2.04.141	Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)		
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Section:	2.0 Medicine	**Page:**	Page 1 of 26

Policy Statement

I. The use of circulating tumor DNA and/or circulating tumor cells is considered **investigational** for all indications reviewed herein (see Policy Guidelines).

Note: For individuals enrolled in health plans subject to the Biomarker Testing Law (Health & Safety Code Section 1367.667 and the Insurance Code Section 10123.209), Centers for Medicare & Medicaid Services (CMS) Local Coverage Determination (LCD) may also apply. Please refer to the Medicare National and Local Coverage section of this policy and to MolDX: Plasma-Based Genomic Profiling in Solid Tumors for reference.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

- 2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- 2.04.45 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, NTRK) **(to be published)**
- 2.04.61 Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer **(to be published)**
- 2.04.111 Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management
- 2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- 2.04.151 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1, NTRK)
- 2.04.153 Tumor-Informed Circulating Tumor DNA Testing for Cancer Management
- 2.04.155 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, NTRK Gene Fusion)
- 2.04.156 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK)

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

Coding

See the Codes table for details.

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.

Summary of Evidence

For individuals who have advanced cancer who receive testing of circulating tumor DNA (ctDNA) to select targeted treatment, the evidence includes observational studies. Relevant outcomes are overall survival (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 circulating tumor cells (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 randomized controlled trial (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.

Additional Information
Not applicable

Related Policies

- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer **(to be published)**
- Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management
- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1, NTRK)

- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, NTRK Gene Fusion)
- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK)
- Tumor-Informed Circulating Tumor DNA Testing for Cancer Management

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. 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.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 535
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

SB 496
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

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

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

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

Diagnostic Name (Manufacturer)	Indication	Biomarker	Drug Trade Name (Generic)	Related Evidence Opinion
Agilent Resolution ctDx FIRST assay	NSCLC	KRAS	Krazati (adagrasib)	2.04.45
cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	NSCLC	*EGFR* (*HER1*)	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Iressa (gefitinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Tarceva (erlotinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Gilotrif (afatinib)	2.04.45
FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NSCLC	*EGFR (HER1)*	Exkivity (mobocertinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Iressa (gefitinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Tarceva (erlotinib)	2.04.45
	NSCLC	*MET*	Tabrecta (capmatinib)	2.04.45
	NSCLC	*ROS1*	Rozlytrek (entrectinib)	2.04.45
	NSCLC	ALK	Alecensa (alectinib)	2.04.45
	Ovarian Cancer	*BRCA1* and *BRCA2*	Rubraca (rucaparib)	2.04.156
	Solid Tumors	*ROS1*	Rozlytrek (entrectinib)	5.01.31
	Breast Cancer	*PIK3CA*	Piqray (alpelisib)	2.04.151
	Metastatic Castrate Resistant Prostate Cancer	*BRCA1,BRCA2* and *ATM*	Lynparza (olaparib)	2.04.155
	Metastatic Castrate Resistant Prostate Cancer	*BRCA1 and BRCA2*	Rubraca (rucaparib)	2.04.155
Guardant360 CDx (Guardant Health, Inc.)	NSCLC	*EGFR* (*HER1*)	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Rybrevant (amivantamb)	2.04.45
	NSCLC	*KRAS*	Lumakras (sotorasib)	2.04.45
	NSCLC	ERBB2	ENHERTU (fam-trastuzumab deruxtecan-nxki)	2.04.45
	Breast Cancer	*ESR1* *ERB2*	Orserdu (elacestrant)	2.04.151 In development for 2.04.151

Diagnostic Name (Manufacturer)	Indication	Biomarker	Drug Trade Name (Generic)	Related Evidence Opinion
			ENHERTU (fam-trastuzumab deruxtecan-nxki)	
***therascreen* PIK3CA RGQ PCR Kit (QIAGEN GmbH)**	Breast Cancer	*PIK3CA*	Piqray (alpelisib)	2.04.151

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

Rationale

Background

Liquid Biopsy

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

Circulating Tumor DNA

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

Circulating Tumor Cells

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

Detecting Circulating Tumor DNA and Circulating Tumor Cells

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

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

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

Circulating tumor cell assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size,

density, electric charge). Circulating tumor cells can then be detected using immunologic, molecular, or functional assays.[1]

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

Literature Review

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.

