



Louisiana

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

Policy # 00497

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

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 (ctDNA) and circulating tumor cells (CTCs) to be **investigational*** for all indications (see Policy Guidelines).

Policy Guidelines

This policy does not address the use of blood-based testing for epidermal growth factor receptor variants in non-small-cell lung cancer or the use of AR-V7 CTCs for metastatic prostate cancer.

Background/Overview

Liquid biopsy refers to the analysis of ctDNA or CTCs as methods of noninvasively characterizing tumors and tumor genome from the peripheral blood.

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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. 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. 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. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for detecting CTCs is prognostic, through quantification of circulating levels.

DETECTING CTDNA AND CTCs

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total 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 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.

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.

Examples of liquid biopsy tests related to indications covered in this review are shown in Table 1. Note that targeted therapy in non-small-cell lung cancer and use of AR-V7 CTC liquid biopsy for metastatic prostate cancer are addressed in separate reviews.

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Table 1. Examples of Liquid Biopsy Tests

Manufacturer	Test	Type of Liquid Biopsy
Biocept	Liquid Biopsies for breast, colorectal, gastric, prostate, and melanoma	ctDNA
CellMax Life	CellMax-LBx Liquid Biopsy	CTC plus ctDNA
	CellMax-CRC Colorectal Cancer Early Detection Test	CTC
	CellMax-PanCa Monitoring Test	CTC
	CellMax-Prostate Cancer Test	CTC
Cynvenio	ClearID ^{®†} Solid Tumor Panel	ctDNA
	ClearID ^{®†} HER2 Expression LiquidBiopsy	CTC
Foundation Medicine	FoundationACT ^{®†}	ctDNA
Guardant Health	Guardant360 ^{®†}	ctDNA
IVDiagnostics	Velox ^{™†}	CTC
Pathway Genomics	CancerIntercept ^{®†} Detect	ctDNA
Personal Genome Diagnostics	PlasmaSELECT ^{™†}	ctDNA
Sysmex Inostics	OncoBEAM ^{™†}	ctDNA
Circulogene	Theranostics	ctDNA

CTC: circulating tumor cell; ctDNA: circulating tumor DNA.

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. 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 CRC, 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.

Centers for Medicare and Medicaid Services (CMS)

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 CTC assay.

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits

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and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

This evidence review evaluates uses for liquid biopsies not addressed in other reviews. If a separate evidence review exists, then conclusions reached there supersede conclusions here. The main criterion for inclusion in this review is the limited evidence on the clinical validity. The use of liquid biopsy for non-small-cell lung cancer is addressed in medical policy 00597. The use of AR-V7 CTC liquid biopsy for metastatic prostate cancer will be addressed in medical policy 00403.

SELECTING TREATMENT IN ADVANCED CANCER

Clinical Context and Test Purpose

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. One purpose of liquid biopsy testing of patients who have advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

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

The following PICOTS were used to select literature to inform this review.

Patients

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.

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.

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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 (e.g., 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.

Timing

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

Setting

The setting of interest is oncology care.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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. 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, which is addressed in medical policy 00597 and is not discussed here. 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 and *PIK3CA* and *ESR1* variants in breast cancer were identified.

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The clinical validity of the OncoBEAM RAS CRC assay has been evaluated in 115 patients with metastatic CRC. Study characteristics, and results are shown in Tables 2 and 3. Study relevance, design, and conduct gaps are described in Tables 4 and 5. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. Multiple high-quality studies are needed to establish the clinical validity of a test.

Table 2. Clinical Validity Study Characteristics of the OncoBEAM RAS CRC Assay

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and OncoBEAM	Blinding of Assessors
Vidal et al (2017)	<ul style="list-style-type: none"> Patients from Spain with histologically confirmed metastatic CRC Anti-EGFR treatment-naive Enrolled from 2009 to 2016 	Retrospective-prospective	Analysis of tissue samples conducted using institutional standard-of-care procedures	<ul style="list-style-type: none"> Tissue collected before blood Median interval, 48 d (range, 0-1783 d) 	Yes

CRC: colorectal cancer; EGFR: epidermal growth factor receptor.

Table 3. Clinical Validity Study Results of the OncoBEAM RAS CRC Assay

Study	Initial N	Final N	Excluded Samples	RAS Variant-Positive, % ^a	Sensitivity ^b	Specificity ^b	PPV ^b	NPV ^b
Vidal et al (2017)	NA	115	No description of samples excluded from comparison to tissue results	51	96 (87 to 100)	90 (79 to 96)	90 (79 to 96)	96 (88 to 100)

CI: confidence interval; CRC: colorectal cancer; NA: not available; NPV: negative predictive value; PPV: positive predictive value.

^a With tissue biopsy reference standard.

^b Values are percent with 95% confidence interval.

^b Confidence intervals not reported in publication; calculated from data provided.

Table 4. Relevance Gaps for Clinical Validity Studies of the OncoBEAM RAS CRC Assay

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Vidal et al (2017)	None noted	None noted	None noted	None noted	None noted

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

CRC: colorectal cancer.

^a 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.

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

^c 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.

^d 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).

^e 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).

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Table 5. Study Design and Conduct Gaps for Clinical Validity Studies of the OncoBEAM RAS CRC Assay

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Completeness of Follow-Up ^e	Statistical ^f
Vidal et al (2017)	1. Not clear whether samples were consecutive or convenience	None noted	None noted	1. Registration not described	1. Not clear whether there were samples that were insufficient for analysis or failed to produce results	1. CIs not reported but calculated based on data provided

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CI: confidence interval; CRC: colorectal cancer.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c 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.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Follow-Up key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Circulating Tumor Cells

In breast cancer, observations that estrogen receptor–positive tumors can harbor estrogen receptor–negative CTCs, that overt distant metastases and CTCs can have discrepant human epidermal growth factor receptor 2 status compared with the primary tumor, and that the programmed death-ligand 1 is frequently expressed on CTCs in patients with hormone receptor–positive, *HER2*-negative breast cancer have suggested that trials investigating whether CTCs can be used to select targeted treatment are needed.

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.

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.



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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 (see Medical policy 00597); 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.

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.

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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 PICOTS were used to select literature to inform this review.

Patients

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.

Comparators

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

Outcomes

The outcome of primary interest is progression-free survival.

Timing

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

Setting

The setting of interest is oncology care.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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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. 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, CRC, hepatocellular cancer, prostate cancer, head and neck cancer, and melanoma.

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

Clinically Useful

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.

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). 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

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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 metastatic breast cancer receiving first-line chemotherapy, but also that there was no effect on OS if patients with persistently increased CTC levels after 21 days of first-line chemotherapy were switched to alternative cytotoxic therapy.

Trials demonstrating that use of CTCs to monitor treatment for the purpose of making treatment changes are needed to demonstrate clinical utility.

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 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

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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 with cancer improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

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 interest is progression-free survival.

Timing

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

Setting

The setting of interest is oncology care.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

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. 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

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using the CellSearch System. 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, CRC, bladder cancer, liver cancer, and esophageal cancer.

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. 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

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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 PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is asymptomatic individuals.

Interventions

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

Comparators

Outcomes

The outcome of primary interest is progression-free survival.

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.

Timing

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

Setting

The setting of interest is primary care or oncology care.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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Clinically Valid

Circulating Tumor DNA

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

Circulating Tumor Cells

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer. 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.

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

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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 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 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. 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. 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 monitor treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

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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 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 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 risk of relapse, the evidence includes observational studies. 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 risk of relapse, the evidence includes observational studies. 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 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. 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. 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.

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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

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.

Next Scheduled Review Date: 07/2019

Coding

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