

PHP_2.04.141		Tumor-Uninformed Circulating Tumor DNA (Guardant Reveal™) for Cancer Management (Liquid Biopsy)	
Original Policy Date:	March 1, 2026	Effective Date:	November 1, 2026
Section:	2.0 Medicine	Page:	Page 1 of 31

Policy Statement

- I. The use of tumor-uninformed circulating tumor DNA (i.e., Guardant Reveal™) in individuals with colorectal cancer may be considered **medically necessary** when **all** of the following are met:⁴⁶
 - A. Member has a diagnosis of stage II to IV colorectal cancer and monitoring is needed to diagnose cancer recurrence, relapse, or progression
 - B. Identification of cancer recurrence, relapse, or progression will require a change in management
 - C. Member is not receiving other molecular testing for minimal residual disease analysis concurrently with this test
 - D. **One** of the following:
 1. Member is currently being treated for cancer, and the test has not been previously performed for this cancer diagnosis
 2. Member is currently being treated for cancer and there is clinical suspicion that the molecular profile of the member's tumor has changed
 3. Member is not currently being treated for their cancer (in other words, when there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and subsequently the member is no longer being subjected to therapeutic interventions for cancer), and the test has not been performed in the last 12 months
 4. Member is not currently being treated for their cancer, and now there is clinical suspicion for tumor recurrence.

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) National and Local Coverage Determinations (NCDs or LCDs) may also apply. Please refer to the Medicare National and Local Coverage section of this policy. LCD selection is contingent upon the location of the servicing provider (i.e., laboratory).

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

State Guideline Resources

Applicable State Guideline resources as of the effective date of this policy:

- I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
 - N/A
- II. Department of Health Care Services (DHCS) Provider Manual Guideline:
 - [TAR and Non-Standard Benefits List: Codes 0001M thru 0999U \(tar and non cd0\)](#)
 - [Proprietary Laboratory Analyses \(PLA\) \(prop lab\)](#)
- III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:
 - [APL 22-010](#) – Cancer Biomarker Testing

Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.

For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.

Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:

- Advanced or metastatic stage 3 or 4 cancer.
- Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer.

MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.

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 genetic 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 Blue Shield of California Promise Medical Policies for indications not covered here:

- PHP_2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- PHP_2.04.54 - Molecular Genomic Profiling for Cancers of Unknown Primary
- PHP_2.04.61 - Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer
- PHP_2.04.111 - Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management
- PHP_2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- PHP_2.04.146 - Gene Expression Profiling for Cutaneous Melanoma
- PHP_2.04.151 - Genetic Variant Testing (Including Liquid Biopsy) for Targeted Treatment in Advanced Cancer
- PHP_2.04.153 - Tumor-Informed Circulating Tumor DNA Testing (Signatera™) for Cancer Management

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) is tumor-derived cell-free DNA released into the bloodstream by cancer cells. Blood-based analysis of ctDNA, commonly referred to as a liquid biopsy, may provide information about tumor burden, minimal residual disease (MRD), recurrence, relapse, or disease progression without requiring an invasive tissue biopsy.

In individuals with stage II to IV colorectal cancer, ctDNA testing may provide clinically useful information regarding the presence of residual disease following treatment, molecular evidence of recurrence before radiographic detection, or disease progression requiring a change in management. The clinical relevance of ctDNA testing depends on the clinical setting, timing of testing, and whether the results will influence treatment decisions, surveillance strategies, or additional diagnostic evaluation.

This policy addresses the use of tumor-uninformed ctDNA testing with Guardant Reveal™ for monitoring recurrence, relapse, or progression in individuals with colorectal cancer. Other liquid biopsy applications, including comprehensive genomic profiling, tumor-informed ctDNA testing, and liquid biopsy testing used to select targeted therapies, are addressed in separate medical policies.

Summary of Evidence

For individuals with stage II to IV colorectal cancer who receive tumor-uninformed ctDNA testing to monitor for recurrence, relapse, or progression, the evidence includes randomized trials, observational studies, and systematic reviews evaluating the clinical validity and clinical utility of ctDNA testing.

Available evidence demonstrates that detection or persistence of ctDNA following treatment is associated with an increased risk of recurrence and adverse clinical outcomes. Randomized evidence in colon cancer also supports the use of ctDNA to inform selected management decisions. In the DYNAMIC trial, ctDNA-guided management reduced the use of adjuvant chemotherapy without compromising recurrence-free survival, and longer-term follow-up reported comparable recurrence-free and overall survival outcomes between ctDNA-guided and standard-management groups.

The evidence has limitations. Clinical performance varies among assays, testing methodologies, disease stages, and testing time points. Evidence specific to tumor-uninformed Guardant Reveal testing should therefore be distinguished from evidence involving tumor-informed assays or other liquid-biopsy technologies. Testing is most clinically relevant when recurrence, relapse, or progression is being evaluated and when the result is expected to change management.

Based on the available evidence and applicable coverage requirements, Guardant Reveal testing may be considered medically necessary for the colorectal cancer indications specified in the Policy Statement. Evidence is insufficient to support uses outside those criteria unless coverage is required under applicable state or federal guidance.

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
- Gene Expression Profiling for Cutaneous Melanoma
- 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
- Genetic Variant Testing (Including Liquid Biopsy) for Targeted Treatment in Advanced Cancer
- Molecular Genomic Profiling for Cancers of Unknown Primary
- Tumor-Informed Circulating Tumor DNA Testing (Signatera™) for Cancer Management
- Medical Services Committee Policy and Procedure: Utilization Management Decision Making & Timeframes

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

California Children's Services (CCS) is a Medi-Cal benefit provided by the State in partnership with County Public Health Departments. Blue Shield Promise coordinates the benefits for eligible members. The CCS program provides medical case management, diagnostic and treatment services, and physical and occupational therapy services to children under the age 21 with CCS eligible medical conditions managed by CCS paneled providers. The program's goal is to provide medical and allied services necessary to achieve maximum physical and social function for children. Members identified with CCS-eligible conditions are referred to the County CCS program immediately upon identification.

