B	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	03101 - MAC A	J - F	Arizona
Noridian Healthcare Solutions, LLC	A and B MAC	03102 - MAC B	J - F	Arizona
Noridian Healthcare Solutions, LLC	A and B MAC	03201 - MAC A	J - F	Montana
Noridian Healthcare Solutions, LLC	A and B MAC	03202 - MAC B	J - F	Montana
Noridian Healthcare Solutions, LLC	A and B MAC	03301 - MAC A	J - F	North Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03302 - MAC B	J - F	North Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03401 - MAC A	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03402 - MAC B	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03501 - MAC A	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03502 - MAC B	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03601 - MAC A	J - F	Wyoming
Noridian Healthcare Solutions, LLC	A and B MAC	03602 - MAC B	J - F	Wyoming

LCD Information

Document Information

LCD ID

L39232

LCD Title

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

MolDX: Plasma-Based Genomic Profiling in Solid Tumors

Proposed LCD in Comment Period
N/A

Source Proposed LCD
DL39232

Original Effective Date
For services performed on or after 12/26/2022

Revision Effective Date
N/A

Revision Ending Date
N/A

Retirement Date
N/A

Notice Period Start Date
11/10/2022

Notice Period End Date
12/25/2022

Issue

Issue Description

This LCD outlines limited coverage for this service with specific details under Coverage Indications, Limitations and/or Medical Necessity.

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.

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

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.

CMS Internet-Only Manual, Pub. 100-02, Medicare Benefit Policy Manual, Chapter 15, §80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests, §80.1.1 Certification Changes.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This is a limited coverage policy for next-generation sequencing (NGS) assays performed on solid tumor cell-free deoxyribonucleic acid (DNA) in plasma, from here on called "liquid biopsies."

Criteria for Coverage

Guardant360® is covered only when **all** of the following conditions are met:

- Patient has been diagnosed with a recurrent, relapsed, refractory, metastatic, or advanced solid tumor that did not originate from the central nervous system. Patients who would meet all of the indications on the Food and Drug Administration (FDA) label for larotrectinib if they are found to have a neurotrophic receptor tyrosine kinase (NTRK) mutation may be considered to have advanced cancer, **and**
- Patient has not previously been tested with the Guardant360® test for the same genetic content. For a patient who has been tested previously using Guardant360® for cancer, that patient may not be tested again unless there is clinical evidence that the cancer has evolved wherein testing would be performed for different genetic content. Specifically, in patients with previously tested cancer, who have evidence of new malignant growth despite response to a prior targeted therapy, that growth may be considered to be sufficiently genetically different to require additional genetic testing, **and**
- Patient is untreated for the cancer being tested, or the patient is not responding to treatment (e.g., progression or new lesions on treatment), **and**
- The patient has decided to seek further cancer treatment with the following conditions:
    - The patient is a candidate for further treatment with a drug that is either FDA-approved for that patient's cancer, or has a National Comprehensive Cancer Network (NCCN) 1 or NCCN 2A recommendation for that patient's cancer, **and**
    - The FDA-approved indication or NCCN recommendation is based upon information about the presence or absence of a genetic biomarker tested for in the Guardant360® assay, **and**
- Tissue-based, comprehensive genomic profiling (CGP) is infeasible (e.g., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated) **or** specifically in NSLC Tissue-based CGP has shown no actionable mutations.

If no alteration is detected by Guardant360® or if circulating tumor deoxyribonucleic acid (ctDNA) is insufficient/not detected, tissue-based genotyping should be considered.

Other liquid biopsies will be covered for the same indications if they display similar performance in their intended used applications to Guardant360®.

