

Medical Coverage Policy | Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)



EFFECTIVE DATE: 12|01|2016

POLICY LAST UPDATED: 11|07|2017

OVERVIEW

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.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

BlueCHiP for Medicare and Commercial Products

The use of circulating tumor DNA and circulating tumor cells is considered not medically necessary for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

BACKGROUND

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 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 (e.g., Sanger sequencing) are needed. Highly sensitive and specific methods have been

developed to detect ctDNA, for both single-nucleotide mutations (e.g. 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 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 (e.g., *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.

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 population have consisted of 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. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether mutation analysis by ctDNA can replace mutation analysis in tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

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. Therefore, this service is considered not medically necessary for BlueCHiP for Medicare and Commercial products.

CODING

BlueCHiP for Medicare and Commercial Products

The following codes should be reported and are considered not medically necessary:

- 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

RELATED POLICIES

None

PUBLISHED

Provider Update, December 2017

Provider Update, November 2016

REFERENCES

1. Alix-Panabieres C, Pantel K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. *Cancer Discov.* May 2016;6(5):479-491. PMID 26969689
2. Newman AM, Bratman SV, To J, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med.* May 2014;20(5):548-554. PMID 24705333
3. Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med.* Feb 19 2014;6(224):224ra224. PMID 24553385
4. Mao C, Yuan JQ, Yang ZY, et al. Blood as a substitute for tumor tissue in detecting egfr mutations for guiding EGFR TKIs treatment of nonsmall cell lung cancer: a systematic review and meta-analysis. *Medicine (Baltimore).* May 2015;94(21):e775. PMID 26020382
5. Qiu M, Wang J, Xu Y, et al. Circulating tumor DNA is effective for the detection of EGFR mutation in non-small cell lung cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* Jan 2015;24(1):206-212. PMID 25339418
6. Sacher AG, Paweletz C, Dahlberg SE, et al. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. *JAMA Oncol.* Apr 7 2016. PMID 27055085
7. Pailler E, Adam J, Barthelemy A, et al. Detection of circulating tumor cells harboring a unique ALK rearrangement in ALK-positive non-small-cell lung cancer. *J Clin Oncol.* Jun 20 2013;31(18):2273-2281. PMID 23669222
8. Pailler E, Auger N, Lindsay CR, et al. High level of chromosomal instability in circulating tumor cells of ROS1-rearranged non-small-cell lung cancer. *Ann Oncol.* Jul 2015;26(7):1408-1415. PMID 25846554
9. Lyberopoulou A, Aravantinos G, Efstathopoulos EP, et al. Mutational analysis of circulating tumor cells from colorectal cancer patients and correlation with primary tumor tissue. *PLoS One.* 2015;10(4):e0123902. PMID 25902072
10. Tabernero J, Lenz HJ, Siena S, et al. Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: a retrospective, exploratory analysis of the CORRECT trial. *Lancet Oncol.* Aug 2015;16(8):937-948. PMID 26184520
11. CMS.gov, Centers for Medicare and Medicaid Services Local Coverage Determination (LCD): Non-covered Services (L33629): <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33629&ver=12&SearchType=Advanced&CoverageSelection=Local&PolicyType=Both&s=47&CtrctrType=13&DateTag=C&kq=true&bc=IAAAACAAAAAAA%3d%3d&>

CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.

