2.04.141	Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)		
Original Policy Date:	August 1, 2016	**Effective Date:**	November 1, 2022
Section:	2.0 Medicine	**Page:**	Page 1 of 22

Policy Statement

Note: 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).

I. The use of circulating tumor DNA (ctDNA) is considered **investigational** for all indications except as allowed for in other policies such as for Non-Small Cell Lung Cancer (NSCLC) or breast cancer (see Policy Guidelines and Related Policies section).

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 for "driver mutations" to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for use of liquid biopsy for detection or risk assessment of prostate cancer, the use of AR-V7 circulating tumor cells for metastatic prostate cancer, or liquid biopsy to select targeted treatment for breast, ovarian, prostate, or pancreatic cancer. Refer to the following related Blue Shield of California Medical Policies for indications not covered in this policy:

- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer
- Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer
- Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Coding

There are no specific CPT codes for most ctDNA tests other than some specific PLA codes. These tests would likely be reported using any existing CPT molecular pathology code(s) that is applicable (81161-81355 and 81400-81408), or 81445, 81455 (for solid tumor testing), along with or as a single code, the unlisted molecular pathology procedure code (81479). Solid tumor test codes may be used as the closest available code to ctDNA tests in some cases:

- **81445**: Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
- **81455**: Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK,

BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

The following CPT code that may be billed as a companion diagnostic test:

- **0239U**: Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations

There is a Tier 1 CPT code to more accurately describe single-nucleotide polymorphism (SNP) array-derived copy number (CN) for neoplasia. This uses the patient's chromosomal microarray (CMA) results to look for abnormalities:

- **81277**: Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities

Detection and quantification of circulating tumor cells (such as for measurable residual disease) would be reported using the following codes:

- **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

The following CPT code is specific to the FirstSight$^{CRC™}$ test:

- **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

Effective October 1, 2022, there is a new CPT code that represents CellSearch® HER2 Circulating Tumor Cell (CTC-HER2) Test by Menarini Silicon Biosystems. Per the manufacturer this test performed on peripheral blood evaluates HER2 status at first cancer recurrence, metastasis, and/or when progression occurs in unresectable, locally advanced, recurrent or metastatic breast, colorectal, gastric, head and neck, or other HER2-overexpressing adenocarcinomas. CTC testing is a non-invasive method for HER2 biomarker detection to inform treatment, including HER2 targeted therapies, particularly in patients with HER2 negative primary tumors, when biopsy is difficult/ contraindicated or upon cancer progression.

- **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

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.

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
- Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer
- Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the 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 mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

The FDA maintains a list of cleared or approved companion diagnostic tests at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

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. The use of liquid biopsy for detection or risk assessment of prostate cancer is addressed in Blue Shield of California Medical Policy: Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer. The use of AR-V7 circulating tumor cell (CTC) liquid biopsy for metastatic prostate cancer is addressed in Blue Shield of California Medical Policy: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management. The use of liquid biopsy to select targeted treatment for breast cancer is addressed in Blue Shield of California Medical Policy: Biomarker Testing

(Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer. The use of liquid biopsy to select therapy in ovarian, pancreatic, and prostate cancer will be addressed in other reviews in development.

Selecting Treatment in Advanced Cancer

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does use of circulating tumor DNA (ctDNA) or CTC testing to select treatment in patients with cancer improve the net health outcome compared with standard tissue testing? Note that the use of a liquid biopsy to select therapy in metastatic prostate cancer is addressed in Blue Shield of California Medical Policy: Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management, and to select targeted treatment for breast cancer is addressed in Blue Shield of California Medical Policy: Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer. The use of liquid biopsy to select therapy in ovarian, pancreatic, and prostate cancer will be addressed in other reviews in development.

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

Populations

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

Interventions

The test being considered is liquid biopsy using either ctDNA or CTCs. Both targeted polymerase chain reaction-based assays and broad next-generation sequencing-based approaches are available. Patients with negative liquid biopsy results should be reflexed to tumor biopsy testing if they are able to undergo tissue biopsy.[2,]

Comparators

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

Outcomes

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

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

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

Review of Evidence

Clinically Valid

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

Circulating Tumor DNA

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

Much of the literature to date on the use of ctDNA to guide treatment selection is for non-small-cell lung cancer, which is addressed in 2.04.143, metastatic CRC, which is addressed in 2.04.53, and breast cancer, which is addressed in 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.

Since the end date of the searches conducted by Merkel et al (2018), 2 observational studies of the clinical validity of FoundationOne Liquid (formerly FoundationACT) in patients with cancers covered herein have been published (Table 1). Both studies compared liquid biopsy to tissue biopsy with FoundationOne comprehensive genomic testing. Test characteristics are shown in Table 2. Relevance, design, and conduct Imitations of these studies are summarized in Tables 3 and 4.