Selecting Treatment in Advanced Cancer

Clinical Context and Test Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

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

Review of Evidence

Clinically Valid

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

Circulating Tumor DNA

Systematic Reviews

The American Society of Clinical Oncology and College of American Pathologists jointly convened an expert panel to review the current evidence on the use of ctDNA assays.[3,] The literature review included a search for publications on the use of ctDNA assays for solid tumors in March 2017 and covers several different indications for the use of liquid biopsy. The search identified 1338 references to which an additional 31 references were supplied by the expert panel. Seventy-seven articles were selected for inclusion. The summary findings are discussed in the following sections by indication.

Much of the literature to date on the use of ctDNA to guide treatment selection is for non-small-cell lung cancer, which is addressed in evidence opinion 2.04.143, metastatic colorectal cancer (CRC) , which is addressed in evidence opinion 2.04.53, and breast cancer, which is addressed in evidence opinion 2.04.151. Therefore, they are not discussed here.

Merker et al (2018) concluded that while a wide range of ctDNA assays have been developed to detect driver mutations, there is limited evidence of the clinical validity of ctDNA analysis in tumor types outside of lung cancer and CRC.

Circulating Tumor Cells

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

Clinically Useful

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

Circulating Tumor DNA

Direct Evidence

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

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

Chain of Evidence

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

A chain of evidence for ctDNA tests could be established if the ctDNA test has a high agreement with standard tissue testing (clinical validity) for identifying driver mutations, and the standard tissue

testing has proven clinical utility with high levels of evidence. A chain of evidence can also be demonstrated if the ctDNA test is able to detect driver mutations when standard methods cannot, and the information from the ctDNA test leads to management changes that improve outcomes. For the indications reviewed herein, the evidence is insufficient to demonstrate test performance for currently available ctDNA tests; therefore, no inferences can be made about clinical utility.

Circulating Tumor Cells

Direct Evidence

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

Trials of using CTCs to select treatment are ongoing (see Table 2 in Supplemental Information).

Chain of Evidence

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

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

Section Summary: Selecting Treatment in Advanced Cancer

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

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

Monitoring Treatment Response in Cancer

Clinical Context and Test Purpose

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

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

Patients

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

Interventions

The test being considered is liquid biopsy using either ctDNA or CTCs. For ctDNA tests, the best unit for quantifying DNA burden has not been established.[3,]

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

Outcomes
The outcome of primary interest is progression-free survival.
The timing of interest for survival outcomes varies by type of cancer.

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

Circulating Tumor DNA
Merker et al (2018) identified several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes, as well as studies demonstrating that ctDNA can identify the emergence of resistant variants.[3,] However, they reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and concluded that clinical validity had not been established.

Circulating Tumor Cells
Systematic reviews and meta-analyses describing an association between CTCs and poor prognosis have been reported for metastatic breast cancer,[4,5,6,7,] CRC,[8,9,] hepatocellular cancer,[10,] prostate cancer,[11,12,13,] head and neck cancer,[14,] and melanoma.[15,]

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

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

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

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

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

Circulating Tumor Cells
Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. Smerage et al (2014) reported on the results of an RCT of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after 1 cycle of first-line therapy could improve overall survival (OS; the primary study outcome).[16,] Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of

therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median OS between arms C1 (10.7 months) and C2 (12.5 months; p=.98). Circulating tumor cell levels were strongly prognostic, with a median OS for arms A, B, and C (C1 and C2 combined) of 35 months, 23 months, and 13 months, respectively (p<.001). This trial showed the prognostic significance of CTCs in patients, which rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility through a chain of evidence.