Regulatory Status

Cal. Health & Safety Code § 1367.665 and Insurance Code Section 10123.20

California laws that prohibit health plans and insurers from requiring prior authorization for biomarker testing for advanced or metastatic stage 3 or 4 cancer, and cancer progression or recurrence.

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09

California laws that require 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.

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 Medical Policy (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 Medical Policy
Agilent Resolution ctDx FIRST assay	NSCLC	KRAS	Krazati (adagrasib)	PHP_2.04.151
cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Tagrisso (osimertinib)	PHP_2.04.151
	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Iressa (gefitinib)	PHP_2.04.151
	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Tarceva (erlotinib)	PHP_2.04.151
	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Gilotrif (afatinib)	PHP_2.04.151
FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Exkivity (mobocertinib)	PHP_2.04.151
	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Iressa (gefitinib)	PHP_2.04.151
	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Tagrisso (osimertinib)	PHP_2.04.151
	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Tarceva (erlotinib)	PHP_2.04.151
	NSCLC	<i>MET</i>	Tabrecta (capmatinib)	PHP_2.04.151
	NSCLC	<i>ROS1</i>	Rozlytrek (entrectinib)	PHP_2.04.151
	NSCLC	ALK	Alecensa (alectinib)	PHP_2.04.151
	Ovarian Cancer	<i>BRCA1</i> and <i>BRCA2</i>	Rubraca (rucaparib)	2.04.156
	Solid Tumors	<i>ROS1</i>	Rozlytrek (entrectinib)	
	Breast Cancer	<i>PIK3CA</i>	Piqray (alpelisib)	PHP_2.04.151
	Metastatic Castrate Resistant Prostate Cancer	<i>BRCA1</i> , <i>BRCA2</i> and <i>ATM</i>	Lynparza (olaparib)	PHP_2.04.151
	Metastatic Castrate Resistant Prostate Cancer	<i>BRCA1</i> and <i>BRCA2</i>	Rubraca (rucaparib)	PHP_2.04.151
Guardant360 CDx (Guardant Health, Inc.)	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Tagrisso (osimertinib)	PHP_2.04.151
	NSCLC	<i>EGFR</i> (<i>HER1</i>)	Rybrevant (amivantamb)	PHP_2.04.151
	NSCLC	<i>KRAS</i>	Lumakras (sotorasib)	PHP_2.04.151
	NSCLC	ERBB2	ENHERTU (fam-trastuzumab deruxtecan-nxki)	PHP_2.04.151
	Breast Cancer	<i>ESR1</i> <i>ERB2</i>	Orserdu (elacestrant)	2.04.151 In development for 2.04.151

Diagnostic Name (Manufacturer)	Indication	Biomarker	Drug Trade Name (Generic)	Related Medical Policy
<i>therascreen</i> PIK3CA RQ PCR Kit (QIAGEN GmbH)	Breast Cancer	<i>PIK3CA</i>	ENHERTU (fam- trastuzumab deruxtecán-nxki) Piqray (alpelisib)	PHP_2.04.151
xT CDx (Tempus Labs, Inc.)	Colorectal Cancer	<i>KRAS</i>	Erbitux (cetuximab)	PHP_2.04.151
	Colorectal Cancer	<i>KRAS</i> and <i>NRAS</i>	Vectibix (panitumumab)	PHP_2.04.151

Source: FDA (2025)²

FDA: U.S. Food and Drug Administration; NSCLC: non-small cell lung cancer

Health Equity Statement

Blue Shield of California Promise Health Plan’s mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan’s mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

Liquid Biopsy

Liquid biopsy refers to the analysis of circulating tumor DNA (ctDNA) as a method 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.

Detecting Circulating Tumor DNA

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.

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.

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 ctDNA. For ctDNA tests, the best unit for quantifying DNA burden has not been established.³ The kinetics of ctDNA correlate with treatment response and may identify responses earlier than clinical/radiological detection. Across multiple different tumor types, and type of treatment (chemotherapy, targeted therapy, and immunotherapy), patients who respond to treatment have a drop in ctDNA levels within weeks of starting therapy.⁴

Comparators

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

Outcomes

The outcomes of primary interest are progression-free survival (PFS) and overall survival (OS).

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

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 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 ctDNA. Substantial evidence suggests that detection of ctDNA following potentially curative treatment is associated with a high-risk of future relapse with two terms, minimal/molecular residual disease (MRD) and molecular relapse (MR), commonly used in the literature for predicating relapse via liquid biopsy. To ensure benefit of early treatment and limit false-negative cases, it is critical that assays can detect ultra-low ctDNA concentrations.⁴

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 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

Randomized Clinical Trials

Numerous randomized clinical trials (RCTs) have investigated ctDNA testing as an exploratory analysis either prospectively or retrospectively as a post hoc analysis to determine the utility of ctDNA testing in the management of cancer. Characteristics of these RCTs are listed in Table 2 with their key results recorded in Table 3.

