

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



**EFFECTIVE DATE:** 12|01|2016  
**POLICY LAST UPDATED:** 11|02|2022

**OVERVIEW**

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as “liquid biopsy,” have several potential uses for guiding therapeutic decisions in patients with cancer or being screened for cancer.

**MEDICAL CRITERIA**

Not applicable

**PRIOR AUTHORIZATION**

Not applicable

**POLICY STATEMENT**

**Medicare Advantage Plans**

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

**Commercial Products**

The use of circulating tumor DNA and/or 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 methods 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). Cell-free DNA 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. Circulating tumor DNA 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.

## Detecting Circulating Tumor DNA and Circulating Tumor Cells

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cell free DNA. 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 with magnetic beads and flow cytometry] and digital polymerase chain reaction 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 advanced cancer who receive testing of ctDNA to select targeted treatment, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether variant analysis of ctDNA can replace variant analysis of tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have advanced cancer who receive testing of CTCs to select targeted treatment, the evidence includes observational studies. The relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs can replace variant analysis of tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who receive testing of ctDNA to monitor treatment response, the evidence includes observational studies. The relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to monitor treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who receive testing of CTCs to monitor treatment response, the evidence includes a randomized controlled trial, observational studies, and systematic reviews of observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. The available

randomized controlled trial found no effect on overall survival when patients with persistently increased CTC levels after first-line chemotherapy were switched to an alternative cytotoxic therapy. Other studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to monitor treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have received curative treatment for cancer who receive testing of ctDNA to predict risk of relapse, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to predict relapse response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have received curative treatment for cancer who receive testing of CTCs to predict risk of relapse, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to predict relapse response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at high risk for cancer who receive testing of ctDNA to screen for cancer, no evidence was identified. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Published data on clinical validity and clinical utility are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at high risk for cancer who receive testing of CTCs to screen for cancer, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

## **CODING**

The following codes are not covered for Medicare Advantage Plans and not medically necessary for Commercial products:

- 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**

Not applicable

## **PUBLISHED**

Provider Update, January 2023  
Provider Update, May 2021  
Provider Update, June 2019  
Provider Update, Sep 2018  
Provider Update, December 2017