Section Summary: Monitoring Treatment Response in Cancer

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

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

Predicting Risk of Relapse

Clinical Context and Test Purpose

Monitoring for relapse after curative therapy in individuals with cancer may be performed using imaging methods and clinical examination. Another proposed purpose of liquid biopsy testing in individuals who have cancer is to detect and monitor for residual tumor, which could lead to early treatment that would eradicate residual disease and potentially improve outcomes.

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Review of Evidence

Clinically Valid

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

Circulating Tumor DNA

Merker et al (2018) identified several proof-of-principle studies demonstrating an association between persistent detection of ctDNA after local therapy and high-risk of relapse.[3] However, current studies are retrospective and have not systematically confirmed that ctDNA is being detected before the metastatic disease has developed. They concluded that the performance characteristics had not been established for any assays.

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

Circulating Tumor Cells

Rack et al (2014) published the results of a large multicenter study in which CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy using the CellSearch® System.[18] After chemotherapy, 22% of patients were CTC-positive, and CTC positivity was negatively associated with prognosis.

Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer,[19] CRC[20] bladder cancer,[21,22] liver cancer,[23] and esophageal cancer.[24] The clinical validity of each commercially available CTC test must be established independently.

Clinically Useful

Circulating Tumor DNA and Circulating Tumor Cells

Direct Evidence

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

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

Chain of Evidence

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

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

Section Summary: Predicting Risk of Relapse

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

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

Screening for Cancer in Asymptomatic Individuals

Clinical Context and Test Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

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

Review of Evidence

Clinically Valid

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

Circulating Tumor DNA

Merker et al (2018) reported there is no evidence of clinical validity for the use of ctDNA in asymptomatic individuals.[3,]

Circulating Tumor Cells

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer.[25,26,] Reported sensitivity was low in both cancers (42% and 35%) overall. Sensitivity was lower in patients with early-stage cancer, suggesting that the test would not be useful as an initial screen.

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

Clinically Useful

The evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests for screening for cancer in asymptomatic individuals; therefore, no inferences can be made about clinical utility.

Circulating Tumor DNA and Circulating Tumor Cells

Direct Evidence

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

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

Chain of Evidence

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

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

Section Summary: Screening for Cancer in Asymptomatic Individuals

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

Summary of Evidence

For individuals who have advanced cancer who receive testing of circulating tumor DNA (ctDNA) to select targeted treatment, the evidence includes observational studies. Relevant outcomes are overall survival (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 circulating tumor cells (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 randomized controlled trial (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.

American Society of Clinical Oncology

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

The discussion also included the following points:

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

National Comprehensive Cancer Network

There is no general National Comprehensive Cancer Network (NCCN) guideline on the use of liquid biopsy. Refer to treatment recommendations by cancer type for specific recommendations.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National and Local Coverage

There is no national coverage determination specifically for liquid biopsy. The national coverage determination on next generation sequencing (NCD 90.2) would apply to liquid biopsy tests meeting the criteria below:[28]

"Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:
   i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
   ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
   iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:
   i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
   ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
   iii. results provided to the treating physician for management of the patient using a report template to specify treatment options."

FDA Approved Device Indication for a Specific Group of Oncology Therapeutic Products