Table 2. Summary of Key Characteristics of Randomized Clinical Trials on Circulating Tumor DNA Testing in Individuals with Cancer

Study	Countries	Sites	Participants	Methods	Interventions	
					<i>Active</i>	<i>Comparator</i>
Ruiz-Vico et al (2025) ⁵	Global	89	Patients with histologically confirmed prostate adenocarcinoma, bone or soft tissue metastases, progression despite serum testosterone ≤ 1.73 nmol/L, and ECOG performance status 0–1	An exploratory analysis of the PRESIDE (NCT02288247), a multicenter, two-period, double-blind, randomized, placebo-controlled phase 3b clinical trial, to assess the associations of PFS and circulating	Enzalutamide	Placebo

Study	Countries	Sites	Participants	Methods	Interventions	
					Active	Comparator
				tumor DNA (ctDNA) prior to and after one cycle of docetaxel.		
LaPelusa et al (2025) ⁶	U.S.	1	Patients ≥18 years of age with locally advanced, histologically confirmed deficient mismatch repair/microsatellite instability-high solid tumors.	An exploratory analysis of a phase II clinical trial (NCT04082572) to investigate the ctDNA kinetics over the course of treatment with pembrolizumab to determine whether ctDNA has utility as a biomarker for pathologic complete response, event-free survival, and overall survival.	Pembrolizumab	None
Rodrigues et al (2024) ⁷	France	5	Patients ≥18 years of age with any tumoral disease (proven or suspected), of any type and stage.	An exploratory analysis of the phase II, IMCgp100-102, and phase III, IMCgp100-202 tebentafusp, clinical trials (NCT02866149) on blood-borne biological markers and their correlation with clinical and pathological characteristics.	Tebentafusp	None
Knutson et al (2024) ⁸	U.S., Canada, and Puerto Rico	539	Men ≥18 years of age with previously untreated metastatic castration-resistant prostate cancer and progressive metastatic disease despite ongoing androgen deprivation therapy.	An exploratory liquid biopsy analysis of plasma cell free DNA from patients who enrolled in the randomized phase III clinical trial, Alliance A031201 (NCT01949337), to interrogate the utility of ctDNA in understanding clinical outcomes.	Enzalutamide	Enzalutamide plus abiraterone and prednisone
Han et al (2024) ⁹	South Korea	16	Patients ≥20 years of age with histologically or cytologically confirmed diagnosis of advanced <i>EGFR</i> -mutated non-small cell lung cancer, ECOG performance status 0 to 1, at least one measurable extracranial lesion, and confirmed T790M+ variant status, and previous therapy with <i>EGFR</i> tyrosine kinase inhibitors.	An exploratory analysis of a multicenter, open-label, phase 1/2 clinical trial, LASER201 study (NCT03046992), to assess the relationship of ctDNA testing for <i>EGFR</i> variants and efficacy parameters.	Lazertinib	None

Study	Countries	Sites	Participants	Methods	Interventions	
					Active	Comparator
Herbst et al (2025) ¹⁰	U.S., Japan and China	210	Patients ≥18 years of age (20 years or older in Japan and Taiwan) and had postsurgical stage IB (T2a tumors >3 cm and ≤5 cm in size), II or IIIA non-small cell lung cancer, with a centrally confirmed <i>EGFR</i> mutation (Ex19del/L858R) and a World Health Organization performance status of 0 or 1.	An exploratory analysis of the ADAURA phase III trial (NCT02511106) to investigate whether plasma-based, tumor-informed MRD analysis (ctDNA) could predict disease recurrence during and after adjuvant treatment in 220 patients with viable ctDNA during or after adjuvant therapy with Osimertinib.	Osimertinib	Placebo
Syeda et al (2025) ¹¹	Global	210	Patients with completely resected, histologically confirmed, <i>BRAF</i> V600E/K mutation-positive, high-risk [Stage IIIa (lymph node metastasis >1 mm), IIIb, or IIIc] cutaneous melanoma were screened for eligibility and had undergone complete lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before randomization, had recovered from definitive surgery, and had an ECOG performance status of 0 or 1.	A biomarker analysis from a double-blind, randomized phase 3 trial (COMBI-AD; NCT01682083) to investigate whether ctDNA could predict survival outcomes during adjuvant targeted therapy or placebo treatment in stage II melanoma.	Dabrafenib or Trametinib	Placebo
Ademuyiwa et al (2025) ¹²	U.S.	1	Patients ≥18 years of age, with newly diagnosed AJCC7 clinical stage II or III breast cancer with complete surgical excision of the breast cancer after neoadjuvant chemotherapy as the treatment goal, an ECOG performance status <2.	A biomarker analysis of a single arm open label phase II study on patients with stage II or III TNBC undergoing neoadjuvant docetaxel and carboplatin chemotherapy on a clinical trial (NCT02124902) followed by surgery with or without adjuvant therapy were included in this study to determine the postoperative surveillance sensitivity and specificity for detecting distant	docetaxel and carboplatin	Historical controls

Study	Countries	Sites	Participants	Methods	Interventions	
					Active	Comparator
metastatic recurrence in patients with TNBC.						
Yoo et al (2025) ¹³	South Korea	1	Patients ≥19 years of age, with histologically confirmed extrahepatic cholangiocarcinoma, complete (R0 or R1) surgical resection within 12 weeks before randomization, and metastasis to at least one regional lymph node.	A biomarker analysis from a multicenter, open-label, randomized phase II study (STAMP) of 89 patients. Longitudinal plasma samples (n = 254) were prospectively collected post-surgery before ACT, and on-ACT at 12 and 24 weeks from cycle 1 day 1 (CID1). ctDNA was evaluated using a personalized, tumor-informed, 16-plex PCR next-generation sequencing assay and was correlated with clinical outcomes.	Gemcitabine plus cisplatin	Capecitabine
Taieb et al (2025) ¹⁴	France and Greece	153	Patients ≥18 years and older, with stage III histologically confirmed colon cancer, curative-intent surgery no more than 8 weeks before random assignment, an ECOG performance status of 0 or 1, and postoperative carcinoembryonic antigen (CEA) level <10 ng/mL.	A biomarker analysis from two multicenter, two-arm, open-label, randomized phase III trials (IDEA-France, NCT00958737, and IDEA-Greece, NCT01308066, trials). Plasma samples (ctDNA) were collected after surgery or before ACT and analyzed for time to recurrence (TTR; patients without recurrence or death due to colon cancer) and overall survival (OS). Treatment was randomly assigned (1:1) to 3 or 6 months of adjuvant chemotherapy.	modified FOLFOX6	capecitabine plus oxaliplatin
Mayadev et al (2025) ¹⁵	Global	117	Adult women with untreated histologically and radiologically confirmed cervical adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma, International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage IB2-IIIB node	An exploratory analysis in a large cohort of patients from a phase III, randomized, double-blind, placebo-controlled trial (CALLA study; NCT03830866) to evaluate the association of pretreatment and on-treatment ctDNA	Durvalumab with CRT	Placebo

