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## Medical Policy



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**\*Current Policy Effective Date: 5/1/22**  
(See policy history boxes for previous effective dates)

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

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#### **Description/Background**

##### **Liquid Biopsy**

Liquid biopsy refers to analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as a method 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). cfDNA 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 an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. ctDNA 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 cfDNA. 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 [PCR] with magnetic beads and flow cytometry] and digital PCR) 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.(1)

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## Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA 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>.

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## Medical Policy Statement

The clinical utility of circulating tumor DNA and circulating tumor cells has not been demonstrated. The peer reviewed medical literature has not shown that the test has sufficient diagnostic accuracy to provide clinically relevant information when compared to other available diagnostic studies. This test is experimental/investigational.

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## Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

**Established codes:**

N/A

**Other codes (investigational, not medically necessary, etc.):**

86152

86153

0239U

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**Rationale**

**SELECTING TREATMENT IN ADVANCED CANCER**

**Clinical Context and Test Purpose**

One purpose of liquid biopsy testing of patients who have advanced cancer is to inform a decision regarding treatment selection (eg, whether to select a targeted treatment or standard treatment). Treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations.

The question addressed in this evidence review is: Does use of circulating tumor DNA (ctDNA) or circulating tumor cell (CTCs) testing to select treatment in patients with cancer to improve the net health outcome compared with standard tissue testing?

The following PICO was used to select literature to inform this review.

**Populations**

The relevant population of interest is patients with advanced cancer for whom the selection of treatment depends on molecular characterization of the tumor(s).

**Interventions**

The test being considered is liquid biopsy using either ctDNA or CTCs. Both targeted polymerase chain reaction-based assays and broad next-generation sequencing-based approaches are available. Patients with negative liquid biopsy results should be reflexed to tumor biopsy testing if they are able to undergo tissue biopsy.(2)

**Comparators**

For patients who are able to undergo biopsy, molecular characterization of the tumor is performed using standard tissue biopsy samples. Patients unable to undergo biopsy generally receive standard therapy.

**Outcomes**

Liquid biopsies are easier to obtain and less invasive than tissue biopsies. True-positive liquid biopsy test results lead to the initiation of appropriate treatment (eg, targeted therapy) without tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival.

In patients able to undergo tissue biopsy, negative liquid biopsies reflex to tissue testing. In patients unable to undergo tissue biopsy, a negative liquid biopsy result would not change

empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

The timing of interest for survival outcomes varies by type of cancer.

**Review of Evidence**

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Circulating Tumor DNA**

The American Society of Clinical Oncology and College of American Pathologists jointly convened an expert panel to review the current evidence on the use of ctDNA assays.(2) The literature review included a search for publications on the use of ctDNA assays for solid tumors in March 2017 and covers several different indications for the use of liquid biopsy. The search identified 1338 references to which an additional 31 references were supplied by the expert panel. Seventy-seven articles were selected for inclusion. The summary findings are discussed in the following sections, by indication.

Much of the literature, to date, on the use of ctDNA to guide treatment selection is for non-small-cell lung cancer, metastatic colorectal cancer, and breast cancer which are not discussed in this policy. Merker et al (2018) concluded that while a wide range of ctDNA assays have been developed to detect driver mutations, there is limited evidence of the clinical validity of ctDNA analysis in tumor types outside of lung cancer and colorectal cancer (CRC). Preliminary clinical studies of ctDNA assays for detection of potentially targetable variants in other cancers such as *BRAF* variants in melanoma (3) and *PIK3CA* and *ESR1* variants in breast cancer were identified.(3)

Since the end date of the searches conducted by Merkel et al (2018), 2 observational studies of the clinical validity of FoundationOne Liquid (formerly FoundationACT) in patients with cancers covered herein have been published (Table 1). Both studies compared liquid biopsy to tissue biopsy with FoundationOne comprehensive genomic testing. Test characteristics are shown in Table 2. Relevance, design, and conduct limitations of these studies are summarized in Tables 3 and 4.