Diagnostic Name (Manufacturer)	Indication(s) - Sample Type	PMA (Approval Date)	Device Indication for a Specific Group of Oncology Therapeutic Products and Trade Name (Generic) – NDA/BLA
cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	Non-Small Cell Lung Cancer (NSCLC) - Tissue or Plasma	P120019/S031 (10/27/2020)	Non-small cell lung cancer (tissue): "Identifying patients with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor approved by FDA for that indication" List of tyrosine kinase inhibitors approved by FDA for this indication: • Tarceva (erlotinib) - NDA 021743 • Tagrisso (osimertinib) - NDA 208065 • Iressa (gefitinib) - NDA 206995 • Gilotrif (afatinib) - NDA 201292 • Vizimpro (dacomitinib) - NDA 211288 • Lazcluze (Lazertinib) - NDA 219008 as part of a combination therapy Non-small cell lung cancer (plasma): "Identifying patients with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor approved by FDA for that indication" List of tyrosine kinase inhibitors approved by FDA for this indication: • Tarceva (erlotinib) - NDA 021743 • Tagrisso (osimertinib) - NDA 208065 • Iressa (gefitinib) - NDA 206995 • Lazcluze(Lazertinib) - NDA 219008 as part of a combination therapy
FoundationOne CDx (Foundation Medicine, Inc.)	Melanoma - Tissue	P170019/S025 (11/10/2021)	"Identifying patients with melanoma whose tumors have BRAF V600E and are suitable for treatment with BRAF Inhibitors approved by FDA for that indication" List of BRAF Inhibitors approved by FDA for this indication: • Tafinlar (dabrafenib) - NDA 202806 • Zelboraf (vemurafenib) - NDA 202429 "Identifying patients with melanoma whose tumors have *BRAF* V600E and V600K and are suitable for treatment with BRAF/MEK Inhibitor Combinations approved by FDA for that indication" List of BRAF/MEK Inhibitor Combinations approved by FDA for this indication: • Cotellic (cobimetinib) - NDA 206192 in combination with Zelboraf (vemurafenib) - NDA 202429

Diagnostic Name (Manufacturer)	Indication(s) - Sample Type	PMA (Approval Date)	Device Indication for a Specific Group of Oncology Therapeutic Products and Trade Name (Generic) – NDA/BLA
			• Braftovi (encorafenib) - NDA 210496 in combination with Mektovi (Binimetinib) - NDA 210498 • Tafinlar (dabrafenib) - NDA 202806in combination with Mekinist (trametinib) - NDA 204114
FoundationOne CDx (Foundation Medicine, Inc.)	Non-Small Cell Lung Cancer (NSCLC) - Tissue	P170019/S033 (03/16/2022)	"Identifying patients with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor (TKI) approved by FDA for that indication" List of tyrosine kinase inhibitors approved by FDA for this indication: • Tarceva (erlotinib) - NDA 021743 • Tagrisso (osimertinib) - NDA 208065 • Iressa (gefitinib) - NDA 206995 • Gilotrif (afatinib) - NDA 201292 • Vizimpro (dacomitinib) - NDA 211288 • Lazcluze(Lazertinib) - NDA 219008 as part of a combination therapy
FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Non-Small Cell Lung Cancer (NSCLC) - Plasma	P190032/S008 (12/19/2022)	Non-small cell lung cancer (plasma) "Identifying patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor approved by FDA for that indication" List of tyrosine kinase inhibitors approved by FDA for this indication: • Tarceva (erlotinib) - NDA 021743 • Tagrisso (osimertinib) - NDA 208065 • Iressa (gefitinib) - NDA 206995 • Lazcluze(Lazertinib) - NDA 219008 as part of a combination therapy
ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA) (Pillar Biosciences, Inc.)	Non-Small Cell Lung Cancer (NSCLC) - Tissue	P200011 (07/30/2021)	Non-Small Cell Lung Cancer (tissue): "Identifying patients with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor approved by FDA for that indication" List of tyrosine kinase inhibitors approved by FDA for this indication: • Tarceva (erlotinib) - NDA 021743 • Tagrisso (osimertinib) - NDA 208065 • Iressa (gefitinib) - NDA 206995 • Gilotrif (afatinib) - NDA 201292 • Vizimpro (dacomitinib) - NDA 211288 • Lazcluze(Lazertinib) - NDA 219008 as part of a combination therapy
MI Cancer Seek (Caris Life Sciences)	Melanoma - Tissue	P240010 (11/05/2024)	Melanoma (Tissue): "Identifying patients with melanoma whose tumors have BRAF V600E and are suitable for treatment with BRAF Inhibitors approved by FDA for that indication" List of BRAF Inhibitors approved by FDA for this indication: • Tafinlar (dabrafenib) - NDA 202806 • Zelboraf (vemurafenib) - NDA 202429
MI Cancer Seek (Caris Life Sciences)	Melanoma - Tissue	P240010 (11/05/2024)	Melanoma (Tissue): "Identifying patients with melanoma whose tumors have BRAF V600E and V600K and are suitable for treatment with

