MASSACHUSETTS

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Medical Policy

Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

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Policy Number: **797**

BCBSA Reference Number: 2.04.141

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Policy[1]

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Plasma-based comprehensive somatic genomic profiling testing (CGP) using Guardant360® for patients with Stage IIIB/IV non-small cell lung cancer (NSCLC) is considered **MEDICALLY NECESSARY** when the following criteria have been met:

Diagnosis:

- When tissue-based CGP is infeasible (i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated), AND
- When prior results for ALL of the following tests are not available:
    - EGFR single nucleotide variants (SNVs) and insertions and deletions (indels)
    - ALK and ROS1 rearrangements
    - PDL1 expression.

Progression:

- Patients progressing on or after chemotherapy or immunotherapy who have never been tested for EGFR SNVs and indels, and ALK and ROS1 rearrangements, and for whom tissue-based CGP is infeasible (i.e., quantity not sufficient for tissue-based CGP), OR

- For patients progressing on EGFR tyrosine kinase inhibitors (TKIs).

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

Other plasma-based CGP tests are considered **INVESTIGATIONAL**.

CGP and the use of circulating tumor DNA is considered **INVESTIGATIONAL** for all other indications.

The use of circulating tumor cells is considered **INVESTIGATIONAL** for all indications.

Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Medical necessity criteria and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the link below.

Guardant360® plasma-based comprehensive somatic genomic profiling test (hereafter called CGP) for patients with Stage IIIB/IV non-small cell lung cancer (NSCLC) is a covered service.

Local Coverage Determination (LCD): MolDX: Guardant360® Plasma-Based Comprehensive Genomic Profiling in Non-Small Cell Lung Cancer (NSCLC) (L37699)

For medical necessity criteria and coding guidance for M**edicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

The use of circulating tumor cells is not a covered service.

Local Coverage Determination (LCD): Non-covered Services (L33629)

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue[SM]	Prior authorization is **not required**.
Medicare PPO Blue[SM]	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above <u>medical necessity criteria MUST</u> be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

CPT codes:	Code Description
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
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, 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

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if <u>medical necessity criteria</u> are met:

ICD-10 Diagnosis Codes

ICD-10-CM diagnosis codes:	Code Description
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

The following CPT codes are considered investigational for <u>Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:</u>

CPT Codes

CPT codes:	Code Description
86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required

Description

Liquid biopsy refers to analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as a method of noninvasively characterizing tumors and tumor genome from the peripheral blood.

Circulating Tumor DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA (cfDNA). cfDNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs. Unlike apoptosis, necrosis is considered a pathologic process, and generates larger DNA fragments due to an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. ctDNA can be used for genomic characterization of the tumor.

Circulating Tumor Cells

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for in detecting CTCs is prognostic, through quantification of circulating levels.

Technologies for Detecting ctDNA and CTCs

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (eg, Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single-nucleotide mutations (eg BEAMing [which combines emulsion polymerase chain reaction [PCR] with magnetic beads and flow cytometry] and digital PCR) and copy-number changes. Digital genomic technologies allow for enumeration of rare mutant variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which h includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver mutations, which can impact therapy decisions (eg, *EGFR* and *ALK* in non-small-cell lung cancer), or untargeted without knowledge of specific mutations present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either on the basis of biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.

Summary

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as “liquid biopsy,” potentially offer a noninvasive alternative to tissue biopsy for therapeutic decisions and clinical prognosis in patients with cancer.

For individuals who have cancer who receive molecular characterization of tumor using ctDNA, the evidence includes case series and systematic reviews of these case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use.

Ultrasensitive methods to detect mutations from ctDNA have been developed, but there is limited evidence on the analytic validity of these methods. There is a need for further optimization and standardization of testing methods. Clinical validity consists of case series that report correlations between mutations detected in ctDNA with mutations detected in tumor tissue. Results have shown variable results for clinical sensitivity. Although some reports have suggested that clinical sensitivity may be high, this finding has not been consistent. Published studies have consistently reported high clinical specificity; however, most study populations are small and heterogeneous, and it is not known to what degree mutations detected by ctDNA are representative of the primary tumor. Published studies reporting clinical outcomes and/or clinical utility are lacking. However, specifically for ctDNA in non-small cell lung cancer (NSCLC), the evidence supports improved health outcomes at tumor progression and at diagnosis if tissue sample is unobtainable.

For individuals who have cancer or are at high risk of developing cancer who receive identification and quantification of CTCs, the evidence includes case series and meta-analyses of these case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and test validity.

Published data on analytic validity are lacking. Most of the literature consists of reports of levels of CTCs and cancer prognosis, and have shown a correlation with survival in certain cancer types. However, the cutoff levels that should be used to signal a change in patient management are unknown, and there are no studies showing clinical utility and improved patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes. If a separate evidence review exists, then conclusions reached there supersede conclusions in this review.

Policy History

Date	Action
8/2018	Local Coverage Determination (LCD): MolDX: Guardant360® Plasma-Based Comprehensive Genomic Profiling in Non-Small Cell Lung Cancer (NSCLC) (L37699) added. Effective 8/27/2018.
10/2017	Clarified coding information.
9/1/2017	New medically necessary indications described. Clarified coding information. Effective 9/1/2017.
10/2016	New medical policy describing investigational indications. Effective 10/1/2016.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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Endnotes

[1] Based on MPRM 2.04.141 and expert opinion.