**Table 1. Study Characteristics of the Clinical Validity of FoundationOne Liquid**

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Clark et al (2018) <sup>4</sup>	Patients with advanced cancer	Retrospective (tissue) and prospective (liquid biopsy)	Tissue biopsy (FoundationOne)	0 to 60 days	Not stated
Zhou et al (2018) <sup>5</sup>	Patients with locally advanced or metastatic solid tumors	Retrospective	Tissue biopsy (FoundationOne)	Not reported; only considered patient with no intervening treatment between liquid and tissue biopsy	Not stated

**Table 2. Clinical Validity of FoundationOne Liquid**

Study	Initial N	Final N	PPA	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Clark et al (2018) <sup>4</sup>	NR	36					
Overall	NR	36	75%	--	--	--	--
Base substitutions/indels	NR	36		82.7% (69.7-91.8)	97.5% (95.9-98.5)	72.9% (59.7-83.6)	98.6% (97.3-99.4)
Rearrangements	NR	36		100% (15.8-100)	99.1% (94.3-100)	66.7% (9.4-99.2)	100% (96.5-100)
Amplifications	NR	36		38.5% (13.9-68.4)	100% (98.5-100)	100% (47.8-100)	96.8% (93.6-98.6)
Zhou et al (2018) <sup>5</sup>							
Overall	NR	42	82%				
Base substitutions	NR	42		77.2% (66.4-85.9)	96.0% (94.6-97.1)	59.2% (49.1-68.8)	98.3% (97.3-99.0)
Insertions/deletions	NR	42		7.1% (0.9-23.5)	98.2% (95.5-99.5)	33.3% (4.3-77.7)	89.4% (84.9-93)
Amplifications	NR	42		23.7% (11.4-40.2)	99.8% (98.8-100)	90.0% (53.2-100)	94.1% (91.7-96)
Rearrangements or fusions	NR	42		100.0% (39.8-100)	97.6% (93.9-99.3)	50.0% (15.7-84.3)	100.0% (97.7-100)

CI: confidence interval; PPA: positive percent agreement; PPV: positive predictive value; NPV: negative predictive value; NR: not reported

**Table 3. Relevance Limitations of Clinical Validity Studies of FoundationOne Liquid**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Duration of Follow-Up <sup>e</sup>
Clark et al (2018) <sup>4</sup>	1. Included patients with a range of cancers	Earlier version of test used (FoundationACT)	2. FoundationOne tissue biopsy		
Zhou et al (2018) <sup>5</sup>	1. Included patients with a range of cancers	Earlier version of test used (FoundationACT)	2. FoundationOne tissue biopsy		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

<sup>c</sup> Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

<sup>d</sup> Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

<sup>e</sup> Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

**Table 4. Study Design and Conduct Limitations**

Study	Selection <sup>a</sup>	Blinding <sup>b</sup>	Delivery of Test <sup>c</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Statistical <sup>f</sup>
Clark et al (2018) <sup>4</sup>	2. convenience sample	1. Blinding unclear	1. Timing of liquid and tissue biopsy varied (0-60 days)		1. No description of indeterminate and missing samples	
Zhou et al (2018) <sup>5</sup>	2. convenience sample	1. Blinding unclear	1. Timing of liquid and tissue biopsy not reported		1. No description of indeterminate and missing samples-	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

<sup>a</sup> Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

<sup>b</sup> Blinding key: 1. Not blinded to results of reference or other comparator tests.

<sup>c</sup> Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

<sup>d</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>e</sup> Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

<sup>f</sup> Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

## ***Circulating Tumor Cells***

The clinical validity of each commercially available CTC test must be established independently, which has not been done to date.

### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

## ***Circulating Tumor DNA***

### ***Direct Evidence***

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Merker et al (2018) concluded that no such trials have been reported for ctDNA tests.(2)

### ***Chain of Evidence***

To develop a chain of evidence or a decision model requires explication of the elements in the model and evidence that is sufficient to demonstrate each of the links in the chain of evidence or the validity of the assumptions in the decision model.

A chain of evidence for ctDNA tests could be established if the ctDNA test has high agreement with standard tissue testing (clinical validity) for identifying driver mutations and the standard tissue testing has proven clinical utility with high levels of evidence. A chain of evidence can also be demonstrated if the ctDNA test is able to detect driver mutations when standard methods cannot, and the information from the ctDNA test leads to management changes that improve outcomes.

The evidence is insufficient to demonstrate test performance for currently available ctDNA tests except for lung cancer; therefore, no inferences can be made about clinical utility.

