BlueCross BlueShield of Alabama

Name of Policy:
Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Policy #: 256
Category: Laboratory

Latest Review Date: June 2018
Policy Grade: C

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

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 that are not addressed in a separate review. If a separate evidence review exists, then conclusions reached there supersede conclusions here.

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 (cfDNA). Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs. Unlike apoptosis, necrosis is considered a pathologic process, and generates larger DNA fragments due to an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

Circulating Tumor Cells

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary use in detecting CTCs is for prognostic purposes through quantification of circulating levels.

Detecting ctDNA and CTCs

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

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

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

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either on the basis of biologic properties (expression of protein markers) or physical properties (size,

density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.

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

Table 1. Examples of Liquid Biopsy Test

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

Policy:

The use of circulating tumor DNA and circulating tumor cells does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for **all indications**.

NOTE: This policy does not address the use of blood-based testing for EGFR variants in non-small cell lung cancer or the use of AR-V7 circulating tumor cells for metastatic prostate cancer. For blood-based testing for EGFR mutations, refer to medical policy, *Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies.*

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was conducted through March 5, 2018. Following, is a summary of the key literature to date.

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 the clinical validity.

Selecting Treatment in Advanced Cancer

Clinical Context and Test Purpose

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

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

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

Patients

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

Interventions

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

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

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

In patients able to undergo tissue biopsy, negative liquid biopsies reflex to tissue testing. In patients unable to undergo tissue biopsy, a negative liquid biopsy result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

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

Setting
The setting of interest is oncology care.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition and to predicting a response to therapy.

Technically Reliable

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

Clinically Valid

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

Circulating Tumor DNA

The American Society of Clinical Oncology and College of American Pathologists jointly convened an expert panel to review the current evidence on the use of ctDNA assays. The literature review included a search for publications on the use of ctDNA assays for solid tumors in March 2017 and covers several different indications for 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. Merker et al (2018) concluded that while a wide range of ctDNA assays have been developed to detect driver mutations, there is limited evidence of the clinical validity of ctDNA analysis in tumor types outside of lung cancer and colorectal cancer (CRC). Preliminary clinical studies of ctDNA assays for detection of potentially targetable variants in other cancers such as BRAF variants in melanoma and PIK3CA and ESR1 variants in breast cancer were identified.

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

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

Study	Study Population	Design	Reference Standard	Timing of Tissue Biopsy and OncoBEAM	Blinding of Assessors
Vidal et al (2017)	• Patients from Spain with histogically confirmed metastatic CRC • Anti EGFR treatment-naïve • Enrolled from 2009 to 2016	Retrospective-prospective	Analysis of tissue samples conducted using institutional standard of care procedures	• Tissue collected before blood • Medical interval, 48 d (range, 0-1783 d)	Yes

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

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

Study	Initial N	Final N	Excluded Samples	RAS Variant Positive, %[a]	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Vidal et al (2017)	NA	115	No description of samples excluded from comparison to tissue results	51	96 (87 to 100)	90 (79 to 96)	90 (79 to 96	96 (88 to 100)

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

[a] With tissue biopsy reference standard

[b] CI is not reported in publication; calculated from data provided

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

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

CRC: colorectal cancer.

[a] Population Key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5. Study population is subpopulation of intended use.

[b] Intervention Key: 1. Classification thresholds not defined; 2. Version used unclear.

[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 (TP, TN, FP, FN cannot be determined).

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

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

CI: confidence interval; CRC: colorectal cancer

[a] Selection Key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

[b] Blinding Key: 1. Not blinded to results of reference or other comparator tests.

[c] Test Delivery Key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

[d] Selective Reporting Key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

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

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

Circulating Tumor Cells
In breast cancer, observations that estrogen receptor−positive tumors can harbor estrogen receptor−negative CTCs, that overt distant metastases and CTCs can have discrepant human epidermal growth factor receptor 2 (HER2) status compared with the primary tumor, and that the programmed death-ligand 1 (PD-L1) is frequently expressed on CTCs in patients with hormone receptor–positive, HER2-negative breast cancer12 have suggested that trials investigating whether CTCs can be used to select targeted treatment are needed.

