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* ▪ *Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer* ▪ *Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced cancer	**Interventions of interest are:**	**Comparators of interest are:** • Using tissue biopsy to select treatment	**Relevant outcomes include:** • Overall survival

Populations	Interventions	Comparators	Outcomes
	• Testing of circulating tumor DNA to select targeted treatment		• 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 patients 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. This policy does not address the use of blood-based testing for "driver mutations" to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for detection or risk assessment of prostate cancer, use of AR-V7 circulating tumor cells for metastatic prostate cancer, or liquid biopsy to select targeted treatment for breast, ovarian, or pancreatic cancer.

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 (1-2 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 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.

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.

POLICY

The use of circulating tumor DNA and/or circulating tumor cells is considered **experimental / investigational** for all indications reviewed herein.

POLICY GUIDELINES

This policy does not address the use of blood-based testing for "driver mutations" to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for detection or risk assessment of prostate cancer, the use of AR-V7 circulating tumor cells for metastatic prostate cancer, or liquid biopsy to select treatment for breast, ovarian, or pancreatic 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 July 8, 2021.

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. The use of liquid biopsy for non-small-cell lung cancer is addressed in 2.04.143. The use of liquid biopsy for metastatic colorectal cancer (CRC) is addressed in 2.04.53. The use of liquid biopsy for detection or risk assessment of prostate cancer is addressed in 2.04.33. The use of AR-V7 CTC liquid biopsy for metastatic prostate cancer is addressed in 2.04.111. The use of liquid biopsy to select targeted treatment for breast cancer will be addressed in the new policy (to be developed) on Gene Expression Profiling and Circulating Tumor DNA Testing for Breast Cancer Management. The use of liquid biopsy to select therapy in ovarian, pancreatic, and prostate cancer will be addressed in other policies in development.

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 (e.g., 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 cells (CTCs) testing to select treatment in patients with cancer to improve the net health outcome compared with standard tissue testing? Note that the use of a liquid biopsy to select therapy for non-small-cell lung cancer is addressed in 2.04.143, to select therapy for metastatic CRC is addressed in 2.04.53, to select therapy in metastatic prostate cancer is addressed in 2.04.111, and to select targeted treatment for breast cancer is addressed in 2.04.151.will be addressed in the new policy (to be developed) on Gene Expression Profiling and Circulating Tumor DNA Testing for Breast Cancer Management.

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

Populations

The relevant population of interest are patients 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 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 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 patients able to undergo a tissue biopsy, negative liquid biopsies reflex to tissue testing. In patients 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
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, which is addressed in 2.04.143, metastatic CRC, which is addressed in 2.04.53, and breast cancer, which will be addressed in the new policy (to be developed) on Gene Expression Profiling and Circulating Tumor DNA Testing for Breast Cancer Management. Therefore, they are not discussed here.

Merker et al (2018) concluded that while a wide range of ctDNA assays has 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. Preliminary clinical studies of ctDNA assays for detection of potentially targetable variants in other cancers such as *BRAF* variants in melanoma 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 Imitations 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)[4]	Patients with advanced cancer	Retrospective (tissue) and prospective (liquid biopsy)	Tissue biopsy (FoundationOne)	0 to 60 days	Not stated
Zhou et al (2018)[5]	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)[4]	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)[5]							
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. Study Relevance Limitations of Clinical Validity Studies of FoundationOne Liquid

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Clark et al (2018)[4]	1. Included patients with a range of cancers	3. Earlier version of test used (FoundationACT)	2. FoundationOne tissue biopsy		
Zhou et al (2018)[5]	1.Included patients with a	3. Earlier version of test used (FoundationACT)	2. FoundationOne tissue biopsy		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
	range of cancers				

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

Table 4. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Clark et al (2018)[4,]	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)[5,]	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 gaps assessment.
[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] 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.
[f] 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 (RCTs).

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 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.

The evidence is insufficient to demonstrate test performance for currently available ctDNA tests except for lung cancer (see 2.04.143); 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 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
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 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.

Patients
The relevant population of interest are 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
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.[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,[6,7,8,9,] CRC,[10,11,] hepatocellular cancer,[12,] prostate cancer,[13,14,15,] head and neck cancer,[16,] 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

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.[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 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).[18,] 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 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 are 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 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.[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 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.[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

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.[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
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.

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 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 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 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.[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
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 CTC 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.

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 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 profiling was evaluated in 4 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 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 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 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 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 single RCT, 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 RCT found no effect on OS when patients with persistently increased CTC levels after first-line chemotherapy were switched to alternative cytotoxic therapy. Other studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to monitor treatment response. The evidence is insufficient to determine 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 the 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 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 the 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 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 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 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 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 that the technology results in an improvement in the net health outcome.

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.

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 Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study	15000	Mar 2024
Unpublished			
NCT02140463	Next generation personalized therapy with plasma DNA Trial 2 in refractory solid tumors (The NEXT-2 Trial)	260	Dec 2020

[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 (Eg, 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

ICD-10 DIAGNOSES
Experimental / Investigational For All Diagnoses Related To This Medical Policy.

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

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