## ***Circulating Tumor Cells***

### ***Direct Evidence***

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Trials of using CTCs to select treatment are ongoing (see Table 5 in Supplemental Information).

### *Chain of Evidence*

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility.

## **Section Summary: Selecting Treatment in Advanced Cancer**

### ***Circulating Tumor DNA***

For indications reviewed herein, there is no direct evidence that selecting targeted treatment using ctDNA improves the net health outcome compared with selecting targeted treatment using tumor tissue testing. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. One commercially available test (OncoBEAM RAS CRC assay) has promising clinical validity data that needs replication. The evidence is insufficient to demonstrate test performance for currently available ctDNA tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

### ***Circulating Tumor Cells***

For indications reviewed herein, there is no direct evidence that selecting targeted treatment using CTCs improves the net health outcome compared with selecting targeted treatment using tumor tissue testing. Trials are ongoing. 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 evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

## **MONITORING TREATMENT RESPONSE IN CANCER**

### **Clinical Context and Test Purpose**

Monitoring of treatment response in cancer may be performed using tissue biopsy or imaging methods. Another proposed purpose of liquid biopsy testing in patients who have advanced cancer is to monitor treatment response, which could allow for changing therapy before clinical progression and potentially improve outcomes.

The question addressed in this evidence review is: Does ctDNA or CTC testing to monitor treatment response in patients with cancer improve the net health outcome?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is patients who are being treated for cancer.

### ***Interventions***

The test being considered is liquid biopsy using either ctDNA or CTCs. For ctDNA tests, the best unit for quantifying DNA burden has not been established.(2)

### ***Comparators***

Standard monitoring methods for assessing treatment response are tissue biopsy or imaging methods.

### **Outcomes**

The outcome of primary interest is progression-free survival.

The timing of interest for survival outcomes varies by type of cancer.

### **Review of Evidence**

#### **Clinically Valid**

##### ***Circulating Tumor DNA***

Merker et al (2018) identified several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes as well as studies demonstrating that ctDNA can identify the emergence of resistance variants.(2) However, they reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and concluded that clinical validity had not been established.

##### ***Circulating Tumor Cells***

Systematic reviews and meta-analyses describing an association between CTCs and poor prognosis have been reported for metastatic breast cancer,(6-9) CRC,(10,11) hepatocellular cancer,(12) prostate cancer,(13-15) head and neck cancer,(26) and melanoma.(17)

The clinical validity of each commercially available CTC test must be established independently, which has not been done to date.

#### **Clinically Useful**

### **Review of Evidence**

##### ***Circulating Tumor DNA***

###### ***Direct Evidence***

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Merker et al (2018) concluded that there is no evidence that changing treatment before clinical progression, at the time of ctDNA progression, improves patient outcomes.(2)

###### ***Chain of Evidence***

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate test performance for currently available ctDNA tests for monitoring treatment response; therefore, no inferences can be made about clinical utility.

##### ***Circulating Tumor Cells***



### *Direct Evidence*

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. Smerage et al (2014) reported on the results of a randomized controlled trial of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after 1 cycle of first-line therapy could improve overall survival (OS; the primary study outcome).<sup>(18)</sup> Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median OS between arms C1 (10.7 months) and C2 12.5 months;  $p=0.98$ ). CTC levels were strongly prognostic, with a median OS for arms A, B, and C (C1 and C2 combined) of 35 months, 23 months, and 13 months, respectively ( $p<0.001$ ). This trial showed the prognostic significance of CTCs in patients with rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility through a chain of evidence.

## **Section Summary: Monitoring Treatment Response in Cancer**

### ***Circulating Tumor DNA***

For indications reviewed herein, there is no direct evidence that using ctDNA to monitor treatment response improves the net health outcome compared with standard methods. 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. The evidence is insufficient to demonstrate test performance for currently available ctDNA tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

### ***Circulating Tumor Cells***

For indications reviewed herein, there is no direct evidence that using CTCs to monitor treatment response improves the net health outcome compared with standard methods. 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 evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

## **PREDICTING RISK OF RELAPSE**

### **Clinical Context and Test Purpose**

Monitoring for relapse after curative therapy in patients with cancer may be performed using imaging methods and clinical examination. Another proposed purpose of liquid biopsy testing

in patients who have cancer is to detect and monitor for residual tumor, which could lead to early treatment that would eradicate residual disease and potentially improve outcomes.