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

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

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

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

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

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

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

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

Trials of using CTCs to select treatment are ongoing (see Table 6 in Supplemental Information).

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

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

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

Circulating Tumor Cells
For indications reviewed herein, there is no direct evidence that selecting targeted treatment using CTCs improves the net health outcome compared with selecting targeted treatment using tumor tissue testing. Trials are ongoing. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently and these data are lacking. The evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

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

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

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

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

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

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

Outcomes
The outcome of primary interest is progression-free survival.

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

Setting
The setting of interest is oncology care.

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

Clinically Valid
Circulating Tumor DNA
Merker et al (2018) identified several proof-of-principle studies demonstrating an association between persistent detection of ctDNA after local therapy and high risk of relapse. However, current studies are retrospective and have not systematically confirmed that ctDNA is being detected before the metastatic disease has developed. They

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

Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer, CRC, bladder cancer, liver cancer, and esophageal cancer.

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

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

Circulating Tumor DNA and Circulating Tumor Cells

Direct Evidence

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

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

Chain of Evidence

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

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

Section Summary: Predicting Risk of Relapse

Circulating Tumor DNA

For indications reviewed herein, there is no direct evidence that using ctDNA to predict the risk of relapse improves the net health outcome compared with standard methods. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. The evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

Circulating Tumor Cells

For indications reviewed herein, there is no direct evidence that using CTCs to predict the risk of relapse improves the net health outcome compared with standard methods. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. The evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

Screening for Cancer in Asymptomatic Individuals

Clinical Context and Test Purpose

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

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

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

Patients
The relevant population of interest is asymptomatic individuals.

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

Comparators
Outcomes
The outcome of primary interest is progression-free survival.
Diagnosis of cancer that is not present or would not have become clinically important (false-positives and overdiagnosis) would lead to unnecessary treatment and treatment-related morbidity.

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

Setting
The setting of interest is primary care or oncology care.

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

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

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

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

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

Circulating Tumor DNA and Circulating Tumor Cells

Direct Evidence

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

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

Chain of Evidence

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

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

Section Summary: Screening for Cancer in Asymptomatic Individuals

Circulating Tumor DNA

For indications reviewed herein, there is no direct evidence that using ctDNA to screen for cancer in asymptomatic individuals improves the net health outcome compared with standard methods. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. The evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

Circulating Tumor Cells

For indications reviewed herein, there is no direct evidence that using CTCs to screen for cancer in asymptomatic individuals improves the net health outcome compared with standard methods. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. The evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

Summary of Evidence

For individuals who have advanced cancer who receive testing of ctDNA to select targeted treatment, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking.

Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether variant analysis of ctDNA can replace variant analysis of tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have advanced cancer who receive testing of CTCs to select targeted treatment, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs can replace variant analysis of tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who receive testing of ctDNA to monitor treatment response, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to monitor treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who receive testing of CTCs to monitor treatment response, the evidence includes a randomized controlled trial, observational studies, and systematic reviews of observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. The available randomized controlled trial found no effect on overall survival when patients with persistently increased CTC levels after first-line chemotherapy were switched to an alternative cytotoxic therapy. Other studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to monitor treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have received curative treatment for cancer who receive testing of ctDNA to predict risk of relapse, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The

uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to predict relapse response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have received curative treatment for cancer who receive testing of CTCs to predict risk of relapse, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to predict relapse response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at high risk for cancer who receive testing of ctDNA to screen for cancer, no evidence was identified. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Published data on clinical validity and clinical utility are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at high risk for cancer who receive testing of CTCs to screen for cancer, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

National Comprehensive Cancer Network (NCCN) guidelines for colon cancer (v.2.2018) and melanoma (v.2.2018) do not address circulating tumor cells or circulating tumor DNA. The guidelines for breast cancer (v.1.2018) state that the use of circulating tumor cells in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:

CellSearch System, CellSearch Epithelial Cell Kit, circulating tumor cells, CTCs, metastatic disease, MAINTRAC, GeneSearch™ BLN test kit, Janssen, Veridex, Liquid Biopsy, circulating tumor DNA, ctDNA, Oncotype SEQ™, next-generation sequencing (NGS), CancerIntercept™, FoundationACT™, Safe Sequencing System (Safe-SeqS), CAncer Personalized Profiling by deep Sequencing (CAPP-Seq), Circulogene, Theranostics, Biocept, CellTracks® Autoprep, CellSpotter Analyzer®, Trovagene, Trovera, Guardant360 Panel

Approved by Governing Bodies:

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

Genomic Health plans to launch its first liquid biopsy test Oncotype SEQ™ in mid-2016. The test uses next-generation sequencing (NGS) to identify actionable genomic alterations for late-stage lung, breast, colon, melanoma, ovarian, and gastrointestinal cancers.

Circulogene's (Theranostics) liquid biopsy uses a finger stick volume of blood and NGS to monitor known tumor mutations (~3000) in 50 cancer-associated genes for targeted therapy. The test uses a proprietary method to recover necrotic and apoptotic cell-death-associated cell-free DNA.

Pathway Genomics Cancer Intercept is a 96-gene mutation panel designed to detect mutations in 9 driver genes involved primarily in breast, ovarian, lung, and colorectal cancers, as well as melanoma.

Biocept Inc. offers assays that target mutations found in lung and breast cancers.

Foundation Medicine's Foundation ACT detects mutations in over 60 genes for targeted therapy in metastatic cancer.

The CellSearch™ system (Janssen Diagnostics, formerly Veridex) has received U.S. Food and Drug Administration (FDA) marketing clearance through the 510(k) process for monitoring metastatic breast cancer (January 2004), for monitoring metastatic colorectal cancer (November 2007), and for monitoring metastatic prostate cancer (February 2008). Veridex LLC, a Johnson & Johnson company, markets the CellSearch system. It uses automated instruments manufactured by Immunicon Corp. for sample preparation (Cell Tracks® AutoPrep) and analysis (CellSpotterAnalyzer®), together with supplies, reagents, and epithelial cell control kits manufactured by Veridex.

The Guardant360 panel (GuardantHealth, Redwood City, CA) analyzes all somatic guideline-recommended genomic biomarkers associated with advanced solid tumors. This panel uses novel technology to analyze cell-free DNA present in the circulating blood rather than analyzing a tumor sample. The manufacturer's website refers to "digital sequencing" using information technology, but there is a lack of published studies that evaluate the analytic validity of this technique.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

There are no specific CPT codes for this type of testing. It would likely be reported using any existing CPT molecular pathology code(s) that is applicable (ie, 81161-81355, 81400-81409), along with the unlisted molecular pathology procedure code.

86152	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); **(Effective 01/01/2013)**
86153	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required **(Effective 01/01/2013)**
81479	Unlisted molecular pathology procedure

References:

1. Allard WJ, Mater J, Miller MC, et al. Tumor cells circulate in the peripheral blood of all major carcinoma but not in healthy subjects or patients with nonmalignant diseases. Clin Cancer Res 2004; 10(20):6897-6904.
2. Alix-Panabieres C, Pantel K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. Cancer Discov. May 2016; 6(5):479-491.
3. Ascierto PA, Minor D, Ribas A, et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J Clin Oncol. Sep 10 2013;31(26):3205-3211.
4. Babayan A, Hannemann J, Spotter J, et al. Heterogeneity of estrogen receptor expression in circulating tumor cells from metastatic breast cancer patients. *PLoS One.* Sep 2013;8(9):e75038.
5. Baselga J, Im SA, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. Jul 2017;18(7):904-916.
6. Ben Hsieh H, Marrinucci D, Bethel K, et al. High speed detection of circulating tumor cells. Biosensors and Bioelectronics 2006; 21: 1893-1899.
7. Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. Sci Transl Med. Feb 19 2014; 6(224):224ra224.