A wide array of cancer treatments have developed ranging from surgery to medications. One of the newer approaches to the medical treatment of cancer has been to use drugs based on genetic features of a malignancy. While many patients will not benefit from genetic testing to select treatment, for those whose cancers have select biomarkers, the treatment of choice often includes therapy targeting that specific biomarker or therapy being avoided because of a biomarker.[1-13]

In spite of the importance of actionable biomarker identification in cancer, research has shown that many patients do not receive genetic testing for the presence of actionable mutations in their cancers, and there are geographic disparities in testing with patients in rural areas and those receiving care at community treatment centers being less likely to receive testing.[14-16] In addition, logistical challenges to testing such as adequate tissue and the availability of any tissue have been identified as barriers to tissue-based genomic testing.[15] Additionally, even among patients whose cancers were genomically profiled at diagnosis and found to have a mutation for which they are receiving targeted treatment, resistance to the initial targeted treatment may emerge. For some patients, the identification of a new mutation, not present in the original tissue sample and found in the blood, may allow the selection of a new targeted life-prolonging therapy.[17]

Summary of Evidence

Clinical utility of comprehensive genomic profiling using plasma-based testing

Traditionally, tumor genotyping has been conducted by direct interrogation of tumor tissue obtained through invasive tissue sampling procedures. This diagnostic approach, however, is limited by the availability of sufficient tumor tissue and the ability of patients to undergo invasive procedures. In a recent study of over 100 community-based oncologists, nearly one-third of non-small cell lung cancer (NSCLC) patients were not tested for epidermal growth factor receptor (EGFR) or anaplastic large-cell lymphoma kinase (ALK), over 75% were not tested for ROS1 fusions, and fewer than 10% were tested for all guideline-recommended alterations.[15] These results were similar to a study in a single academic center where only 58% of non-squamous NSCLC were tested for EGFR and 40% for ALK fusions, despite 13% of patients undergoing repeat invasive biopsies to obtain sufficient tissue for genomic testing.[18] Tissue availability was similarly limited in several recent series, some of which reported that more than 50% of NSCLC patients had insufficient or unobtainable material for tissue-based CGP.[19-21]

Even when successful, tissue acquisition procedures pose a significant morbidity and mortality risk to Medicare patients. In a recent report, 19% of all lung tissue acquisition procedures resulted in a serious adverse event,[22] while the National Lung Cancer Screening Trial reported 1-2% mortality rates in their cohorts.[23] The FDA has also specifically approved a medication for patients who have cancer (cancer type unspecified on the label) for which there is a high risk associated with surgical resection.[24] Given the high rates of inadequate genotyping described above, plasma-based CGP can provide an opportunity for non- and under-genotyped patients to benefit from therapy matched to a genetic biomarker. Early studies suggested that plasma-based CGP can identify potential genomic targets in both the first and second lines, with response rates similar to those of patients identified using tissue-based CGP and tissue-based CoDX.[20,21,25-27]

It has been shown that the region of DNA sequenced is important, since alterations may occur outside the sequenced region or involve complex alterations (e.g., indels, copy number alterations, or rearrangements) that are not detectable by certain tests.[28] Newer techniques such 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.[29]

While the evidence appears most developed for clinically actionable targets in NSCLC, targeted therapy for cancer has been recommended for a number of other cancers as well. Genetic biomarkers associated with specific guideline recommended targeted therapies for a number of conditions is summarized below in Table 1. These guidelines are updated frequently, so new genes not listed in the table may also become part of guideline-consensus recommendations.

Non-small cell lung cancer[6]	EGFR

	BRAF MET HER2 / ERBB2 ALK ROS1 RET MET KRAS
Colorectal[3,10]	KRAS NRAS BRAF
Breast[2]	HER2 / ERBB2 BRCA1 BRCA2
Endometrial[13]	HER2 / ERBB2
Gastric and Gastroesophageal[4]	HER2 / ERBB2
Gastrointestinal Stromal Tumor[11]	KIT PDGFRA BRAF
Melanoma[5]	BRAF KIT
Ovarian[7]	BRCA1 BRCA2
Pancreatic[8]	BRCA1 BRCA2
Prostate[9]	BRCA1 BRCA2
Thyroid[12]	BRAF RET
Chordoma[1]	EGFR

Additionally, there are now medications, which are FDA approved for cancers based on the presence of genetic mutations regardless of the tissue of origin.