The question addressed in this evidence review is: Does ctDNA or CTC testing to predict the risk of relapse in patients who have received curative treatment for cancer improve the net health outcome?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest patients who have received curative treatment for cancer.

### ***Interventions***

The test being considered is liquid biopsy using either ctDNA or CTCs.

### ***Comparators***

Standard monitoring methods for detecting relapse are imaging methods and clinical examination.

### ***Outcomes***

The outcome of primary are OS, disease-specific survival, test validity, morbid events, and medication use.

The timing of interest for survival outcomes varies by type of cancer.

## **Review of Evidence**

### **Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

### ***Circulating Tumor DNA***

Merker et al (2018) identified several proof-of-principle studies demonstrating an association between persistent detection of ctDNA after local therapy and high risk of relapse.(2) However, current studies are retrospective and have not systematically confirmed that ctDNA is being detected before the metastatic disease has developed. They concluded that the performance characteristics had not been established for any assays.

### ***Circulating Tumor Cells***

Rack et al (2014) published results of a large multicenter study in which CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy using the CellSearch System.(19) After chemotherapy, 22% of patients were CTC-positive, and CTC positivity was negatively associated with prognosis.

Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer,(20) CRC,(21) bladder cancer,(22,23) liver cancer,(24) and esophageal cancer.(25)

The clinical validity of each commercially available CTC test must be established independently.

## **Clinically Useful**

The evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests for predicting relapse; therefore, no inferences can be made about clinical utility.

### ***Circulating Tumor DNA and Circulating Tumor Cells***

#### ***Direct Evidence***

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Merker et al (2018) concluded that there is no evidence that early treatment before relapse, based on changes in ctDNA, improves patient outcomes.(2) Similarly, no trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes.

#### ***Chain of Evidence***

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence to demonstrate clinical utility requires an evidence-based management pathway. There is not an explicated, evidence-based management pathway for the use of ctDNA or CTCs to guide early treatment before relapse.

## **Section Summary: Predicting Risk of Relapse**

### ***Circulating Tumor DNA***

For indications reviewed herein, there is no direct evidence that using ctDNA to predict the risk of relapse improves the net health outcome compared with standard methods. 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. The evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

### ***Circulating Tumor Cells***

For indications reviewed herein, there is no direct evidence that using CTCs to predict the risk of relapse improves the net health outcome compared with standard methods. 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 evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

## **SCREENING FOR CANCER IN ASYMPTOMATIC INDIVIDUALS**

### **Clinical Context and Test Purpose**

It has also been proposed that liquid biopsies could be used to screen asymptomatic patients for early detection of cancer, which could allow for initiating treatment at an early stage, potentially improving outcomes.

The question addressed in this evidence review is: Does ctDNA or CTC testing to screen for cancer in asymptomatic individuals improve the net health outcome?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is asymptomatic individuals at high risk of developing cancer.

The setting of interest is primary care or oncology care.

### ***Interventions***

The test being considered is liquid biopsy using either ctDNA or CTCs.

### ***Comparators***

The following practice is currently being used: standard screening methods.

### ***Outcomes***

The outcomes of primary interest include overall survival, disease-specific survival, and test validity.

The timing of interest for survival outcomes varies by type of cancer.

Diagnosis of cancer that is not present or would not have become clinically important (false-positives and overdiagnosis) would lead to unnecessary treatment and treatment-related morbidity.

## **Review of Evidence**

### **Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

### ***Circulating Tumor DNA***

Merker et al (2018) reported that there is no evidence of clinical validity for the use of ctDNA in asymptomatic individuals.(2)

### ***Circulating Tumor Cells***

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer.(26,27) Reported sensitivity was low in both cancers (42% and 35%) overall. Sensitivity was lower in patients with early-stage cancer, suggesting that the test would not be useful as an initial screen.

The clinical validity of each commercially available CTC test must be established independently.

### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive

correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

## **Review of Evidence**

### ***Circulating Tumor DNA and Circulating Tumor Cells***

#### ***Direct Evidence***

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

To evaluate the utility of the tests for screening, guidelines would be needed to establish criteria for screening intervals and appropriate follow-up for positive tests. After such guidelines are established, studies demonstrating the liquid biopsy test performance as cancer screening test would be needed.

