



# Louisiana

## **Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)**

**Policy #** 00497

**Original Effective Date:** 07/20/2016

**Current Effective Date:** 08/10/2020

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer is addressed separately in medical policy 00272.*

*Note: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing is addressed separately in medical policy 00382.*

*Note: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management is addressed separately in medical policy 00403.*

*Note: Molecular Panel Testing of Cancers to Identify Targeted Therapies is addressed separately in medical policy 00423.*

*Note: Miscellaneous Genetic and Molecular Diagnostic Tests is addressed separately in medical policy 00577.*

*Note: Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy) is addressed separately in medical policy 00597.*

### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of circulating tumor deoxyribonucleic acid DNA (ctDNA) and/or circulating tumor cells (CTCs) for all indications reviewed herein (see Policy Guidelines) to be **investigational**.\*

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### **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.

### **Background/Overview**

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. 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 (1-2 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 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.

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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.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

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 has chosen not to require any regulatory review of this test.

In 2004, the CellSearch<sup>®‡</sup> System (Janssen Diagnostics, formerly Veridex) was cleared by the Food and Drug Administration 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<sup>®‡</sup> AutoPrep) and analysis (CellSpotter Analyzer<sup>®‡</sup>), together with supplies,

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reagents, and epithelial cell control kits manufactured by Veridex. Food and Drug Administration product code: NQI.

### **Rationale/Source**

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 (OS), 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 the lung and colorectal cancer, which are covered in a separate review. The clinical validity of FoundationOne Liquid compared to tissue biopsy with FoundationOne comprehensive genetic profiling was evaluated in four 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 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 OS, 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 OS, disease-specific survival,

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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 OS, 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 OS when patients with persistently increased CTC levels after first-line chemotherapy were switched to 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 OS, 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 OS, 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

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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 OS, 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 OS, 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.

## **Supplemental Information**

### **Practice Guidelines and Position Statements**

National Comprehensive Cancer Network (v.1.2019) guidelines for breast cancer state that the use of circulating tumor cells in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring. The guidelines for melanoma (v.2.2019) reference papers on circulating tumor DNA in the discussion of molecular characteristics of metastatic disease with the statement, ‘A number of tests have been developed for detecting BRAF and KIT mutations common in metastatic melanoma. The sensitivity and accuracy of these tests vary, and improved assays are in development.

### **U.S. Preventive Services Task Force Recommendations**

Not applicable.

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### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers. Palmetto GBA has issued a local noncoverage determination (L35071) for all circulating tumor cell assays.

### Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
<i>Ongoing</i>			
NCT02140463	Next generation personalized therapy with plasma DNA Trial 2 in refractory solid tumors (The NEXT-2 Trial)	260	Dec 2020
NCT02035813	DETECT IV - A Prospective, Multicenter, Open-label, Phase II Study in Patients With HER2-negative Metastatic Breast Cancer and Persisting HER2-negative Circulating Tumor Cells (CTCs).	520	Dec 2019
NCT01619111	DETECT III - A Multicenter, Randomized, Phase III Study to Compare Standard Therapy Alone Versus Standard Therapy Plus Lapatinib in Patients With Initially HER2-negative Metastatic Breast Cancer and HER2-positive Circulating Tumor Cells	120	Mar 2020
NCT03182634	A Multiple Parallel Cohort, Multi-centre Phase IIa Trial Aiming to Provide Proof of Principle Efficacy for Designated Targeted Therapies in Patients With Advanced Breast Cancer Where the Targetable Mutation is Identified Through ctDNA	1000	Nov 2023

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<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
NCT02889978	The Circulating Cell-free Genome Atlas Study	15000	Mar 2024
NCT03079011	Randomized, Open-Label, Multicentric Phase III Trial to Evaluate the Safety and Efficacy of Palbociclib in Combination With HT driven by ctDNA ESR1 Mutation Monitoring in ER+, HER2-negative Metastatic Breast Cancer Patients	800	Apr 2024
<i>Unpublished</i>			
NCT01701050	COMETI Phase 2: Characterization of Circulating Tumor Cells (CTC) From Patients With Metastatic Breast Cancer Using the CTC-Endocrine Therapy Index	121	Nov 2016 (completed)
NCT02612350	Utility of Plasma Circulating Tumor DNA (ctDNA) in Asymptomatic Subjects for the Detection of Neoplastic Disease	1106	Aug 2017
NCT01349842	CirCe01 Study: Evaluation of the Use of Circulating Tumour Cells to Guide Chemotherapy From the 3rd Line of Chemotherapy for Metastatic Breast Cancer	265	Jan 2018
NCT01710605	Randomized Trial to Evaluate the Medico-economic Interest of Taking Into Account Circulating Tumor Cells (CTC) to Determine the Kind of First Line Treatment for Metastatic, Hormone-receptors Positive, Breast Cancers.	800	Sep 2018

NCT: national clinical trial.

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06/30/2016 Medical Policy Committee review

07/20/2016 Medical Policy Implementation Committee approval. New Policy.

01/01/2017 Coding update: Removing ICD-9 Diagnosis codes

07/06/2017 Medical Policy Committee review

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# Louisiana

## Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Policy # 00497

Original Effective Date: 07/20/2016

Current Effective Date: 08/10/2020

- 07/19/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
  - 07/05/2018 Medical Policy Committee review
  - 07/11/2018 Medical Policy Implementation Committee approval. Added a reference to Policy Guidelines at the end of the investigational statement. Added a Policy Guidelines section. Coverage eligibility unchanged.
  - 07/03/2019 Medical Policy Committee review
  - 07/18/2019 Medical Policy Implementation Committee approval. Clarifying edit to the INV statement, added 'reviewed herein' to stress that other indications are reviewed in separate policies. Coverage eligibility unchanged.
  - 07/02/2020 Medical Policy Committee review
  - 07/08/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
  - 12/11/2020 Coding update
- Next Scheduled Review Date: 07/2021

### Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

*The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which*

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*contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479, 86152, 86153 Added code eff 7/1/2020: 0177U Added code eff 1/1/2021: 0229U, 0239U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

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‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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