Microsatellite instability

Microsatellite instability structures are composed of a repeated nucleotide sequences that emerge due to defects in mismatch repair during DNA replication.[30] The importance of them in cancer, is that Microsatellite Instability High (MSI-H) tumors have been found to respond to immunotherapy,[31] and one immunotherapy drug, pembrolizumab, now has an FDA indication for the treatment of patients with unresectable or metastatic, MSI-H solid tumors.[32]

NTRK

The tropomyosin receptor kinase (TRK) receptor family is family of transmembrane proteins, some of which are encoded by the NTRK1, NTRK, and NTRK3 genes. Of these, Guardant360® tests for NTRK1 mutations including fusions. Fusions in the NTRK genes lead to chimeric TRK proteins, which have oncogenic potential, and have been viewed as a potential therapeutic target for cancer.[33]

Larotrectinib, a TRK inhibitor, has received FDA approval for NTRK positive (without a known resistance mutation) tumors in patients with metastatic disease or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or that have progressed following treatment.[24]

Guardant360®

Guardant360® is a comprehensive genomic profiling test that identifies mutations in 73 genetic mutations. It has demonstrated targeted therapy response rates similar to tissue-detected genomic targets in numerous published NSCLC studies. [20,21,25-28] In addition to sequencing accuracy, research has been done evaluating the ability of the test to identify actionable mutations across cancers originating in a number of organ systems.

In a study by Rozenblum et al., tissue biopsies from 101 advanced NSCLC patients were tested locally for EGFR mutations and ALK fusions.[34] Tissue-based CGP identified 15 EGFR and ALK alterations missed locally, but could only be performed in 82 of the 101 (81%) patients because of tissue exhaustion. Guardant360® was used in the 19 remaining patients, and two (11%) additional sensitizing EGFR mutations were found that had been missed with local tissue genotyping. In addition, alterations including MET amplification, ERBB2 (HER2) mutation, and two RET fusions were also identified (missed with local non-CGP genotyping), for a total of 6 driver alterations in 19 patients (32%). Thus, Guardant360® changed treatment in 32% of patients with insufficient samples for tissue-based CGP, with five receiving matched therapy. These five patients achieved a 60% objective response rate and a 100% disease control rate.

A more recent study examined the clinical implications of using plasma-based testing in addition to tissue-based testing in 229 patients with NSCLC.[35] Of the 229 patients in whom both tissue and plasma testing were ordered, the addition of plasma increased the percentage of patients eligible for targeted therapies from 21% (47/229) to 36% (82/229). For the 128 patients with successful tissue testing results, 55 were found to have a therapeutically targetable mutation. Of these 55, only 31 had this mutation found in tissue and plasma, though not necessarily the same actionable mutation(s) in each testing method. For 16 patients, the mutation was found in tissue only, and for 8, it was found in plasma only. To further assess whether the selection of targeted therapy based on the detection of low allele frequency mutations that Guardant360® is able to identify has a clinical benefit, the authors assessed the depth of response to targeted mutations identified in plasma-based testing. A total of 42 patients received a targeted therapy consistent with the plasma-based testing, 12 of whom had that mutation also detectable in tissue-based testing as well. Of this 42, there were 36 (85.7%) who achieved a response of stable disease, partial response, or complete response.

The ability of Guardant 360® to identify actionable mutations in multiple types of cancer, including NSCLC, gastric cancer, and melanoma, was examined in 194 patients with metastatic cancer but no availability of tissue for NGS-based genotyping.[25] Actionable mutations were found in the majority of patients, but the study also evaluated

treatment response when the patients were given therapy matching a genetic mutation in the test. In the group with NSCLC, 15 received matched therapy, and 13 of them responded to the therapy. Among those with gastric cancer, a total of nine received matched therapy, and 6 responded to treatment, with one of those six have a complete response (a patient with an ERBB2 amplification). Only 2 patients with melanoma received matched therapy, and one responded to this treatment.

Guardant360® has been validated recently across genetic mutation types (single nucleotide variants, indels, fusions, and copy number amplifications) and a range of specific actionable mutations in a study using orthogonal tissue and plasma-based methods.[36,37] Analytical performance of Guardant360® is summarized in the table below.

Mutation Type	LOD95	Sensitivity	Positive Predictive Value
SNVs	>0.25% 0.05 - 0.25%	100% 63.8%	99.2% 96.3%
Indels	>0.20% 0.05 -0.20%	100% 67.8%	98.2% 98.2%
Fusions	>0.20% 0.05-0.20%	95% 83%	100% 100%
CNAs	2.24-2.76 copies	95%	100%

Additionally, the study assessed the detection rate of tumor DNA using Guardant360® from 10,585 patients with more than 20 different cancers. Detection rate was >60% for nearly all cancers and around 80-90% for NSCLC, breast cancer, colorectal cancer, prostate cancer, gastroesophageal cancer, and gynecologic cancer. For primary CNS malignancies, the detection rate was less 50%.