#### ***Chain of Evidence***

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Also, a chain of evidence requires an evidence-based management pathway. There is not an explicated, evidence-based management pathway for the use of ctDNA or CTCs for the screening of asymptomatic patients.

The evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests as a screening test for cancer; therefore, no inferences can be made about clinical utility through a chain of evidence.

## **Section Summary: Screening for Cancer in Asymptomatic Individuals**

### ***Circulating Tumor DNA***

For indications reviewed herein, there is no direct evidence that using ctDNA to screen for cancer in asymptomatic individuals improves the net health outcome compared with standard methods. 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. The evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

### ***Circulating Tumor Cells***

For indications reviewed herein, there is no direct evidence that using CTCs to screen for cancer in asymptomatic individuals improves the net health outcome compared with standard methods. 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 evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

## **SUMMARY OF EVIDENCE**

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 for the indications covered in this review. The clinical validity of FoundationOne Liquid compared to tissue biopsy with FoundationOne comprehensive genetic testing 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 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. 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. 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. 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 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 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 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 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 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. 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. 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.

**Supplemental Information**

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**NATIONAL COMPREHENSIVE CANCER NETWORK**

There is no general NCCN guideline on the use of liquid biopsy. Refer to treatment recommendations by cancer type for specific recommendations.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in the Table 5.

**Table 5. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			

NCT02889978 <sup>a</sup>	The Circulating Cell-free Genome Atlas Study	15000	Mar 2024
<b>Unpublished</b>			
NCT02140463	Next generation personalized therapy with plasma DNA Trial 2 in refractory solid tumors (The NEXT-2 Trial)	260	Dec 2020

NCT: national clinical trial

## Government Regulations

### National:

There is no Medicare National Coverage Determination.

### Local:

**MolDX: OncoCee™ Billing and Coding Guidelines** – A55245; Original date 2/16/17; Revision date: 7/24/21, **retired 7/24/21**

The MolDX Contractor has completed a preliminary review of Biocept’s OncoCee, Circulating Tumor Cell (CTC) Assay to detect metastatic disease for breast, prostate, lung, and colon cancer. To date, the assays have insufficient evidence to support reasonable and necessary criteria for Medicare reimbursement. Therefore, we will deny these CTC assay services.

To receive a CTC assay service denial, please submit the following claim information:

- Select the appropriate CPT code for the service rendered:
  - **86152**-Cell enumeration using immunologic selection and identification in fluid specimen (eg, CTC in blood)
  - **86153**-CTC, physician interpretation and report

**Circulating Tumor Cell Marker Assays** - L32218; revision effective date 10/1/2014, **retired 9/30/15**

### Coverage Indications Limitations and/or Medical Necessity

This is a coverage policy for the CellSearch (Veridex) circulating tumor cell (CTC) assay. All other methods for circulating tumor cell detection, including reverse-transcription polymerase chain reaction PCR (RTPCR) Assays, are non-covered.

CTCs represent the point in the metastatic process of solid tumors when cells from a primary tumor invade, detach, disseminate, colonize and proliferate in a distant site. Detection of elevated CTCs during therapy is an accurate indication of subsequent rapid disease progression and mortality in breast, colorectal and prostate cancer. Therefore, CTC will be limited to metastatic breast, colorectal and prostate cancer. CTC testing for all other malignant diagnoses will be denied as not reasonable and necessary.

The CellSearch assay, an independent predictor of progression-free survival and overall survival in patients with metastatic breast, colorectal and prostate cancer, involves the automated immunomagnetic selection of CTCs based on an anti-EpCAM antibody cell capture. To perform this assay, a 7.5 ml aliquot of blood is incubated with EpCAM antibody-covered ferroparticles (nanotechnology). Circulating epithelial cells that express EpCAM are isolated in a magnetic field without centrifugation.



The supernatant containing unbound cells is removed. The enriched cell samples are labeled with a fluorescent nuclei acid dye and two monoclonal antibodies (CD 45 and Cytokeratin 8, 18, 19), each tagged with distinct fluorescent compounds. The stained cells are then analyzed on a fluorescence microscope. Digital fluorescent images are screened by a qualified technician for CTCs; the cell has a nucleus, expresses keratin (EpCAM and CK) and does not express CD45.

