Medical Policy

BlueCross BlueShield Kansas
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Title: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Related Policies:	▪ *Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management* ▪ *Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies* ▪ *Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, NTRK, and HER2)* ▪ *Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer*

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced cancer	Interventions of interest are: • Testing of circulating tumor DNA to select targeted treatment	Comparators of interest are: • Using tissue biopsy to select treatment	Relevant outcomes include: • Overall survival

Populations	Interventions	Comparators	Outcomes
			• Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With advanced cancer	Interventions of interest are: • Testing of circulating tumor cells to select targeted treatment	Comparators of interest are: • Using tissue biopsy to select treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With cancer	Interventions of interest are: • Testing of circulating tumor DNA to monitor treatment response	Comparators of interest are: • Standard methods for monitoring treatment response	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With cancer	Interventions of interest are: • Testing of circulating tumor cells to monitor treatment response	Comparators of interest are: • Standard methods for monitoring treatment response	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • Who have received curative treatment for cancer	Interventions of interest are: • Testing of circulating tumor DNA to predict risk of relapse	Comparators of interest are: • Standard methods for predicting relapse	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • Who have received curative treatment for cancer	Interventions of interest are: • Testing of circulating tumor cells to predict risk of relapse	Comparators of interest are: • Standard methods for predicting relapse	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include:

Populations	Interventions	Comparators	Outcomes
• Who are asymptomatic and at high risk of developing cancer	• Testing of circulating tumor DNA to screen for cancer	• Standard screening methods	• Overall survival • Disease-specific survival • Test validity
Individuals: • Who are asymptomatic and at high risk of developing cancer	Interventions of interest are: • Testing of circulating tumor cells to screen for cancer	Comparators of interest are: • Standard screening methods	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity

DESCRIPTION

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as "liquid biopsy," have several potential uses for guiding therapeutic decisions in patients with cancer or being screened for cancer. This evidence review evaluates uses for liquid biopsies *not addressed in a separate review*. If a separate evidence review exists, then conclusions reached there supersede conclusions here.

OBJECTIVE

The objective of this evidence review is to determine whether circulating tumor DNA or circulating tumor cell testing in individuals with cancer or at risk of developing cancer improves the net health outcome compared with standard screening as well as diagnostic and management practices. This evidence review evaluates uses for liquid biopsies *not addressed in a separate review*. If a separate evidence review exists, then conclusions reached there supersede conclusions here.

BACKGROUND

Liquid Biopsy

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

Circulating Tumor DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs.[1,] Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

Circulating Tumor Cells

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1 to 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 epithelial cell adhesion molecules (EpCAM) and cytokeratins. The primary reason for detecting CTCs is prognostic, through quantification of circulating levels.

Detecting Circulating Tumor DNA and Circulating Tumor Cells

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cell-free DNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (e.g. BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver mutations, which can impact therapy decisions, or untargeted without knowledge of specific variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

Circulating tumor cell assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). Circulating tumor cells can then be detected using immunologic, molecular, or functional assays.[1,]

Note that targeted therapy in non-small-cell lung cancer and metastatic colorectal cancer, use of liquid biopsy for detection or risk assessment of prostate cancer, and use of AR-V7 CTC liquid biopsy for metastatic prostate cancer are addressed in separate reviews.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Certain liquid biopsy-based assays have been cleared or approved by the FDA as companion diagnostic tests (Table 1).[2,] These indication are addressed in other evidence opinions and are listed here for information only. Refer to the associated evidence opinion (Column 5) for details.