Study	Countries	Sites	Participants	Methods	Interventions	
					Active	Comparator
			positive, or stage IIIA-IVA node positive or negative, no evidence of metastatic disease with a World Health Organization or ECOG performance status of 0 or 1, at least one lesion measurable by RECIST version 1.1, and adequate organ and marrow function were enrolled.	levels with long-term clinical outcomes and patient baseline disease characteristics in the context of locally advanced cervical cancer.		
Long et al (2025) ¹⁶	Global	124	Patients ≥12 with resected stage IIIB–D or IV melanoma and no evidence of residual disease on radiographical assessment and had an ECOG performance status of 0 or 1 were randomized 1:1 to receive nivolumab monotherapy 480mg once every 4 weeks or nivolumab 240mg every 2 weeks + ipilimumab 1mg/kg every 6 weeks.	An exploratory analysis from the CheckMate 915 trial (NCT03068455) to evaluate tumor and peripheral biomarkers, including tumor-informed ctDNA at postresection baseline and on-treatment, for their association with RFS and distant metastases-free survival.	Nivolumab + Ipilimumab	Nivolumab
Azaïs et al (2025) ¹⁷	France	36	Female patients ≥18 with histological confirmed (cytology alone excluded) epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer, FIGO–Stages IIIC – IV, an ECOG performance status <2, refusal of primary debulking surgery and maximum surgical effort of cytoreduction with the goal of no residual disease planned as interval debulking surgery.	An exploratory analysis of the prospective CHIVA (NCT01583322) phase II trial to evaluate the prognostic impact of ctDNA detection and quantification at diagnosis and of its early decrease after one cycle of neoadjuvant chemotherapy (NACT) in a cohort of patients with advanced epithelial ovarian cancer.	Vargatef + Nintedanib	Placebo

ACT: adjuvant chemotherapy; AJCC: American Joint Committee on Cancer; CRT: chemoradiotherapy; ctDNA: circulating tumor DNA; CID1: cycle 1 day 1; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; *EGFR*: epidermal growth factor receptor; HR: hazard ratio; MRD: molecular/minimal residual disease; NA: not applicable; NR: not reported; PFS: progression-free survival; OS: overall survival; RFS: Recurrence-free survival

Table 3. Results from RCTs on Circulating Tumor DNA Testing in Individuals with Cancer

Study	PFS (HR, 95% CI)	OS (95% CI)	EFS (%; 95% CI)	DFS (HR, 95% CI)	RFS (HR, 95% CI)	p value
Ruiz-Vico et al (2025) ²⁵	ctDNA at baseline: NR 1.78 (1.20 to 2.64) ctDNA at C2D1: 1.95 (1.15 to 3.30)		NR	NR	NR	p=.004 p=.019

Study	PFS (HR, 95% CI)	OS (95% CI)	EFS (% , 95% CI)	DFS (HR, 95% CI)	RFS (HR, 95% CI)	p value
LaPelusa et al (2025) ^{b6}	NR	ctDNA(-): 100% (1.00 to 1.00) ctDNA(+): 80% (0.52 to 1.00)	ctDNA(-): 92% (0.83 to 1.00) ctDNA(+): 20% (0.03 to 1.00)	NR	NR	OS: p<.001 EFS: p<.001
Rodrigues et al (2024) ⁷	Univariate analysis: 2.8 (1.5 to 5.2) Multivariate analysis: 2.5 (1.1 to 5.9) ^d 5.8 (2.1 to 16.5) ^e	Univariate analysis: HR=10.1 (3.0 to 33.8) Multivariate analysis: HR= 9.3 (1.9 to 45.2) ^d HR= 49.6 (4.5 to 544.5) ^e	NR	NR	NR	Univariate analysis: PFS: p=.001 OS: p<.001 Multivariate analysis: PFS: p=.004 OS: p=.006
Knutson et al (2024) ^{c8}	1.8 (1.5 to 2.1)	HR: 2.0 (1.7 to 2.4)	NR	NR	NR	PFS: p=8.8x10 ⁻¹² OS: p=3.2x10 ⁻¹⁴
Han et al (2024) ^{a9}	ctDNA at baseline: 0.30 (0.15 to 0.59) ctDNA at cycle 3: 0.28 (0.12 to 0.64)	Baseline ctDNA: HR=0.35 (0.14 to 0.90) Cycle 3 ctDNA: HR=0.86 (0.19 to 3.95)	NR	NR	NR	Baseline ctDNA: PFS: p=.0004 OS: NR Cycle 3 ctDNA: PFS: p=.0026 OS: NR
Herbst et al (2025) ¹⁰	NR	HR=0.19 (0.12 to 0.29) ^f	NR	0.42 (0.24 to 0.74) ^f	NR	NR
Syeda et al (2025) ^{a11}	NR	ctDNA(+): Placebo: HR=3.35 (2.01 to 5.55) Combination therapy: HR=4.27 (2.50 to 7.27)	NR	NR	ctDNA(+): Placebo: HR=2.91 (1.99 to 4.25) Combination therapy: HR=2.98 (1.95 to 4.54)	OS: p<.0001 RFS: p<.0001
Ademuyiwa et al (2025) ¹²	NR	NR	NR	NR	post-surgery: 38.8 (32 to 4,761) ^j post-surgery: 37.7 (1.49 to 951) ^j	p<.0001 (both)
Yoo et al (2025) ¹³	NR	ctDNA(-) converted ctDNA(+): HR=3.0 (1.48 to 6.1) ^a Persistently ctDNA(+): HR=4.0 (1.88 to 8.3) ^a	NR	MRD window:1.8 (1.06 to 3.07) ^a post-surgery:3.81 (2.22 to 6.54) ^a 12wks after CID1: 7.72 (4.09 to 14.56) ^a 24wks after CID1: 5.24	NR	OS: p =.002 & p<.001 DFS: p =.029 p<.001 p<.001 p<.001