8. Beveridge RA, Pobert NJ, Hudson M, et al. Early assessment of circulating tumor cells results in a community based practice. 2005 ASCO Annual Meeting Proceedings. J Clin Oncol (Meeting Abstracts) June 2005 vol. 23 no. 16_suppl 621.
9. Bidard FC, Madic J, Mariani P et al. Detection rate and prognostic value of circulating tumor cells and circulating tumor DNA in metastatic uveal melanoma. Int J Cancer. Mar 1 2014; 134(5):1207-1213.
10. Bidard FC, Mathiot C, Delaloge S, et al. Single circulating tumor cell detection and overall survival in nonmetastatic breast cancer. Ann Oncol, April 2010; 21(4): 729-733.
11. Bork U, Rahbari NN, Scholch S, et al. Circulating tumour cells and outcome in non-metastatic colorectal cancer: a prospective study. Br J Cancer. Apr 14 2015; 112(8):1306-1313.
12. Braun S and Marth C. Circulating tumor cells in metastatic breast cancer-toward individualized treatment? N Engl J Med 2004; 351(8):824-826.
13. Budd GT, Cristofanilli M, Ellis MJ, et al. Monitoring circulating tumor cells in non-measurable metastatic breast cancer. 2005 ASCO Annual Meeting Proceedings. J Clin Oncol (Meeting Abstracts) June 2005 vol. 23 no. 16_suppl 503.
14. Budd GT, Cristofanilli M, Ellis MJ, et al. Circulating tumor cells versus imaging—predicting overall survival in metastatic breast cancer. Clinical Cancer Research, November 2006, Vol. 12, pp. 6403-6409.
15. CellSearch Brochure. www.cellsearchctc.com/sites/default/files/docs/cellsearch-ctc-test-brochure.pdf.
16. Cohen SJ, Punt CJ, Iannotti N, et al. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. J Clin Oncol, July 2008; 26(19): 3213-3221.
17. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression and survival in metastatic breast cancer. N Engl J Med 2004; 351(8):781-791.
18. Danila DC, Heller G, Gignac GA et al. Circulation tumor cell number and prognosis in progressive castration-resistant prostate cancer. Clin Cancer Res 2007; 13(23):7053-7058.
19. Dawood S, Broglio K, et al. Circulating tumor cells in metastatic breast cancer. From prognostic stratification to modification of the staging system? Cancer, November 2008, Vol. 113, No. 9, pp. 2422-2430.
20. de Albuquerque A, Kubisch I, Breier G et al. Multimarker gene analysis of circulating tumor cells in pancreatic cancer patients: a feasibility study. Oncology 2012; 82(1):3-10.
21. de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res, October 2008; 14(19): 6302-6309.
22. Deneve E, Riethdorf S, Ramos J, et al. Capture of viable circulating tumor cells in the liver of colorectal cancer patients. Clin Chem. Sep 2013;59(9):1384-1392.
23. Fan JL, Yang YF, Yuan CH, et al. Circulating Tumor Cells for Predicting the Prognostic of Patients with Hepatocellular Carcinoma: A Meta Analysis. Cell Physiol Biochem. Sep 2015;37(2):629-640.
24. Fehm T, Muller V, Aktas B, et al. HER2 status of circulating tumor cells in patients with metastatic breast cancer: a prospective, multicenter trial. *Breast Cancer Res Treat.* Nov 2010;124(2):403-412.