Diagnostic Name (Manufacturer)	Indication(s) - Sample Type	PMA (Approval Date)	Device Indication for a Specific Group of Oncology Therapeutic Products and Trade Name (Generic) – NDA/BLA
			BRAF/MEK Inhibitor Combinations approved by FDA for that indication" List of BRAF/MEK Inhibitor Combinations approved by FDA for this indication: • Cotellic (cobimetinib) - NDA 206192 in combination with Zelboraf (vemurafenib) - NDA 202429 • Braftovi (encorafenib) - NDA 210496 in combination with Mektovi (Binimetinib) - NDA 210498 • Tafinlar (dabrafenib) - NDA 202806 in combination with Mekinist (trametinib) - NDA 204114
MI Cancer Seek (Caris Life Sciences)	Non-Small Cell Lung Cancer (NSCLC) - Tissue	P240010 (11/05/2024)	Non-Small Cell Lung Cancer (tissue): "Identifying patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor approved by FDA for that indication" List of tyrosine kinase inhibitors approved by FDA for this indication: • Tarceva (erlotinib) - NDA 021743 • Tagrisso (osimertinib) - NDA 208065 • Iressa (gefitinib) - NDA 206995 • Gilotrif (afatinib) - NDA 201292 • Vizimpro (dacomitinib) - NDA 211288 • Lazcluze (Lazertinib) - NDA 219008 as part of a combination therapy

Local coverage guidance for California is provided by the provided by the Molecular Diagnostic Services Program (MolDx) in the document **MolDX: Plasma-Based Genomic Profiling in Solid Tumors** **and** the associated **Billing and Coding: MolDX: Plasma-Based Genomic Profiling in Solid Tumors**. Moldx specifies criteria for limited coverage policy for next-generation sequencing (NGS) assays performed on solid tumor cell-free deoxyribonucleic acid (DNA) in plasma, from here on called "liquid biopsies."

Moldx states Guardant360® is covered only when **all of the following** conditions are met:

- Patient has been diagnosed with a recurrent, relapsed, refractory, metastatic, or advanced solid tumor that did not originate from the central nervous system, **and**
    - Patients who would meet all of the indications on the Food and Drug Administration (FDA) label for larotrectinib if they are found to have a neurotrophic receptor tyrosine kinase (NTRK) mutation may be considered to have advanced cancer
- Patient has not previously been tested with the Guardant360® test for the same genetic content. For a patient who has been tested previously using Guardant360® for cancer, that patient may not be tested again unless there is clinical evidence that the cancer has evolved wherein testing would be performed for different genetic content. Specifically, in patients with previously tested cancer, who have evidence of new malignant growth despite response to a prior targeted therapy, that growth may be considered to be sufficiently genetically different to require additional genetic testing, **and**
- Patient is untreated for the cancer being tested, or the patient is not responding to treatment (e.g., progression or new lesions on treatment), **and**
- The patient has decided to seek further cancer treatment with the following conditions:
    - The patient is a candidate for further treatment with a drug that is either FDA-approved for that patient's cancer, or has a National Comprehensive Cancer Network (NCCN) 1 or NCCN 2A recommendation for that patient's cancer, **and**

  - The FDA-approved indication or NCCN recommendation is based upon information about the presence or absence of a genetic biomarker tested for in the Guardant360® assay, **and**
- Tissue-based, comprehensive genomic profiling (CGP) is infeasible (e.g., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated) **or** specifically in NSCLC Tissue-based CGP has shown no actionable mutations.