Table 1. FDA Cleared or Approved Liquid Biopsy Companion Diagnostic Tests

Diagnostic Name (Manufacturer)	Indication	Biomarker	Drug Trade Name (Generic)	Related Evidence Opinion
Agilent Resolution ctDx FIRST assay	NSCLC	KRAS	Krazati (adagrasib)	2.04.45
cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	NSCLC	*EGFR* (*HER1*)	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Iressa (gefitinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Tarceva (erlotinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Gilotrif (afatinib)	2.04.45
FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NSCLC	*EGFR (HER1)*	Exkivity (mobocertinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Iressa (gefitinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Tarceva (erlotinib)	2.04.45
	NSCLC	*MET*	Tabrecta (capmatinib)	2.04.45
	NSCLC	*ROS1*	Rozlytrek (entrectinib)	2.04.45
	NSCLC	ALK	Alecensa (alectinib)	2.04.45
	Ovarian Cancer	*BRCA1* and *BRCA2*	Rubraca (rucaparib)	2.04.156
	Solid Tumors	*ROS1*	Rozlytrek (entrectinib)	5.01.31
	Breast Cancer	*PIK3CA*	Piqray (alpelisib)	2.04.151
	Metastatic Castrate Resistant Prostate Cancer	*BRCA1,BRCA2* and *ATM*	Lynparza (olaparib)	2.04.155

Diagnostic Name (Manufacturer)	Indication	Biomarker	Drug Trade Name (Generic)	Related Evidence Opinion
	Metastatic Castrate Resistant Prostate Cancer	*BRCA1 and BRCA2*	Rubraca (rucaparib)	2.04.155
Guardant360 CDx (Guardant Health, Inc.)	NSCLC	*EGFR* (*HER1*)	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Rybrevant (amivantamb)	2.04.45
	NSCLC	*KRAS*	Lumakras (sotorasib)	2.04.45
	NSCLC	ERBB2	ENHERTU (fam-trastuzumab deruxtecan-nxki)	2.04.45
	Breast Cancer	*ESR1* *ERB2*	Orserdu (elacestrant) ENHERTU (fam-trastuzumab deruxtecan-nxki)	2.04.151 In development for 2.04.151
therascreen PIK3CA RGQ PCR Kit (QIAGEN GmbH)	Breast Cancer	*PIK3CA*	Piqray (alpelisib)	2.04.151

Source: FDA (2023)[2,]
FDA: US Food and Drug Administration; NSCLC: non-small cell lung cancer

POLICY

The use of circulating tumor DNA and/or circulating tumor cells is considered **experimental / investigational** for all indications reviewed herein not otherwise addressed in policy guidelines.

POLICY GUIDELINES

This policy does not address the use of blood-based testing (liquid biopsy) to select targeted treatment for breast cancer, non-small cell lung cancer, melanoma/glioma, ovarian cancer, pancreatic cancer, and prostate cancer, the use of liquid biopsy to select immune checkpoint inhibitor therapy, tumor-Informed circulating tumor DNA testing for cancer management, comprehensive genomic profiling for selecting targeted cancer therapies, the use of blood-based testing for detection or risk assessment of prostate cancer; or the use of AR-V7 circulating tumor cells for metastatic prostate cancer.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through June 14, 2024.

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 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 clinical validity.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

SELECTING TREATMENT IN ADVANCED CANCER

Clinical Context and Test Purpose

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

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

Populations

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

Interventions

The test being considered is liquid biopsy using either circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs). Both targeted polymerase chain reaction-based assays and broad next-generation sequencing-based approaches are available. Individuals with negative liquid biopsy results should be reflexed to tumor biopsy testing if they are able to undergo tissue biopsy.[3,]

Comparators

For individuals who are able to undergo a biopsy, molecular characterization of the tumor is performed using standard tissue biopsy samples. Patients unable to undergo a 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 (e.g., targeted therapy) without a tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival.

In individuals able to undergo a tissue biopsy, negative liquid biopsies reflex to tissue testing. In individuals unable to undergo a 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

Systematic Reviews
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.[3,] 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 (CRC), and breast cancer. Therefore, they are 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 CRC.

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 (RCTs).

Merker et al (2018) concluded that no such trials have been reported for ctDNA tests.[3,]

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 a 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.

For the indications reviewed herein, the evidence is insufficient to demonstrate test performance for currently available ctDNA tests; 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 RCTs.

Trials of using CTCs to select treatment are ongoing (see Table 2 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

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. 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.

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 individuals who have advanced cancer is to monitor treatment response, which could allow for changing therapy before clinical progression and potentially improve outcomes.