Study	PFS (HR, 95% CI)	OS (95% CI)	EFS (% , 95% CI)	DFS (HR, 95% CI)	RFS (HR, 95% CI)	p value
				(2.75 to 9.97) ^a		
Taieb et al (2025) ¹⁴	NR	5.21 (3.59 to 7.58) ^a	NR	NR	4.84 (3.40 to 6.89) ^a	OS: p<.001 RFS: p<.001
Mayadev et al (2025) ¹⁵	ctDNA at baseline: 1.72 (0.99 to 3.00) ^b ctDNA at C3D1: 5.27 (2.95 to 9.40) ^a	NR	NR	NR	NR	PFS: p=.054 and p<.001
Long et al (2025) ¹⁶	NR	NR	NR	NR	1.97 (1.57 to 2.46) ^a	NR
Azaïs et al (2025) ¹⁷	1.68 (1.03 to 2.74) ⁱ	1.83 (1.02 to 3.26) ⁱ	NR	NR	NR	PFS: p=.02 OS: p=.043

ACT: adjuvant chemotherapy; ctDNA: circulating tumor DNA; C1D1: cycle 1 day 1; DFS: disease-free survival; EFS: event-free survival; HR: hazard ratio; MRD: molecular/minimal residual disease; NR: not reported; OS: overall survival; RFS: Recurrence-free survival

^a ctDNA detection versus negative.

^b ctDNA detection after completion of pembrolizumab.

^c ctDNA detection at baseline versus negative; radiographic progression-free survival (rPFS) was used instead of PFS as the statistical endpoint.

^d ctDNA detection at baseline versus negative.

^e ctDNA clearance at 12w (versus negative at baseline and 12w)

^f MRD detected via ctDNA for Osimertinib vs placebo. DFS was analyzed using a log-rank test. Due to the low number of events OS for the MRD analysis set was analyzed by an unstratified log-rank test.

^g The dynamics of ctDNA from the MRD window (pre-ACT) to the time-points on-ACT (12 weeks or 24 weeks from C1D1) were assessed for their association with DFS and OS.

^h ctDNA low levels versus high levels; the median ctDNA level across all samples was 5268.2 parts per million (ppm); this median value was used as a cut-off to define high (greater than or equal to median) and low (less than median) ctDNA levels.

ⁱ ctDNA decrease after 1 cycle of neoadjuvant chemotherapy.

^j Recurrence-free interval (RFI) based on ctDNA detection at the first post-surgery time point analyzed, and RFI based on ctDNA detection at any point after surgery.

Systematic Review and Meta-analysis

Systematic reviews and meta-analyses describing an association between ctDNA and poor prognosis have been reported for esophageal cancer,¹⁸ breast cancer,^{19,20} lung cancer,²¹⁻²⁴ colorectal cancer,²⁵⁻²⁹ melanoma,^{30,31} cervical cancer,³² head and neck cancer,³³ bladder cancer,³⁴⁻³⁶ gastrointestinal stromal tumors,³⁷ and solid tumors.³⁸

Observational Studies

Chiang et al (2025) analyzed plasma samples collected from non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) patients in the real-world prospective clinico-genomic study (PCG; NCT04180176) to evaluate the validity of circulating tumor DNA (ctDNA) monitoring and to elucidate ctDNA dynamics across 4 different therapy modalities.³⁹ Two primary, pre-specified analyses were performed: first, real-world overall survival (rwOS), real-world progression-free survival (rwPFS), and real-world overall response rate (rwORR) were assessed, segmented by on-treatment ctDNA detection irrespective of ctDNA levels at enrollment (cohort A). Second, rwOS, rwPFS, and rwORR were compared by levels of ctDNA change from enrollment to on treatment (cohort B) with a prespecified cutoffs of 90 and 50 percent decrease were used to define a molecular response. Cohorts A and B included patients with liquid biopsies collected 6- to 15-weeks after the start of therapy, regardless of the timing of their first tumor assessment or whether the specimen was collected at disease progression. Each cohort was subjected to a subgroup analysis consisting of an exploratory group (patients tested with the prototype assay and any patients with NSCLC treated with non-immune-checkpoint inhibitor [ICIs] regimens, NSCLC validity group [patients with NSCLC treated with ICI-containing regimens and tested with the analytically validated assay], and SCLC validity group [patients receiving all regimens and tested with FoundationOne CDx]). Real-world