25. Gazzaniga P, de Berardinis E, Raimondi C et al. Circulating tumor cells detection has independent prognostic impact in high-risk non-muscle invasive bladder cancer. Int J Cancer. Mar 6 2014.
26. Groot Koerkamp B, Rahbari NN, Buchler MW et al. Circulating Tumor Cells and Prognosis of Patients with Resectable Colorectal Liver Metastases or Widespread Metastatic Colorectal Cancer: A Meta-Analysis. Ann Surg Oncol. Mar 2 2013; 20(7):2156-2165.
27. GuardantHealth I. Guardant360 Know Cancer. www.guardanthealth.com/guardant360/.
28. Guzzo TJ, McNeil BK, Bivalacqua TJ et al. The presence of circulating tumor cells does not predict extravesical disease in bladder cancer patients prior to radical cystectomy. Urol Oncol 2012; 30(1):44-48.
29. Harris L, Fritshe H, Mennel R et al. American Society of Clinical Oncology 2007 Update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007; 25(33):5287-5312.
30. Hirose T, Murata Y, Oki Y et al. Relationship of circulating tumor cells to the effectiveness of cytotoxic chemotherapy in patients with metastatic non-small-cell lung cancer. Oncol Res 2012; 20(2-3):131-137.
31. Huang X, Gao P, Song Y, et al. Meta-analysis of the prognostic value of circulating tumor cells detected with the CellSearch System in colorectal cancer. BMC Cancer. 2015; 15:202.
32. Ignatiadis M, Rothe F, Chaboteaux C, et al. HER2-positive circulating tumor cells in breast cancer. PLoS One. Jan 10 2011;6(1):e15624.
33. Khoja L, Lorigan P, Zhou C et al. Biomarker Utility of Circulating Tumor Cells in Metastatic Cutaneous Melanoma. J Invest Dermatol. Dec 6 2013; 133(6):1582-1590.
34. Krebs MG, Sloane R, Priest L et al. Evaluation and prognostic significance of circulating tumor cells in patients with non-small-cell lung cancer. J Clin Oncol 2011; 29(12):1556-1563.
35. Labgaa I, Villanueva A. Liquid biopsy in liver cancer. Discov Med. Apr 2015; 19(105):263-273.
36. Liu Y, Liu Q, Wang T, et al. Circulating tumor cells in HER2-positive metastatic breast cancer patients: a valuable prognostic and predictive biomarker. *BMC Cancer.* Apr 23 2013;13:202.
37. Lv Q, Gong L, Zhang T, et al. Prognostic value of circulating tumor cells in metastatic breast cancer: a systemic review and meta-analysis. *Clin Transl Oncol.* Mar 2016;18(3):322-330.
38. Lyberopoulou A, Aravantinos G, Efstathopoulos EP, et al. Mutational analysis of circulating tumor cells from colorectal cancer patients and correlation with primary tumor tissue. PLoS One. 2015; 10(4):e0123902.
39. Ma XL, Xiao ZL, Liu L et al. Meta-analysis of circulating tumor cells as a prognostic marker in lung cancer. Asian Pac J Cancer Prev 2012; 13(4):1137-1144.
40. Ma X, Xiao Z, Li X et al. Prognostic role of circulating tumor cells and disseminated tumor cells in patients with prostate cancer: a systematic review and meta-analysis. Tumour Biol 2014.
41. Mao C, Yuan JQ, Yang ZY, et al. Blood as a substitute for tumor tissue in detecting egfr mutations for guiding EGFR TKIs treatment of nonsmall cell lung cancer: a systematic review and meta-analysis. Medicine (Baltimore). May 2015; 94(21):e775.

42. Matsusaka S, Chin K, Ogura M, Suenaga M, et al. Circulating tumor cells as a surrogate marker for determining response to chemotherapy in patients with advanced gastric cancer. Cancer Sci 2010; 101(4)1067-1071.
43. Mazel M, Jacot W, Pantel K, et al. Frequent expression of PD-L1 on circulating breast cancer cells. Mol Oncol. Nov 2015;9(9):1773-1782.
44. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol.* Mar 5 2018:Jco2017768671.
45. Mocellin S, Hoon D, Ambrosi A, et al. The prognostic value of circulating tumor cells in patients with melanoma: a systematic review and meta-analysis. Clin Cancer Res. Aug 1 2006;12(15):4605-4613.
46. Msaouel P, Koutsilieris M. Diagnostic value of circulating tumor cell detection in bladder and urothelial cancer: systematic review and meta-analysis. BMC Cancer. Aug 4 2011;11:336.
47. Naito T, Tanaka F, Ono A et al. Prognostic impact of circulating tumor cells in patients with small cell lung cancer. J Thorac Oncol. 2012; 7(3):512-519.
48. National Academy of Clinical Biochemistry (NACB). The use of tumor markers in testicular, prostate, colorectal, breast and ovarian cancer. 2009. Available online at: www.guideline.gov/content.aspx?id=15553&search=circulating+tumor+cells.
49. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 1.2018). www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf.
50. National Comprehensive Care Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer Version 3, 2018. Available online at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
51. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 2.2018. www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf.
52. National Comprehensive Care Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Version 1, 2014. Available online at: www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
53. Newman AM, Bratman SV, To J, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. Nat Med. May 2014; 20(5):548-554.
54. Nichols AC, Lowes LE, Szeto CC et al. Detection of circulating tumor cells in advanced head and neck cancer using the CellSearch system. Head Neck. Oct 2012; 34(10):1440-1444.
55. Nole F, Munzone E, Zorzino L et al. Variation of circulation tumor cell levels during treatment of metastatic breast cancer: Prognostic and therapeutic implications. Ann Oncol 2008; 19(5):891-897.
56. Okabe H, Tsunoda S, Hosogi H, et al. Circulating Tumor Cells as an Independent Predictor of Survival in Advanced Gastric Cancer. Ann Surg Oncol. Mar 17 2015.
57. Pailler E, Adam J, Barthelemy A, et al. Detection of circulating tumor cells harboring a unique ALK rearrangement in ALK-positive non-small-cell lung cancer. J Clin Oncol. Jun 20 2013; 31(18):2273-2281.