Table 1. Study Characteristics of the Clinical Validity of FoundationOne Liquid

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Clark et al (2018)[3,]	Patients with advanced cancer	Retrospective (tissue) and prospective (liquid biopsy)	Tissue biopsy (FoundationOne)	0 to 60 days	Not stated
Zhou et al (2018)[4,]	Patients with locally advanced or metastatic solid tumors	Retrospective	Tissue biopsy (FoundationOne)	Not reported; only considered patient with no intervening treatment between liquid and tissue biopsy	Not stated

Table 2. Clinical Validity of FoundationOne Liquid

Study	Initial N	Final N	PPA	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Clark et al (2018)[3,]	NR	36					
Overall	NR	36	75%	--	--	--	--
Base substitutions/ indels	NR	36		82.7% (69.7 to 91.8)	97.5% (95.9 to 98.5)	72.9% (59.7 to 83.6)	98.6% (97.3 to 99.4)
Rearrangements	NR	36		100% (15.8 to 100)	99.1% (94.3 to 100)	66.7% (9.4 to 99.2)	100% (96.5 to 100)
Amplifications	NR	36		38.5%(13.9 to 68.4)	100% (98.5 to 100	100% (47.8 to 100)	96.8% (93.6 to 98.6)

Study	Initial N	Final N	PPA	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Zhou et al (2018)[4,]							
Overall	NR	42	82%				
Base substitutions	NR	42		77.2% (66.4 to 85.9)	96.0% (94.6 to 97.1)	59.2% (49.1 to 68.8)	98.3% (97.3 to 99.0)
Insertions/ deletions	NR	42		7.1% (0.9 to 23.5)	98.2% (95.5 to 99.5)	33.3% (4.3 to 77.7)	89.4% (84.9 to 93)
Amplifications	NR	42		23.7% (11.4 to 40.2)	99.8% (98.8 to 100)	90.0% (53.2 to 100)	94.1% (91.7 to 96)
Rearrangements or fusions	NR	42		100.0% (39.8 to 100)	97.6% (93.9 to 99.3)	50.0% (15.7 to 84.3)	100.0% (97.7 to 100)

CI: confidence interval; indels: insertions/deletions; PPA: positive percent agreement; PPV: positive predictive value; NPV: negative predictive value; NR: not reported

Table 3. Study Relevance Limitations of Clinical Validity Studies of FoundationOne Liquid

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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 4. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Clark et al (2018)[3,]	2. convenience sample	1. Blinding unclear	1. Timing of liquid and tissue biopsy varied (0 to 60 days)		1. No description of indeterminate and missing samples	
Zhou et al (2018)[4,]	2. convenience sample	1. Blinding unclear	1. Timing of liquid and tissue biopsy not reported		1. No description of indeterminate and missing samples	

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

[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c]Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Circulating Tumor Cells

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

Clinically Useful

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

Circulating Tumor DNA

Direct Evidence

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

Merker et al (2018) concluded that no such trials have been reported for ctDNA tests.[2,]

Chain of Evidence

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

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

The evidence is insufficient to demonstrate test performance for currently available ctDNA tests except for lung cancer (see 2.04.143); therefore, no inferences can be made about clinical utility.

Circulating Tumor Cells

Direct Evidence

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

Trials of using CTCs to select treatment are ongoing (see Table 5 in Supplemental Information).

Chain of Evidence

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

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

Section Summary: Selecting Treatment in Advanced Cancer

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

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

Monitoring Treatment Response in Cancer

Clinical Context and Test Purpose

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

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

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

Patients

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

Interventions

The test being considered is liquid biopsy using either ctDNA or CTCs. For ctDNA tests, the best unit for quantifying DNA burden has not been established.[2,]

Comparators

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

Outcomes

The outcome of primary interest is progression-free survival.

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

Review of Evidence

Clinically Valid

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

Circulating Tumor DNA

Merker et al (2018) identified several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes, as well as studies demonstrating that ctDNA can identify the emergence of resistant variants.[2,] However, they reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and concluded that clinical validity had not been established.