data of ctDNA monitoring for prognosticating favorable outcomes to standard-of-care therapies for patients with lung cancer are presented in Table 4. To understand if a molecular response determined by ctDNA analysis measures up to traditional imaging methods, patients were grouped by radiographic and ctDNA responses. In all patients with NSCLC (exploratory and validity), those with both complete or partial response (confirmed via real-world radiographic imaging) and molecular response via ctDNA had substantially better outcomes (rwPFS: 10.4 months and rwOS: 28.2 months), whereas patients with neither radiographic nor molecular response had worse outcomes (rwPFS: 2.7 mo and rwOS: 8.2 months). Molecular response via ctDNA was associated with superior rwPFS and rwOS among patients with a documented real-world response (rwPFS HR: 0.31, 95% CI: 0.17 to 0.55; rwOS HR: 0.20, 95% CI: 0.10 to 0.41) than those with no real-world response (rwPFS HR: 0.22, 95% CI: 0.11 to 0.45; rwOS HR: 0.47, 95% CI: 0.24 to 90). Furthermore, a molecular response determined by ctDNA remained independently associated with rwOS in all NSCLC patients (HR: 0.50, 95% CI: 0.28 to 0.89). The results of this study suggest that ctDNA may be able to aid clinicians in deciding whether or not to cease, intensify, or de-intensify treatment for individuals with lung cancer. However, notable limitations include, but are not limited to, real-world assessments are not analogous to response evaluation criteria in solid tumors (RECIST), limited to patients with specimen collection 6- to 15-weeks, and variability within the timing and assessment (on-treatment or after progression) of ctDNA, sample collection (plasma or blood), and treatment regimen.

Table 4. Results of Circulating DNA (ctDNA) Response Monitoring in Lung Cancers: Clinico-Genomic Study (NCT04180176)

	Exploratory Analysis		NSCLC Validity Analysis		SCLC Validity Analysis	
<i>Cohort A (n=450 patients)^a</i>	<i>ctDNA detected</i>	<i>ctDNA not detected</i>	<i>ctDNA detected</i>	<i>ctDNA not detected</i>	<i>ctDNA detected</i>	<i>ctDNA not detected</i>
Median PFS (95% CI)	3.9 (3.0 to 5.4)	8.5 (7.7 to 10.7)	3.3 (2.8 to 4.1)	9.8 (8.3 to 13.2)	4.3 (3.8 to 5.7)	6.1 (5.1 to 9.7)
Hazard Ratio (95% CI)	0.42 (0.30 to 0.58)		0.26 (0.18 to 0.40)		0.39 (0.19 to 0.80)	
Log-rank p	<.0001		<.0001		<.01	
Median OS (95% CI)	8.8 (8.0 to 11.4)	21.8 (19.5 to 26.1)	9.5 (7.7 to 14.6)	23.5 (18.7 to 29.2)	8.3 (6.0 to 11.3)	15.9 (9.6 to 20.6)
Hazard Ratio (95% CI)	0.35 (0.24 to 0.50)		0.34 (0.22 to 0.53)		0.19 (0.08 to 0.42)	
Log-rank p	<.0001		<.0001		<.0001	
<i>Cohort B (n=245 patients)^b</i>	<i><90% decrease/inc crease</i>	<i>≥90% decrease</i>	<i><90% decrease/incr ease</i>	<i>≥90% decrease</i>	<i><90% decrease/incre ase</i>	<i>≥90% decrease</i>
Median PFS (95% CI)	3.1 (2.8 to 4.0)	7.7 (6.3 to 9.3)	2.8 (2.0 to 4.5)	8.6 (6.8 to 27.3)	4.5 (2.8 to 5.7)	5.6 (4.3 to 9.3)
Hazard Ratio (95% CI)	0.24 (0.16 to 0.36)		0.15 (0.06 to 0.37)		0.33 (0.14 to 0.80)	
Log-rank p	<.0001		<.0001		<.0146	
Median OS (95% CI)	8.3 (7.2–9.7)	17.6 (14.2 to 22.0))	8.4 (6.4 to 16.1)	19.4 (12.6 to NR)	7.2 (4.8 to 11.3)	15.7 (10.3 to 20.6)
Hazard Ratio (95% CI)	0.29 (0.19 to 0.44)		0.18 (0.07 to 0.50)		0.11 (0.04 to 0.33)	
Log-rank p	<.0001		<.001		<.0001	

CI: confidence interval; ctDNA: circulating tumor DNA; OS: overall survival; PFS: progression-free survival

^a Patient outcomes assessed by ctDNA detection status 6 to 15 weeks after the start of therapy

^b Patient outcomes assessed by molecular response (≥90% decrease in ctDNA from enrollment)

The substantial heterogeneity among assays and different timepoints employed in ctDNA analysis across these studies prevents any conclusions that can establish a standardized definition for ctDNA molecular response confounding the clinical validity of ctDNA assays. Furthermore, ctDNA analysis was assessed either as a binary variable (ctDNA positive or negative) or as continuous variable within these studies underscoring the need to consider their varying implications for patient outcomes.

Variance in defining ctDNA reduction, often characterized as a decrease in mean variant allele fraction (VAF) or mutant allele frequency (MAF) of tumor-derived alterations over time, and clearance, referring to complete elimination of circulating tumor load, further complicates the interpretation of the results of ctDNA kinetic analysis. Across both ctDNA assays and cancer types, clinical specificity of ctDNA detection for predicting relapse in the absence of further treatment is high, often $\geq 90\%$ if no further treatment is given after the positive test result, however, clinical sensitivity of MRD detection, with current assays, shortly after completion of therapy is suboptimal and often $\leq 50\%$.

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.