The assay findings are verified by a pathologist and issued in a report as a numerical result where more than 5 cells per 7.5 ml of whole blood predicts worse prognosis in patients with known recurrent breast and prostate cancer, and more than 3 cells are predictive of shorter progression free survival (PFS) and overall survival (OS) in metastatic colorectal cancer.

### **Utilization Guidelines**

Services performed for excessive frequency are not medically necessary. Patients should be treated on an individual basis as indicated by the response to treatment. The intent of the following guidelines is to provide the maximum amount of tests required to adequately follow disease progression or treatment response.

WPS Medicare expects physicians to limit CTC testing to only times when the CTC information may change treatment. Documentation maintained in the patient record must support medical necessity and be available upon request.

Frequency:

- Baseline – limited to once prior to initiation of tumor-type specific chemotherapy
- Follow-up during chemotherapy treatment - repeat every 4-6 weeks
- Surveillance with no chemotherapy treatments - repeat every 4-6 months

A rapid rise in the CTC value usually indicates aggressive disease and impending adverse outcome. WPS Medicare would expect to see no further CTC testing after the transition to palliative/hospice care.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## **Related Policies**

- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- Genetic Testing – Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies
- Genetic Testing for *KRAS*, *NRAS* and *BRAF* Mutation Analysis in Metastatic Colorectal Cancer
- Genetic Testing - Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through December, 2021 the date the research was completed.*

### Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/09	12/1/08	10/13/08	Joint policy established
3/1/12	12/13/11	12/21/11	Routine maintenance; references updated
9/1/12	6/12/12	6/19/12	Codes updated. No change in policy status.
7/1/13	4/16/13	4/22/13	Codes updated. Medicare and Medicaid information updated to reflect CMS coverage of CellSearch (Veridex) circulating tumor cell (CTC) assay.
11/01/14	8/19/14	8/25/14	Routine maintenance; references updated
1/1/16	10/13/15	10/27/15	Routine maintenance
1/1/17	10/11/16	10/11/16	Policy extensively revised and title changed to "Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)." Mirrors BCBSA
1/1/18	10/19/17	10/19/17	<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• Added note: policy does not address the use of blood-based testing for epidermal growth factor receptor mutations.</li> </ul>
1/1/19	10/16/18	10/16/18	Routine maintenance
11/1/19	8/20/19		<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• Disclaimer added to MPS regarding what this policy does NOT cover</li> </ul>
5/1/20	2/18/20		<ul style="list-style-type: none"> <li>• Routine maintenance</li> </ul>
5/1/21	2/16/21		<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• Added note: the indication for liquid biopsy to select targeted treatment for breast cancer was removed from this policy. Per BCBSA this indication will be added to a new policy to be developed on gene expression profiling and circulating tumor DNA testing for breast cancer management.</li> </ul>

			<ul style="list-style-type: none"> <li>• Added 0239U code to Investigational, not medically necessary.</li> </ul>
5/1/22	2/15/22		<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• No references added</li> <li>• Policy statement unchanged</li> <li>• 3/23/22 the below paragraph was removed from under the Description/Background and MPS. This policy does not address the use of blood-based testing for driver mutations to select therapy in non-small-cell lung cancer (i.e. EGFR) or metastatic colorectal cancer, blood-based testing for use of liquid biopsy for detection or risk assessment of prostate cancer or AR-V7 circulating tumor cells for metastatic prostate cancer, or liquid biopsy to select targeted treatment for breast, ovarian, or pancreatic cancer.</li> </ul>

Next Review Date: 1<sup>st</sup> Qtr, 2023

**BLUE CARE NETWORK BENEFIT COVERAGE**  
**POLICY: CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER**  
**MANAGEMENT (LIQUID BIOPSY)**

**I. Coverage Determination:**

<b>Commercial HMO (includes Self-Funded groups unless otherwise specified)</b>	Not covered
<b>BCNA (Medicare Advantage)</b>	Refer to the Medicare information under the Government Regulations section of this policy.
<b>BCN65 (Medicare Complementary)</b>	Coinsurance covered if primary Medicare covers the service.

**II. Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.