Circulating Tumor Cells

Systematic reviews and meta-analyses describing an association between CTCs and poor prognosis have been reported for metastatic breast cancer,[5,6,7,8,] CRC,[9,10,] hepatocellular cancer,[11,] prostate cancer,[12,13,14,] head and neck cancer,[15,] and melanoma.[16,]

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

Clinically Useful

Circulating Tumor DNA

Direct Evidence

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

Merker et al (2018) concluded there is no evidence that changing treatment before clinical progression, at the time of ctDNA progression, improves patient outcomes.[2,]

Chain of Evidence

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

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

Circulating Tumor Cells

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. Smerage et al (2014) reported on the results of an RCT of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemo-therapy after 1 cycle of first-line therapy could improve overall survival (OS; the primary study outcome).[17,] Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median OS between arms C1 (10.7 months) and C2 (12.5 months; p=.98). Circulating tumor cell levels were strongly prognostic, with a median OS for arms A, B, and C (C1 and C2 combined) of 35 months, 23 months, and 13 months, respectively (p<.001). This trial showed the prognostic significance of CTCs in patients, which rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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

Section Summary: Monitoring Treatment Response in Cancer

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

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

Predicting Risk of Relapse

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does ctDNA or CTC testing to predict the risk of relapse in patients who have received curative treatment for cancer improve the net health outcome?

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Review of Evidence

Clinically Valid

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

Circulating Tumor DNA

Merker et al (2018) identified several proof-of-principle studies demonstrating an association between persistent detection of ctDNA after local therapy and high-risk of relapse.[2,] However,

current studies are retrospective and have not systematically confirmed that ctDNA is being detected before the metastatic disease has developed. They concluded that the performance characteristics had not been established for any assays.

Chidambaram et al (2022) conducted a systematic review and meta-analysis of the clinical utility of circulating tumor DNA testing in esophageal cancer. [18,]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.[19,] After chemotherapy, 22% of patients were CTC-positive, and CTC positivity was negatively associated with prognosis.

Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer,[20,]CRC[21,] bladder cancer,[22,23,] liver cancer,[24,] and esophageal cancer.[25,]

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

Clinically Useful

Circulating Tumor DNA and Circulating Tumor Cells

Direct Evidence

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

Merker et al (2018) concluded that there is no evidence that early treatment before relapse, based on changes in ctDNA, improves patient outcomes.[2,] Similarly, no trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes.

Chain of Evidence

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

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

Section Summary: Predicting Risk of Relapse

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

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

Screening for Cancer in Asymptomatic Individuals

Clinical Context and Test Purpose

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

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

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

Review of Evidence

Clinically Valid

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

Circulating Tumor DNA

Merker et al (2018) reported there is no evidence of clinical validity for the use of ctDNA in asymptomatic individuals.[2,]

Circulating Tumor Cells

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer.[26,27,] Reported sensitivity was low in both cancers (42% and 35%) overall. Sensitivity was lower in patients with early-stage cancer, suggesting that the test would not be useful as an initial screen.

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

Clinically Useful

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

Circulating Tumor DNA and Circulating Tumor Cells

Direct Evidence

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

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

Chain of Evidence

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

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

Section Summary: Screening for Cancer in Asymptomatic Individuals

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

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

Summary of Evidence

For individuals who have advanced cancer who receive testing of ctDNA to select targeted treatment, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking for the indications covered in this review. The clinical validity of FoundationOne Liquid compared to tissue biopsy with FoundationOne comprehensive genetic profiling was evaluated in 4 industry-sponsored observational studies. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether variant analysis of ctDNA can replace variant analysis of tissue. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs can replace variant analysis of tissue. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

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

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

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

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

Supplemental Information

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

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

There is no general 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 Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study	15254	Mar 2024
NCT04168931	Efficacy of Adding Trastuzumab to Standard Chemotherapy in Patients With Advanced HER2-negative Gastric Cancer and HER2 Positive Expression in Circulating Tumor Cells	85	Jan 2025
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

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

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

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
	0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (e.g., colorectal cancer) promoter methylation analysis ***(Code revision effective 7/1/2022)***
	0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
	0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on

Type	Code	Description
		differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood ***(Code effective 10/1/2022)***
	81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
	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
	81408	Molecular Pathology Procedure Level 9
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	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

Effective Date	Action
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

Definitions of Decision Determinations

Medically Necessary: 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, are: (a) consistent with Blue Shield 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 patient; 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/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

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.

We are 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.

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

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. 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 contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member 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**
Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) 2.04.141 **Policy Statement:** I. The use of circulating tumor DNA (ctDNA) is considered **investigational** for all indications except as allowed for in other policies such as for Non-Small Cell Lung Cancer (NSCLC) or breast cancer (see Policy Guidelines and Related Policies section).	**Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) 2.04.141** **Policy Statement:** **Note:** 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). I. The use of circulating tumor DNA (ctDNA) is considered **investigational** for all indications except as allowed for in other policies such as for Non-Small Cell Lung Cancer (NSCLC) or breast cancer (see Policy Guidelines and Related Policies section).