MEDICAL POLICY

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

Original Issue Date (Created):	**10/1/2014**
Most Recent Review Date (Revised):	**3/17/2020**
Effective Date:	**6/1/2020**

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 conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

This policy does not address the use of blood-based testing for driver mutations to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for use of liquid biopsy for detection or risk assessment of prostate cancer or the use of AR-V7 circulating tumor cells for metastatic prostate cancer.

Cross-Reference:

MP-2.235 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
MP-2.277 Miscellaneous Genetic and Molecular Diagnostic Tests
MP-2.280 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

II. PRODUCT VARIATIONS

TOP

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

FEP PPO-Refer to FEP Medical Policy Manual MP-2.04.141, Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy). The FEP Medical Policy Manual can be found at https://www.fepblue.org.

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III. DESCRIPTION/BACKGROUND

TOP

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.[1] 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 (1-2 hours), and CTCs are cleared through extravasation into secondary organs.[1] 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 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 (eg, Sanger sequencing) are needed.
Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (eg 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.CTC 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). CTCs 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 reviews.

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 CellSearch® System (Janssen Diagnostics, formerly Veridex) is the only FDA-approved device for monitoring patients with metastatic disease and CTCs. In 2004, the CellSearch® System was cleared by FDA for marketing through the 510(k) process for monitoring metastatic breast cancer, in 2007 for monitoring metastatic colorectal cancer, and in 2008 for monitoring metastatic prostate cancer. The system uses automated instruments manufactured by Immunicon for sample preparation (CellTracks® AutoPrep) and analysis (CellSpotter Analyzer®), together with supplies, reagents, and epithelial cell control kits manufactured by Veridex. FDA product code: NQI.

IV. RATIONALE

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Summary of Evidence

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

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, outside of lung and colorectal cancer, which are covered in a separate review. 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. 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 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 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 the effects of the technology on health outcomes.

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 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. 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 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. 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 the effects of the technology on health outcomes.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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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 BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross'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 BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. 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:

CPT Codes®								
0091U	81277	86152	86153					

IX. REFERENCES

TOP

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X. POLICY HISTORY

TOP

MP-2.267	**CAC 5/20/14** Policy criteria removed from MP-2.212 Tumor Markers and Tumor Related Molecular Testing. References updated and rationale added. No changes to policy statements. Policy coded.
	11/1/14 Administrative change. Deleted Medicare variation and references to LCD 32930 – retired. Also deleted LCD for Biomarkers for Oncology – code is not listed on this LCD.
	CAC 6/2/15 Consensus review. No changes to the policy statements. Rationale and references updated. Coding reviewed.
	CAC 5/31/16 Consensus review. Policy statement unchanged. Description/Background, Rationale and References updated. Coding reviewed.
	Admin update 1/1/17: Product variation section updated.

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	CAC 9/27/16 Minor Review. BCBSA retired existing policy of Detection of Circulating Tumor Cells in the Management of Patients with Cancer; BCBSA policy #2.04.37 on 5/19/2016 and created the policy Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) BCBSA # 2.04.141 with same investigational statement and codes used. It was decided for us to keep our existing policy number and update it with new name and rational. Policy statement remained the same with rational and references updated. Coding reviewed.
	CAC 9/26/17 Consensus review. No changes to the policy statement. Language added to the policy guidelines that the policy does not apply to the use of blood-based testing for EGFR mutations. Rationale and references updated. Coding reviewed.
	5/29/18 Consensus review with clarification. Clarifying edit to the policy statement, add 'or' to the following sentence: "The use of circulating tumor DNA and/or circulating tumor cells…" The policy intent is unchanged. FEP variation revised. Description/Background, Rationale and Reference sections updated.
	4/5/19 Consensus review. No changes to policy statement; however, Policy Guidelines reference added. Changes made to Policy Guidelines. Rationale updated. References updated. New code 0091U added as investigational. Effective 7/1/19.
	1/1/2020 Admin Update. Added new code 81277.
	3/17/2020 Consensus review. No changes to policy statements.

Top