While MolDX initially covered the Guardant360® assay for the selection of targeted therapy in NSCLC, the assay tests for the presence of mutations in over 70 genes and Microsatellite Instability (MSI). More recent research looking beyond NSCLC has shown that the analytical and clinical performance of the Guardant360® assay varies little between mutation type and tissue origin, with the exception of malignancies arising in the central nervous system.[36,37]

Guardant360® Test Description and Intended Use

Guardant360® analyzes tumor-derived cell-free DNA (also known as ctDNA) to detect somatic alterations, though it also reports germline alterations.

Guardant360® detects the following classes of alterations:

- Base pair substitutions (also known as SNVs)
- Small (≤20 bp) and large (>20 bp) indels
- Copy number amplifications (CNAs)
- Fusions
- Microsatellite Instability

The analytical performance characteristics of Guardant360® are similar across mutation types, specific actionable mutations, and tissue types, except primary CNS cancers.

Analysis of Evidence (Rationale for Determination)

Level of Evidence

Quality: Moderate
Strength: Limited
Weight: Limited

The clinical utility of plasma-based genomic testing for patients with advanced cancer at diagnosis or at progression, as defined in the intended use above, appears to be a viable alternative to solid tumor genotyping, when tissue is unavailable. At present, Guardant360®, one such assay, appears to have similar performance to detect mutations regardless of the tissue of origin or mutation type.

While tissue-based testing remains the preferred tool to test for actionable mutations in cancer, for patients in whom obtaining this tissue is not feasible, liquid biopsy with Guardant360® represents an alternative which may allow more patients to get potentially effective cancer treatment.

General Information

Associated Information

N/A

Sources of Information

N/A

Bibliography

1. NCCN Bone Cancer Panel. *Bone Cancer Version 1.2019.* August 3 2018.
2. NCCN Breast Cancer Panel. *Breast Cancer Version 4.2018.* February 8 2019.
3. NCCN Colon Cancer Panel. *Colon Cancer Version 4.2018.* October 19 2018.
4. NCCN Gastric Cancer Panel. *Gastric Cancer Version 2.2018.* May 22 2018.
5. NCCN Melanoma Panel. *Cutaneous Melanoma Version 1.2019.* November 1 2018.
6. NCCN Non-Small Cell Lung Cancer Panel. *Non-Small Cell Lung Cancer Version 3.2019.* January 18 2019.
7. NCCN Ovarian Cancer Panel. *Ovarian Cancer Version 2.2018.* March 9 2018.
8. NCCN Pancreatic Adenocarcinoma Panel. *Pancreatic Adenocarcinoma Version 1.2019.* November 8 2018.
9. NCCN Prostate Cancer Panel. *Prostate Cancer Version 4.2018.* August 15 2018.
10. NCCN Rectal Cancer Panel. *Rectal Cancer Version 3.2018.* August 7 2018.
11. NCCN Soft Tissue Sarcoma Panel. *Soft Tissue Sarcoma Version 2.2019.* February 4 2019.
12. NCCN Thyroid Carcinoma Panel. *Thyroid Carcinoma Version 3.2018.* December 20 2018.
13. NCCN Uterine Neoplasms Panel. *Uterine Neoplasms Version 3.2019.* February 11 2019.
14. Charlton ME, Karlitz JJ, Schlichting JA, Chen VW, Lynch CF. Factors associated with guideline-recommended KRAS testing in colorectal cancer patients: A population-based Study. *American journal of clinical oncology.* 2017;40(5):498-506.