Tie et al (2022) published early data results from a phase 2, multicenter, randomized, controlled clinical trial (DYNAMIC study) in which individuals with stage 2 colon cancer received ctDNA-guided adjuvant chemotherapy (ACT; n=302) or standard of care (SOC; n=153) to assess whether a ctDNA-guided approach could reduce the use of ACT without compromising 2-year recurrence risk.⁴⁰ In the evaluation of 2-year recurrence-free survival (RFS), ctDNA-guided management was noninferior to standard management (93.5% and 92.4%, respectively; absolute difference, 1.1 percentage points; 95% confidence interval [CI], -4.1 to 6.2 [noninferiority margin, -8.5 percentage points]) illustrating that the use of ACT can be reduced without compromising 2-year RFS. Furthermore, the updated results for this trial were published in 2025 when the RFS and overall survival (OS) data was mature with sufficient follow-up and demonstrated that the 5-year RFS and OS were comparable for both ctDNA-guided and SOC groups and corroborated the results of the early analysis.⁴¹

Tie et al (2025) presented an oral abstract of early results for the randomized AGITG DYNAMIC-III clinical trial that further corroborated the results of the DYNAMIC trial with the 2-year RFS for ctDNA informed and SOC cohorts were comparable (hazard ratio [HR]: 1.09, 90% CI 0.78 to 1.53; p=.7).⁴² Limitations for this study are listed in Table 5 and 6.

Table 5. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Tie et al (2022) ⁴⁰	4. Diversity of the population was not reported.	1. ctDNA concentration thresholds to determine a positive result were not defined.			

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. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^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 6. Study Design and Conduct Limitations

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Tie et al (2022) ⁴⁰			3. Procedure for interpreting a positive test were not described			

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 to other tests not reported.

Section Summary: Monitoring Treatment Response and Disease Surveillance in Colorectal Cancer

Circulating tumor DNA testing has emerged as a clinically relevant biomarker for monitoring disease status in individuals with colorectal cancer. Evidence from randomized clinical trials, observational studies, and systematic reviews demonstrates that the presence or persistence of ctDNA is associated with an increased risk of recurrence, disease progression, and worse survival outcomes. ctDNA may provide an earlier indication of treatment response or disease recurrence than conventional clinical or radiographic monitoring alone.

Evidence from the DYNAMIC trial demonstrated that incorporation of ctDNA results into management decisions reduced the use of adjuvant chemotherapy without compromising recurrence-free survival, with long-term follow-up showing comparable recurrence-free and overall survival outcomes between ctDNA-guided and standard-management strategies. Additional studies have consistently demonstrated that ctDNA positivity is associated with increased risk of recurrence and poorer clinical outcomes across multiple colorectal cancer populations.

Although uncertainties remain regarding optimal testing intervals, assay-specific performance characteristics, and thresholds for molecular response, available evidence supports the clinical validity and clinical usefulness of ctDNA testing for monitoring recurrence, relapse, or progression in appropriately selected individuals with colorectal cancer when test results are expected to influence clinical management.

Section Summary: Guardant Reveal™ for Colorectal Cancer Management

Guardant Reveal™ is a tumor-uninformed ctDNA assay designed to detect molecular evidence of residual, recurrent, or progressive colorectal cancer through analysis of circulating tumor DNA in peripheral blood. The available evidence demonstrates that ctDNA detection is associated with recurrence risk and adverse clinical outcomes and supports the use of ctDNA testing as a management tool in selected individuals with colorectal cancer.

Coverage is therefore limited to clinical circumstances in which the member has stage II to IV colorectal cancer, testing is performed to evaluate recurrence, relapse, or progression, and the results are expected to alter clinical management. Use of the test outside these criteria has not been established within this policy and may require separate review under applicable medical policy, regulatory, or coverage requirements.

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 U.S. professional society, an international society with U.S. 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.⁴³ 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:⁴⁴

"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."

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT06640283	Dynamic Assessment of ctDNA in Patients With Cervical and Anal Canal Tumors to Optimize Follow-up and Clinical Outcomes in the Brazilian Unified Health System (SUS)	150	Jan 2027
NCT06875609	ctDNA Clearance and ctDNA Monitoring Study in Cutaneous Squamous Cell Carcinoma	60	Apr 2028
NCT06225505	Early Detection of Triple Negative Breast Cancer Relapse: a Clinical Utility Phase II Trial	450	Dec 2028
NCT06450314	De-escalation of Medical Therapies in HER2-positive Metastatic Breast Cancer in Long-term Persistent Response and Minimal Residual Disease Undetectable in Circulating Tumor DNA	170	Dec 2029
NCT06561178	Individualized Tumor-Informed Circulating Tumor DNA (ctDNA) Analysis for Monitoring Postoperative Recurrence Following Neoadjuvant Therapy in Esophageal Squamous Cell Carcinoma (NEOCRTEC2401)	50	June 2027
NCT07058519	The Efficacy and Safety of Osimertinib-based Adaptive Treatment Guided by Circulating Tumour DNA (ctDNA) Epidermal Growth Factor Receptor Mutation-positive (EGFRm) Dynamic Monitoring in Locally Advanced or Metastatic EGFRm Non-small Cell Lung Cancer (NSCLC) Participants With ctDNA EGFRm Clearance After First-line Osimertinib Plus Chemotherapy: A Phase II, Multicentre, Prospective Study (Adaptive)	250	Jan 2029
NCT07001085	A Prospective Randomized Trial Assessing the Impact of ctDNA Testing in Patients After Liver Resection or Transplantation Due to Metastases From Colorectal Cancer or Hepatocellular Carcinoma (HCC) on Treatment Strategies and Long-term Survival"	300	Apr 2028
NCT06893133	Personalized ctDNA-MRD in Recurrence Monitoring for Gastric Cancer Patients Undergoing Perioperative Treatment Combined With Curative Surgical Resection	110	Apr 2027
NCT06902272	A Phase 2 Study of Circulating Tumor DNA to Predict Response to Neoadjuvant Treatment and De-escalation Adjuvant Immunotherapy in Early-Stage NSCLC (DNA-PREDICT)	30	June 2029
NCT06283875	A Prospective, Single Center Clinical Study on the Clinical Significance of Personalized ctDNA-MRD in Predicting the Efficacy and Monitoring the Risk of Recurrence of Cervical Cancer	80	Jan 2029
NCT06490536	A Precision Medicine Trial Leveraging Blood-Based Tumor Genomics to Optimize Treatment in Operable Stage III and High-Risk Stage II Colon Cancer Patients	700	Sept 2028
NCT06614647	RESPONSE: Colorectal Cancer Survivors' Follow-up Care - Now Digital and Need-based: a National Interventional Effectiveness Trial for Stage I and II Patients	400	Feb 2030
NCT06606028	Tumor-informed ctDNA Testing for Minimal Residual Disease Monitoring Following Curative-intent Treatment of Squamous Cell Carcinoma of the Head and Neck	200	Dec 2029
NCT07035587	Diagnosis of Multiple Cancer and Monitoring of Minimal Residual Tumors After Treatment Using Blood and High-Sensitivity Genetic Analysis Techniques	1200	July 2027