58. Pailler E, Auger N, Lindsay CR, et al. High level of chromosomal instability in circulating tumor cells of ROS1-rearranged non-small-cell lung cancer. Ann Oncol. Jul 2015; 26(7):1408-1415.
59. Pierga JY, Hajage D, Bachelot T et al. High independent prognostic and predictive value of circulating tumor cells compared with serum tumor markers in a large prospective trial in first-line chemotherapy for metastatic breast cancer patients. Ann Oncol 2012; 23(3):618-624.
60. Qiu M, Wang J, Xu Y, et al. Circulating tumor DNA is effective for the detection of EGFR mutation in non-small cell lung cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev. Jan 2015; 24(1):206-212.
61. Racila E, Euhus D, Weiss AJ, Rao C, et al. Detection and characterization of carcinoma cells in the blood. Proc Natl Acad Sci USA 1998; 95:4589-4594.
62. Rack B, Schindlbeck C, Juckstock J, et al. Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. J Natl Cancer Inst. May 15 2014;106(5).
63. Reinholz Monica M, Nibbe Andrea, Jonart Leslie M, et al. Evaluation of a panel of tumor markers for molecular detection of circulating cancer cells in women with suspected breast cancer. Clinical Cancer Research, May 2005, Vol. 11, pp. 3722-3732.
64. Riethdorf S, Muller V, Zhang L, et al. Detection and HER2 expression of circulating tumor cells: prospective monitoring in breast cancer patients treated in the neoadjuvant GeparQuattro trial. *Clin Cancer Res.* May 1 2010;16(9):2634-2645.
65. Rink M, Chun FK, Minner S et al. Detection of circulating tumor cells in peripheral blood of patients with advanced non-metastatic bladder cancer. BJU Intl 2011; 107(10):1668-1675.
66. Riva F, Dronov OI, Khomenko DI, et al. Clinical applications of circulating tumor DNA and circulating tumor cells in pancreatic cancer. Mol Oncol. Mar 2016; 10(3):481-493.
67. Sacher AG, Paweletz C, Dahlberg SE, et al. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. JAMA Oncol. Apr 7 2016.
68. Sanguedolce F, Cormio A, Bufo P, et al. Molecular markers in bladder cancer: Novel research frontiers. Crit Rev Clin Lab Sci. 2015; 52(5):242-255.
69. Schiavon G, Hrebien S, Garcia-Murillas I, et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. Sci Transl Med. Nov 11 2015;7(313):313ra182.
70. Schulze K, Gasch C, Staufer K et al. Presence of EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. Int J Cancer 2013; 133(9):2165-2171.
71. Seeberg LT, Waage A, Brunborg C et al. Circulating Tumor Cells in Patients With Colorectal Liver Metastasis Predict Impaired Survival. Ann Surg. Feb 6 2014.
72. Serrano MJ, Lorente JA, Rodriguez MD et al. Circulating tumour cells in peripheral blood: potential impact on breast cancer outcome. Clin Transl Oncol 2011; 13(3):204-208.
73. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. Nov 1 2014; 32(31):3483-3489.
74. Stopeck A, Cristofanilli M, Budd GT et al. Circulating tumor cells-not serum tumor markers-predict survival in metastatic breast cancer. 2005 ASCO Annual Meeting Proceedings. J Clin Oncol (Meeting Abstracts) June 2005 vol. 23 no. 16_suppl 9516.