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

Patients

The relevant population of interest are individuals 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.[3,]

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
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 correlations between changes in ctDNA levels and tumor response or outcomes, as well as studies demonstrating that ctDNA can identify the emergence of resistant variants.[3,] 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,[4,5,6,7,] CRC,[8,9,] hepatocellular cancer,[10,] prostate cancer,[11,12,13,] head and neck cancer,[14,] and melanoma.[15,]

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

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 RCTs.

Merker et al (2018) concluded there is no evidence that changing treatment before clinical progression, at the time of ctDNA progression, improves patient outcomes.[3,]

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 RCTs. Smerage et al (2014) reported on the results of an RCT 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).[16,] 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=.98). Circulating tumor cell 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<.001). This trial showed the prognostic significance of CTCs in patients, which 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

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.

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 individuals with cancer may be performed using imaging methods and clinical examination. Another proposed purpose of liquid biopsy testing in individuals 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 following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals 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 outcomes of primary interest 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.[3,] 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.

Chidambaram et al (2022) conducted a systematic review and meta-analysis of the clinical utility of circulating tumor DNA testing in esophageal cancer. [17,] Four retrospective studies (N=233, N range 35 to 97) provided data to assess ctDNA for monitoring for recurrence after treatment. The pooled sensitivity was 48.9% (range, 29.4% to 68.8%) and specificity was 95.5% (range, 90.6% to 97.9%).

Circulating Tumor Cells

Rack et al (2014) published the 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.[18,] 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,[19,]CRC[20,] bladder cancer,[21,22,] liver cancer,[23,] and esophageal cancer.[24,]

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

CLINICALLY USEFUL

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 RCTs.

Merker et al (2018) concluded that there is no evidence that early treatment before relapse, based on changes in ctDNA, improves patient outcomes.[3,] 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

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 ctDNA tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

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

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

Populations

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

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 OS , 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 overdiagnoses) 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 there is no evidence of clinical validity for the use of ctDNA in asymptomatic individuals.[3,]

Circulating Tumor Cells

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer.[25,26,] 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

The evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests for screening for cancer in asymptomatic individuals; 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 RCTs.

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 a 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

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 ctDNA tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

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.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given

to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology
In 2022, the American Society of Clinical Oncology (ASCO) published a Provisional Clinical Opinion on somatic genetic testing in individuals with metastatic or advanced cancer.[27,] The Opinion addressed circulating tumor DNA (ctDNA) testing under additional topics but did not include a specific statement with a strength of recommendation rating. The panel noted, "There is a growing body of evidence on the clinical utility of genomic testing on cfDNA in the plasma," citing the systematic review conducted by Merker et al (2018)[3,] The panel also noted that ASCO will update that systematic review over the next few years.

The discussion also included the following points:

- "In patients without tissue-based genomic test results, treatment may be based on actionable alterations identified in cfDNA."
- "Testing is most helpful when genomic testing is indicated, archival tissue is unavailable, and new tumor biopsies are not feasible."
- "cfDNA levels themselves may be prognostic and early cfDNA dynamics may serve as an early predictor of therapy response or resistance."
- "Ongoing studies are expected to better delineate the clinical utility of serial liquid biopsies."

National Comprehensive Cancer Network
There is no general National Comprehensive Cancer Network (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 ongoing trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06090214	Circulating Tumor Cells for the Diagnosis of Intestinal-type Adenocarcinoma of the Ethmoid : a Pilot Study	42	Dec 2025
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study	15254	Mar 2024
NCT03957564	Liquid Biopsy in Monitoring the Neoadjuvant Chemotherapy and Operation in Patients With Resectable or Locally Advanced Gastric or Gastro-oesophageal Junction Cancer	40	May 2024
NCT05582122	SURVEILLE-HPV: National, Multicenter, Open-label, Randomized, Phase II Study Evaluating HPV16 Circulating DNA as Biomarker to Detect the Recurrence, in Order to	420	Apr 2031

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Improve Post Therapeutic Surveillance of HPV16-driven Oropharyngeal Cancers		
NCT05764044	Adjuvant Chemotherapy in Cell-free Human Papillomavirus Deoxyribonucleic Acid (cfHPV-DNA) Plasma Positive Patients: A Biomarker In Locally Advanced Cervical Cancer (CC)	50	Dec 2023

