

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:	RETIRED 7/1/2026

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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.

Cross-References:

MP 2.235 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
MP 2.241 Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small Cell Lung 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 Gene Expression Profiling and Protein Biomarkers for the Management, Diagnosis, and Cancer Risk Assessment of Prostate Cancer
MP 2.315 Gene Expression Profile Testing and Circulating Tumor DNA testing for Predicting Recurrence in Colon Cancer

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MP 2.316 Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment of Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, NTRK, and HER2)

MP 2.364 Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy

II. PRODUCT VARIATIONS

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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

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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.

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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.

Certain liquid biopsy-based assays have been cleared or approved by the FDA as companion diagnostic tests. These indications are addressed in other reviews.

IV. RATIONALE

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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

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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

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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

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N/A

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the

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date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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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	0453U	0491U	0492U	0530U	

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.267	03/17/2020 Consensus Review. No changes to policy statements.
	04/23/2021 Consensus Review. No change to policy statement. Addition of NCCN statement under policy guidelines. References updated.
	09/15/2022 Administrative Update. New codes 0337U & 0338U added effective 10/01/2022
	11/16/2022 Consensus Review. No change to policy statement. Cross Referenced policies updated. FEP language revised. Background, Rationale and References updated.
	03/16/2023 Administrative Update. New code 0368U added effective 04/01/2023
	10/06/2023 Consensus Review. No change to policy statement. Policy Guidelines revised. Cross Referenced policies updated. References added. Removed code 81277.
	06/12/2024 Administrative Update. New code 0453U added; effective 07/01/2024.
	09/19/2024 Administrative Update. New codes 0491U and 0492U added, effective 10/01/2024
	12/06/2024 Consensus Review. No change to policy statement. Cross Referenced policies and Background updated.
	12/11/2024 Administrative Update. Added 0530U. Effective 01/01/2025
	08/05/2025 Consensus Review. No change to policy statement. Removed codes 86152 & 86153. Removed Benefit Variations Section and updated Disclaimer.
	03/04/2026 Retirement Review. EviCore delegation

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