75. Sun T, Zou K, Yuan Z, et al. Clinicopathological and prognostic significance of circulating tumor cells in patients with head and neck cancer: a meta-analysis. Onco Targets Ther. Jun 2017;10:3907-3916.
76. Tabernero J, Lenz HJ, Siena S, et al. Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: a retrospective, exploratory analysis of the CORRECT trial. Lancet Oncol. Aug 2015; 16(8):937-948.
77. Tanaka F, Yoneda K, Kondo N, et al. Circulating tumor cell as a diagnostic marker in primary lung cancer. Clin Cancer Res, November 2009; 15(22): 6980-6986.
78. Tang L, Zhao S, Liu W, et al. Diagnostic accuracy of circulating tumor cells detection in gastric cancer: systematic review and meta-analysis. BMC Cancer. Jun 27 2013;13:314.
79. Terstappen LW, Rao C, Gross S, and Weiss AJ. Peripheral blood tumor cell load reflects the clinical activity of the disease in patients with carcinoma of the breast. Int J Oncol 2000; 17(3):573-578.
80. Thalgott M, Rack B, Horn T, et al. Detection of circulating tumor cells in locally advanced high-risk prostate cancer during neoadjuvant chemotherapy and radical prostatectomy. Anticancer Res. Oct 2015;35(10):5679-5685.
81. U.S. Food and Drug Administration (FDA). FDA Executive Summary for the GeneSearch BLN assay. Available online at www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4249b1_04.pdf.
82. Vashist YK, Effenberger KE, Vettorazzi E, et al. Disseminated tumor cells in bone marrow and the natural course of resected esophageal cancer. Ann Surg. Jun 2012;255(6):1105-1112.
83. Vidal J, Muinelo L, Dalmases A, et al. Plasma ctDNA RAS mutation analysis for the diagnosis and treatment monitoring of metastatic colorectal cancer patients. *Ann Oncol.* Jun 1 2017;28(6):1325-1332.
84. Wang CH, Chang CJ, Yeh KY, et al. The prognostic value of HER2-positive circulating tumor cells in breast cancer patients: a systematic review and meta-analysis. Clin Breast Cancer. Aug 2017;17(5):341-349.
85. Wang FB, Yang XQ, Yang S et al. A higher number of circulating tumor cells (CTC) in peripheral blood indicates poor prognosis in prostate cancer patients--a meta-analysis. Asian Pac J Cancer Prev. 2011; 12(10):2629-2635.
86. Xu MJ, Dorsey JF, Amaravadi R, et al. Circulating tumor cells, DNA, and mRNA: potential for clinical utility in patients with melanoma. Oncologist. Jan 2016; 21(1):84-94.
87. Yagata H, Nakamura S, et al. Evaluation of circulating tumor cells in patients with breast cancer: Multi-institutional clinical trial in Japan. Int J Clin Oncol 2008; 13(3): 252-256.
88. Zhang L, Riethdorf S, Wu G et al. Meta-analysis of the prognostic value of circulating tumor cells in breast cancer. Clin Cancer Res 2012; 18(20):5701-5710.
89. Zhang J, Wang HT, Li BG. Prognostic significance of circulating tumor cells in small--cell lung cancer patients: a meta-analysis. Asian Pac J Cancer Prev. 2014; 15(19):8429-8433.
90. Zhao S, Liu Y, Zhang Q et al. The prognostic role of circulating tumor cells (CTCs) detected by RT-PCR in breast cancer: a meta-analysis of published literature. Breast Cancer Res Treat 2011; 130(3):809-816.