[a]Denotes industry sponsored or co-sponsored trial.
NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
81400	Molecular Pathology Procedure, Level 1 (Eg, Identification Of Single Germline Variant [Eg, Snp] By Techniques Such As Restriction Enzyme Digestion Or Melt Curve Analysis)
81401	Molecular Pathology Procedure, Level 2 (Eg, 2-10 Snps, 1 Methylated Variant, Or 1 Somatic Variant [Typically Using Nonsequencing Target Variant Analysis], Or Detection Of A Dynamic Mutation Disorder/Triplet Repeat
81402	Molecular Pathology Procedure, Level 3 (Eg, >10 Snps, 2-10 Methylated Variants, Or 2-10 Somatic Variants [Typically Using Non-Sequencing Target Variant Analysis], Immunoglobulin And T-Cell Receptor Gene Rearrangements, Duplication/Deletion Variants Of 1 Exon
81403	Molecular pathology procedure, level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex pcr in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular Pathology Procedure, Level 5 (Eg, Analysis Of 2-5 Exons By DNA Sequence Analysis, Mutation Scanning Or Duplication/Deletion Variants Of 6-10 Exons, Or Characterization Of A Dynamic Mutation Disorder/Triplet Repeat By Southern Blot Analysis)
81405	Molecular Pathology Procedure, Level 6 (Eg, Analysis Of 6-10 Exons By DNA Sequence Analysis, Mutation Scanning Or Duplication/Deletion Variants Of 11-25 Exons, Regionally Targeted Cytogenomic Array Analysis)
81406	Molecular Pathology Procedure, Level 7 (Eg, Analysis Of 11-25 Exons By DNA Sequence Analysis, Mutation Scanning Or Duplication/Deletion Variants Of 26-50 Exons)
81407	Molecular Pathology Procedure, Level 8 (Eg, Analysis Of 26-50 Exons By DNA Sequence Analysis, Mutation Scanning Or Duplication/Deletion Variants Of >50 Exons, Sequence Analysis Of Multiple Genes On One Platform)
81408	Molecular Pathology Procedure, Level 9 (Eg, Analysis Of >50 Exons In A Single Gene By DNA Sequence Analysis)
81479	Unlisted Molecular Pathology Procedure
86152	Cell Enumeration Using Immunologic Selection And Identification In Fluid Specimen (Eg, Circulating Tumor Cells In Blood);

CPT/HCPCS	
86153	Cell Enumeration Using Immunologic Selection And Identification In Fluid Specimen (Eg, Circulating Tumor Cells In Blood); Physician Interpretation And Report, When Required
0091U	Oncology (Colorectal) Screening, Cell Enumeration Of Circulating Tumor Cells, Utilizing Whole Blood, Algorithm, For The Presence Of Adenoma Or Cancer, Reported As A Positive Or Negative Result
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood. CellSearch® HER2 Circulating Tumor Cell

REVISIONS	
01-27-2021	New Policy added to the bcbsks.com web site.
04-01-2021	In Coding section: • Added CPT code 0242U
01-04-2022	Updated Description Section
	Updated Rationale Section
	Updated References Section
09-27-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Added 0338U (effective 10-01-2022)
	Updated References Section
01-03-2023	Updated Coding Section ▪ Added 0357U (eff. 01-01-2023)
10-02-2023	Updated Descriptions Section
	Updated Policy Section ▪ Added "not otherwise addressed in policy guidelines." at the end of the statement
	Updated Policy Guidelines ▪ Changed to read: "This policy does not address the use of blood-based testing (liquid biopsy) to select targeted treatment for breast cancer, non-small cell lung cancer, melanoma/glioma, ovarian cancer, pancreatic cancer, and prostate cancer, the use of liquid biopsy to select immune checkpoint inhibitor therapy, tumor-Informed circulating tumor DNA testing for cancer management, comprehensive genomic profiling for selecting targeted cancer therapies, the use of blood-based testing for detection or risk assessment of prostate cancer; or the use of AR-V7 circulating tumor cells for metastatic prostate cancer."
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box ▪ Removed deleted code 0357U (eff. 10-01-2023)
	Updated References Section
10-08-2024	Updated Descriptions Section

	Updated Rationale Section
	Updated References Section

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