MEDICAL POLICY

POLICY TITLE	**CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (LIQUID BIOPSY)**
POLICY NUMBER	**MP 2.267**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**2/1/2024**

I. POLICY

The use of circulating tumor DNA and/or circulating tumor cells is considered **investigational** for all indications reviewed herein (see Policy Guidelines). There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

This policy does not address the use of blood-based testing (liquid biopsy) to select targeted treatment for breast cancer, non-small cell lung cancer, melanoma/glioma, ovarian cancer, pancreatic cancer, and prostate cancer, the use of liquid biopsy to select immune checkpoint inhibitor therapy, tumor-Informed circulating tumor DNA testing for cancer management, comprehensive genomic profiling for selecting targeted cancer therapies, the use of blood-based testing for detection or risk assessment of prostate cancer; or the use of AR-V7 circulating tumor cells for metastatic prostate cancer.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

Cross-Reference:

MP 2.235 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
MP 2.259 Molecular Panel Testing of Cancers to Identify Targeted Therapies
MP 2.277 Investigational Miscellaneous Genetic and Molecular Diagnostic Tests
MP 2.280 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
MP 2.283 Circulating Tumor DNA for Management of Non-Small Cell Lung Cancer (Liquid Biopsy)

POLICY TITLE	CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (LIQUID BIOPSY)
POLICY NUMBER	MP 2.267

MP 2.315 Gene Expression Profile Testing and Circulating Tumor DNA testing for Predicting Recurrence in Colon Cancer
MP 2.316 Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2, and TMB)
MP 2.364 Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

TOP

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. This policy evaluates uses for liquid biopsies *not addressed in a separate policy*. If a separate policy exists, then conclusions reached there supersede conclusions here.

LIQUID BIOPSY

Liquid biopsy refers to the analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as 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 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 to 2 hours), and CTCs are cleared through extravasation into secondary organs. Most assays detect CTCs through the use of surface epithelial markers such as epithelial cell adhesion molecules (EpCAM) and cytokeratins. The primary reason for detecting CTCs is prognostic, through quantification of circulating levels.

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 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 variants (e.g. BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare 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 or untargeted without knowledge of specific variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

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

Note that targeted therapy in non-small-cell lung cancer and metastatic colorectal cancer, use of liquid biopsy for detection or risk assessment of prostate cancer, and use of AR-V7 CTC liquid biopsy for metastatic prostate cancer are addressed in separate policies.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

The FDA maintains a list of cleared or approved companion diagnostic tests at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

IV. RATIONALE

TOP

Summary of Evidence

For individuals who have advanced cancer who receive testing of ctDNA to select targeted treatment, the evidence includes observational studies. The relevant outcomes are overall survival,

disease-specific survival, test 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 for the indications covered in this review. The clinical validity of FoundationOne® Liquid compared to tissue biopsy with FoundationOne comprehensive genetic profiling was evaluated in 4 industry-sponsored observational studies. 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 ctDNA can replace variant analysis of tissue. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

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. 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. The available RCT 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 that the technology results in an improvement in the net health outcome.

For individuals who have received curative treatment for cancer who receive testing of ctDNA to predict the risk of relapse, 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 predict relapse response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have received curative treatment for cancer who receive testing of CTCs to predict the risk of relapse, 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 should be used to predict relapse response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at high-risk for cancer who receive testing of ctDNA to screen for cancer, no evidence was identified. The 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 that the technology results in an improvement in the net health outcome.

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. The 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 that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

TOP

N/A

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs

in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

TOP

Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational, therefore not covered:

Procedure Codes								
0091U	0337U	0338U	0368U	86152	86153			

IX. REFERENCES

TOP

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. Food & Drug Administration. 2023. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)
3. *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*
4. *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*
5. *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*
6. *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*

7. *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*
8. *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*
9. *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*
10. *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*
11. *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*
12. *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*
13. *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 18829513*
14. *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*
15. *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*
16. *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*
17. *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*
18. *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*
19. *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*
20. *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*
21. *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. PMID 22277196*

22. *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. PMID 24599551*
23. *Schulze K, Gasch C, Staufer 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*
24. *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*
25. *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*
26. *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*
27. *Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. Apr 10 2022; 40(11): 1231-1258. PMID 35175857*
28. *Centers for Medicare & Medicaid Services. 2020. National Coverage Determination: Next Generation Sequencing (90.2)*
29. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.141, Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy). September 2023*

X. POLICY HISTORY

TOP

MP-2.267	**3/17/20 Consensus review. No changes to policy statements.**
	4/23/21 Consensus review. No change to policy statement. Addition of NCCN statement under policy guidelines. References updated.
	9/15/2022 Admin update. New codes 0337U & 0338U added effective 10/1/22
	11/16/2022 Consensus review. No change to policy statement. Cross Referenced policies updated. FEP language revised. Background, Rationale and References updated.
	3/16/2023 Admin update. New code 0368U added effective 4/1/23
	10/6/2023 Consensus review. No change to policy statement. Policy Guidelines revised. Cross Referenced policies updated. References added. Removed code 81277.

TOP

MEDICAL POLICY

POLICY TITLE	**CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (LIQUID BIOPSY)**
POLICY NUMBER	**MP 2.267**

Health Plan® Central. Independent licensees of the Blue Cross BlueShield Association. Communications issued by Capital Blue Cross in its capacity as administrator of programs and provider relations for all companies.