Policy History:

Medical Policy Group, September 2005 **(2)**
Medical Policy Administration Committee, October 2005
Available for comment December 1, 2005-January 14, 2006
Medical Policy Group, October 2006 **(1)**
Medical Policy Group, October 2007 **(1)**
Medical Policy Group, February 2008 **(2)**
Medical Policy Administration Committee, February 2008
Medical Policy Group, December 2008 **(2)**
Medical Policy Group, September 2009 **(3)** new policy Biomarker Genes for Detection of Lymph Node Metastases in Breast Cancer (archived medical policy #385 August 2015)
Medical Policy Administration Committee, September 2009 presented new policy Biomarker Genes for Detection of Lymph Node Metastases in Breast Cancer (archived medical policy #385 August 2015)
Available for comment September 18-November 2, 2009 new policy Biomarker Genes for Detection of Lymph Node Metastases in Breast Cancer (archived medical policy #385 August 2015)
Medical Policy Group, December 2009 **(1)**
Medical Policy Group, June 2010 **(1)**
Medical Policy Group, January 2011 updated Key Points & References on policy Biomarker Genes for Detection of Lymph Node Metastases in Breast Cancer (archived medical policy #385 August 2015)
Medical Policy Group, July 2011 **(1):** Update to Description, Key Points and References
Medical Policy Group, November 2011 **(1):** Added 2012 CPT Codes Effective 1/1/12
Medical Policy Group, February 2012 **(1):** Deleted S3711 HCPCS Code effect 4/1/12
Medical Policy Group, June 2012 **(1):** 2012 Updates to Key Points and References
Medical Policy Group, November 2012: 2013 Coding Updates – Added 86152 & 86153
Medical Policy Group, January 2013 **(1)** Update to Coding on policy Biomarker Genes for Detection of Lymph Node Metastases in Breast Cancer (archived medical policy #385 August 2015)with addition of new codes 81479 and 81599 and deletion of code range 83890-83914; no change in policy statement
Medical Policy Group, February 2013 **(1)**: policy Biomarker Genes for Detection of Lymph Node Metastases in Breast Cancer (archived medical policy #385 August 2015) **Effective 02/01/2013 - Active Policy but no longer scheduled for regular literature reviews and updates.**
Medical Policy Panel, June 2013
Medical Policy Group, September 2013 **(1):** Update to Key Points and References; no change to policy statement
Medical Policy Panel, June 2014
Medical Policy Group, June 2014 **(1):** Update to Key Points and References; no change to policy statement
Medical Policy Panel, June 2015
Medical Policy Group, June 2015 **(3)**: 2015 Update to Key Points & References; no change in policy statement

Medical Policy Group, August 2015 **(3)**: incorporating pertinent information from policy #385 Biomarker Genes for Detection of Lymph Node Metastases in Breast Cancer and archiving medical policy #385; no change in policy statement – remains investigational
Medical Policy Group, November 2015: 2016 Annual Coding Update. Added cpt code 88346 and new cpt code 88350. Moved CPT 88347 from current coding to previous coding.
Medical Policy Panel, May 2016
Medical Policy Group, July 2016 **(3):** 2016 Incorporated Circulating Tumor DNA information. Update to Policy Title, Description, Key Points, Key Words, Approved by Governing Bodies & References. Policy statement- Circulating Tumor DNA added to policy statement as investigational. Removed HCPCS Code- S3711- deleted in 2012.
Medical Policy Panel, October 2016
Medical Policy Group, November 2016 **(3)**: Added note in in policy statement: This policy does not address the use of blood-based testing for EGFR mutations. For blood-based testing for EGFR mutations, refer to medical policy, Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies. No change in intent; also removed CPT codes 88346 and 88350 from current coding; added clarifying statement to coding section on how this service might also be submitted; added note in Key Points - If a separate evidence review exists, then conclusions reached there supersede conclusions in this review.
Medical Policy Group, December 2016 **(3)**: Added Guardant360 Panel to Governing Bodies, Key Words & References sections; no change in policy statement
Medical Policy Panel, May 2018
Medical Policy Group, June 2018 **(2)**: 2018 Updates to Description, Key Points, and References; Policy statement remains unchanged – investigational.