Moldx states other liquid biopsies will be covered for the same indications if they display similar performance in their intended used applications to Guardant360®. Currently MolDx indicates that the following liquid biopsy tests **are covered**:

- Guardant360® (Guardant Health) - 0326U
- Caris Assure™ (Caris Life Sciences) – 0486U
- Northstar Select™ (BillionToOne, Inc.) - 0487U
- LiquidHALLMARK ctDNA and ctRNA (Lucence Health Inc) – 0571U

Resolution ctDx Lung™ (Exact Sciences) is **non-covered** per MolDx.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06090214	Circulating Tumor Cells for the Diagnosis of Intestinal-type Adenocarcinoma of the Ethmoid : a Pilot Study	42	Dec 2025
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study	15254	Mar 2024
NCT03957564	Liquid Biopsy in Monitoring the Neoadjuvant Chemotherapy and Operation in Patients With Resectable or Locally Advanced Gastric or Gastro-oesophageal Junction Cancer	40	May 2024
NCT05582122	SURVEILLE-HPV: National, Multicenter, Open-label, Randomized, Phase II Study Evaluating HPV16 Circulating DNA as Biomarker to Detect the Recurrence, in Order to Improve Post Therapeutic Surveillance of HPV16-driven Oropharyngeal Cancers	420	Apr 2031
NCT05764044	Adjuvant Chemotherapy in Cell-free Human Papillomavirus Deoxyribonucleic Acid (cfHPV-DNA) Plasma Positive Patients: A Biomarker In Locally Advanced Cervical Cancer (CC)	50	Dec 2023

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

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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	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

Type	Code	Description
	0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood
	0486U	Oncology (pan-solid tumor), next-generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction
	0490U	Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular-weight melanoma-associated antigen, CD34 and CD45 protein biomarkers, peripheral blood
	0491U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker-expressing cells, peripheral blood
	0492U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker-expressing cells, peripheral blood
	0498U	Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation
	0501U	Oncology (colorectal), blood, quantitative measurement of cell-free DNA (cfDNA)
	0560U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments
	0561U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD
	0562U	Oncology (solid tumor), targeted genomic sequence analysis, 33 genes, detection of single-nucleotide variants (SNVs), insertions and deletions, copy-number amplifications, and translocations in human genomic circulating cell-free DNA, plasma, reported as presence of actionable variants
	0507U	Oncology (ovarian), DNA, whole-genome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected
	81400	Molecular Pathology Procedure Level 1
	81401	Molecular Pathology Procedure Level 2
	81402	Molecular Pathology Procedure Level 3
	81403	Molecular Pathology Procedure Level 4
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
	81406	Molecular Pathology Procedure Level 7
	81407	Molecular Pathology Procedure Level 8

Type	Code	Description
	81408	Molecular Pathology Procedure Level 9
	81479	Unlisted molecular pathology procedure
	86152	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood)
	86153	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
08/01/2016	BCBSA Medical Policy adoption
12/01/2016	Policy revision without position change
10/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
12/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
07/01/2019	Coding update
10/01/2019	Policy revision without position change
03/01/2020	Coding update
10/01/2020	Annual review. No change to policy statement. Policy guidelines and literature updated.
11/01/2020	Administrative update.
12/01/2020	Administrative update. Policy guidelines updated.
01/01/2021	Coding Update
02/01/2021	Coding Update
10/01/2021	Annual review. Policy statement, guidelines and literature updated.
08/01/2022	Coding Update
10/01/2022	Annual review. Policy statement, guidelines and literature updated.
11/01/2022	Coding update
10/01/2025	Policy reactivated. Previously archived from 06/01/2023 to 09/30/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) 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 the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) 2.04.141** **Policy Statement:** I. The use of circulating tumor DNA and/or circulating tumor cells is considered **investigational** for all indications reviewed herein (see Policy Guidelines). Note: For individuals enrolled in health plans subject to the Biomarker Testing Law (Health & Safety Code Section 1367.667 and the Insurance Code Section 10123.209), Centers for Medicare & Medicaid Services (CMS) Local Coverage Determination (LCD) may also apply. Please refer to the Medicare National and Local Coverage section of this policy and to MolDX: Plasma-Based Genomic Profiling in Solid Tumors for reference.