15. Gutierrez ME, Choi K, Lanman RB, et al. Genomic profiling of advanced non–small cell lung cancer in community settings: Gaps and opportunities. *Clinical Lung Cancer.* 2017;18(6):651-659.
16. Greenbaum A, Wiggins C, Meisner AL, Rojo M, Kinney AY, Rajput A. KRAS biomarker testing disparities in colorectal cancer patients in New Mexico. *Heliyon.* 2017;3(11):e00448-e00448.
17. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum–pemetrexed in EGFR T790M–positive lung cancer. *New England Journal of Medicine.* 2017;376(7):629-640.
18. Lim C, Tsao MS, Le LW, et al. Biomarker testing and time to treatment decision in patients with advanced nonsmall-cell lung cancer. *Ann Oncol.* 2015;26(7):1415-1421.
19. Hagemann IS, Devarakonda S, Lockwood CM, et al. Clinical next-generation sequencing in patients with non-small cell lung cancer. *Cancer.* 2015;121(4):631-639.
20. Thompson JC, Yee SS, Troxel AB, et al. Detection of therapeutically targetable driver and resistance mutations in lung cancer patients by next-generation sequencing of cell-free circulating tumor DNA. *Clin Cancer Res.* 2016;22(23):5772-5782.
21. Villaflor V, Won B, Nagy R, et al. Biopsy-free circulating tumor DNA assay identifies actionable mutations in lung cancer. *Oncotarget.* 2016;7(41):66880-66891.
22. Lokhandwala T, Bittoni MA, Dann RA, et al. Costs of diagnostic assessment for lung cancer: A Medicare claims analysis. *Clinical Lung Cancer.* 2017;18(1):e27-e34.
23. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365(5):395-409.
24. Food and Drug Administration. Vitrakvi Full Prescribing Information. Accessed 10/29/2021.
25. Kim ST, Banks KC, Lee S-H, et al. Prospective feasibility study for using cell-free circulating tumor DNA–guided therapy in refractory metastatic solid cancers: An interim analysis. *JCO Precision Oncology.* 2017;1:1-15.
26. Kim ST, Lee WS, Lanman RB, et al. Prospective blinded study of somatic mutation detection in cell-free DNA utilizing a targeted 54-gene next generation sequencing panel in metastatic solid tumor patients. *Oncotarget.* 2015;6(37):40360-40369.
27. Piotrowska Z, Drapkin B, Engelman JA, Nagy RJ, Lanman RB, Sequist LV. Plasma T790M result alters treatment options in a previously T790 wild-type EGFR-mutant lung cancer. *J Thorac Oncol.* 2016;11(8):e95-e97.
28. Santos ES, Raez LE, Castillero LDC, Marana C, Hunis B. Genomic tissue analysis and liquid biopsy profiles from patients diagnosed with advanced adenocarcinoma of the lung. *Clinics in Oncology.* 2016;1(1099):1-4.
29. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol.* 2013;31(11):1023-1031.
30. Dietmaier W, Wallinger S, Bocker T, Kullmann F, Fishel R, Rüschoff J. Diagnostic microsatellite instability: Definition and correlation with mismatch repair protein expression. *Cancer Research.* 1997;57(21):4749.
31. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *New England Journal of Medicine.* 2015;372(26):2509-2520.
32. Food and Drug Administration. Keytruda Full Prescribing Information. Accessed 11/01/2021.
33. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nature Reviews Clinical Oncology.* 2018;15(12):731-747.
34. Rozenblum AB, Ilouze M, Dudnik E, et al. Clinical impact of hybrid capture-based next-generation sequencing on changes in treatment decisions in lung cancer. *J Thorac Oncol.* 2017;12(2):258-268.
35. Aggarwal C, Thompson JC, Black TA, et al. Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. *JAMA Oncol.* 2018.
36. Odegaard JI, Vincent JJ, Mortimer S, et al. Validation of a plasma-based comprehensive cancer genotyping assay utilizing orthogonal tissue-and plasma-based methodologies. *Clinical Cancer Research.* 2018:clincanres. 3831.2017.
37. Lanman RB, Mortimer SA, Zill OA, et al. Analytical and clinical validation of a digital sequencing panel for quantitative, highly accurate evaluation of cell-free circulating tumor DNA. *PLoS One.* 2015;10(10):e0140712.

Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

A58975 - Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Solid Tumors

A59279 - Response to Comments: MolDX: Plasma-Based Genomic Profiling in Solid Tumors

LCDs

DL39232 - MolDX: Plasma-Based Genomic Profiling in Solid Tumors

Related National Coverage Documents

N/A

Public Versions

UPDATED ON	EFFECTIVE DATES	STATUS
11/03/2022	12/26/2022 - N/A	Currently in Effect (This Version)

Keywords

N/A