## 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): 479-91. PMID 26969689
2. Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol.* Jun 01 2018; 36(16): 1631-1641. PMID 29504847
3. Clark TA, Chung JH, Kennedy M, et al. Analytical Validation of a Hybrid Capture-Based Next-Generation Sequencing Clinical Assay for Genomic Profiling of Cell-Free Circulating Tumor DNA. *J Mol Diagn.* Sep 2018; 20(5): 686-702. PMID 29936259
4. Zhou C, Yuan Z, Ma W, et al. Clinical utility of tumor genomic profiling in patients with high plasma circulating tumor DNA burden or metabolically active tumors. *J Hematol Oncol.* Nov 06 2018; 11(1): 129. PMID 30400986
5. Mazel M, Jacot W, Pantel K, et al. Frequent expression of PD-L1 on circulating breast cancer cells. *Mol Oncol.* Nov 2015; 9(9): 1773-82. PMID 26093818
6. Lv Q, Gong L, Zhang T, et al. Prognostic value of circulating tumor cells in metastatic breast cancer: a systemic review and meta-analysis. *Clin Transl Oncol.* Mar 2016; 18(3): 322-30. PMID 26260915
7. Wang CH, Chang CJ, Yeh KY, et al. The Prognostic Value of HER2-Positive Circulating Tumor Cells in Breast Cancer Patients: A Systematic Review and Meta-Analysis. *Clin Breast Cancer.* Aug 2017; 17(5): 341-349. PMID 28347604
8. Zhang L, Riethdorf S, Wu G, et al. Meta-analysis of the prognostic value of circulating tumor cells in breast cancer. *Clin Cancer Res.* Oct 15 2012; 18(20): 5701-10. PMID 22908097
9. Huang X, Gao P, Song Y, et al. Relationship between circulating tumor cells and tumor response in colorectal cancer patients treated with chemotherapy: a meta-analysis. *BMC Cancer.* Dec 18 2014; 14: 976. PMID 25519477
10. Groot Koerkamp B, Rahbari NN, Buchler MW, et al. Circulating tumor cells and prognosis of patients with resectable colorectal liver metastases or widespread metastatic colorectal cancer: a meta-analysis. *Ann Surg Oncol.* Jul 2013; 20(7): 2156-65. PMID 23456317
11. Fan JL, Yang YF, Yuan CH, et al. Circulating Tumor Cells for Predicting the Prognostic of Patients with Hepatocellular Carcinoma: A Meta Analysis. *Cell Physiol Biochem.* 2015; 37(2): 629-40. PMID 26344495
12. Ma X, Xiao Z, Li X, et al. Prognostic role of circulating tumor cells and disseminated tumor cells in patients with prostate cancer: a systematic review and meta-analysis. *Tumour Biol.* Jun 2014; 35(6): 5551-60. PMID 24563278
13. Wang FB, Yang XQ, Yang S, et al. A higher number of circulating tumor cells (CTC) in peripheral blood indicates poor prognosis in prostate cancer patients--a meta-analysis. *Asian Pac J Cancer Prev.* 2011; 12(10): 2629-35. PMID 22320965
14. de Bono J., Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2008;14(19):6302-6309. PMID
15. Sun T, Zou K, Yuan Z, et al. Clinicopathological and prognostic significance of circulating tumor cells in patients with head and neck cancer: a meta-analysis. *Onco Targets Ther.* 2017; 10: 3907-3916. PMID 28831265
16. Mocellin S, Hoon D, Ambrosi A, et al. The prognostic value of circulating tumor cells in patients with melanoma: a systematic review and meta-analysis. *Clin Cancer Res.* Aug 01 2006; 12(15): 4605-13. PMID 16899608
17. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol.* Nov 01 2014; 32(31): 3483-9. PMID 24888818
18. Chidambaram S, Markar SR. Clinical utility and applicability of circulating tumor DNA testing in esophageal cancer: a systematic review and meta-analysis. *Dis Esophagus.* Feb 11 2022; 35(2). PMID 34286823
19. Rack B, Schindlbeck C, Juckstock J, et al. Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. *J Natl Cancer Inst.* May 15 2014; 106(5). PMID 24832787

20. Thalgott M, Rack B, Horn T, et al. Detection of Circulating Tumor Cells in Locally Advanced High-risk Prostate Cancer During Neoadjuvant Chemotherapy and Radical Prostatectomy. *Anticancer Res.* Oct 2015; 35(10): 5679-85. PMID 26408743
21. Deneve E, Riethdorf S, Ramos J, et al. Capture of viable circulating tumor cells in the liver of colorectal cancer patients. *Clin Chem.* Sep 2013; 59(9): 1384-92. PMID 23695297
22. Rink M, Chun FK, Dahlem R, et al. Prognostic role and HER2 expression of circulating tumor cells in peripheral blood of patients prior to radical cystectomy: a prospective study. *Eur Urol.* Apr 2012; 61(4): 810-7. PMID22277196
23. Gazzaniga P, de Berardinis E, Raimondi C, et al. Circulating tumor cells detection has independent prognostic impact in high-risk non-muscle invasive bladder cancer. *Int J Cancer.* Oct 15 2014; 135(8): 1978-82. PMID24599551
24. Schulze K, Gasch C, Stauffer K, et al. Presence of EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. *Int J Cancer.* Nov 2013;133(9): 2165-71. PMID 23616258
25. Vashist YK, Effenberger KE, Vettorazzi E, et al. Disseminated tumor cells in bone marrow and the natural course of resected esophageal cancer. *Ann Surg.* Jun 2012; 255(6): 1105-12. PMID 22580852
26. Msaouel P, Koutsilieris M. Diagnostic value of circulating tumor cell detection in bladder and urothelial cancer: systematic review and meta-analysis. *BMC Cancer.* Aug 04 2011; 11: 336. PMID 21816094
27. Tang L, Zhao S, Liu W, et al. Diagnostic accuracy of circulating tumor cells detection in gastric cancer: systematic review and meta-analysis. *BMC Cancer.* Jun 27 2013; 13: 314. PMID 23806209

[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.