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT07080021	A Prospective Observational Cohort Study on Longitudinal Monitoring of ctDNA MRD in Neoadjuvant Therapy for Pancreatic Cancer	119	Nov 2027
NCT07057102	Applications of Multiple Omics Sequencing Technologies in Predicting the Efficacy and Monitoring the Recurrence of Non-Small Cell Lung Cancer: A Prospective, Non-Interventional Study	40	Dec 2027
NCT06653127	Evaluation of Circulating Tumor Mitochondrial DNA (ct-mtDNA) As a Biomarker for Minimal Residual Disease (MRD) Assessment and Recurrence Monitoring in Post-treatment Biliary Tract Cancer (BTC)	50	July 2026
NCT06479070	Prognostic Value of Measuring Circulating Tumor DNA in a Cohort of Patients With Stage III and IV UADT Cancer, Treated With Curative RADIotherapy With or Without Concomitant Treatment.	188	Sep 2029
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 (status unknown)
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 (status unknown)
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)	365	Dec 2026

^a Denotes industry sponsored or co-sponsored trial.

NCT: national clinical trial.

References

1. Alix-Panabières C, Pantel K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. *Cancer Discov.* May 2016; 6(5): 479-91. PMID 26969689
2. Food & Drug Administration. 2025. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). <https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>. Accessed October 27, 2025
3. Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol.* Jun 01 2018; 36(16): 1631-1641. PMID 29504847
4. Pascual J, Attard G, Bidard FC, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. *Ann Oncol.* Aug 2022; 33(8): 750-768. PMID 35809752
5. Ruiz-Vico M, Wetterskog D, Orlando F, et al. Liquid Biopsy in Progressing Prostate Cancer Patients Starting Docetaxel with or Without Enzalutamide: A Biomarker Study of the PRESIDE Phase 3b Trial. *Eur Urol Oncol.* Feb 2025; 8(1): 135-144. PMID 39261236
6. LaPelusa M, Qiao W, Iorgulescu B, et al. Long-Term Efficacy of Pembrolizumab and the Clinical Utility of ctDNA in Locally Advanced dMMR/MSI-H Solid Tumors. *Nat Commun.* May 15 2025; 16(1): 4514. PMID 40374594

7. Rodrigues M, Ramtohl T, Rampanou A, et al. Prospective assessment of circulating tumor DNA in patients with metastatic uveal melanoma treated with tebentafusp. *Nat Commun.* Oct 14 2024; 15(1): 8851. PMID 39402032
8. Knutson TP, Luo B, Kobilka A, et al. AR alterations inform circulating tumor DNA detection in metastatic castration resistant prostate cancer patients. *Nat Commun.* Dec 11 2024; 15(1): 10648. PMID 39663356
9. Han JY, Ahn MJ, Lee KH, et al. Updated overall survival and ctDNA analysis in patients with EGFR T790M-positive advanced non-small cell lung cancer treated with lazertinib in the phase 1/2 LASER201 study. *BMC Med.* Oct 08 2024; 22(1): 428. PMID 39379931
10. Herbst RS, John T, Grohé C, et al. Molecular residual disease analysis of adjuvant osimertinib in resected EGFR-mutated stage IB-IIIa non-small-cell lung cancer. *Nat Med.* Jun 2025; 31(6): 1958-1968. PMID 40097663
11. Syeda MM, Long GV, Garrett J, et al. Clinical validation of droplet digital PCR assays in detecting BRAF V600 -mutant circulating tumour DNA as a prognostic biomarker in patients with resected stage III melanoma receiving adjuvant therapy (COMBI-AD): a biomarker analysis from a double-blind, randomised phase 3 trial. *Lancet Oncol.* May 2025; 26(5): 641-653. PMID 40250457
12. Ademuyiwa FO, Ma CX, Weilbaecher K, et al. Detection of Circulating Tumor DNA Using a Tissue-Free Epigenomic Assay Is a Highly Prognostic Biomarker in Early-Stage Triple-Negative Breast Cancer. *Clin Cancer Res.* Jun 03 2025; 31(11): 2173-2182. PMID 40116350
13. Yoo C, Jeong H, Jeong JH, et al. Circulating tumor DNA status and dynamics predict recurrence in patients with resected extrahepatic cholangiocarcinoma. *J Hepatol.* May 2025; 82(5): 861-870. PMID 39532185
14. Taieb J, Souglakos J, Boukovinas I, et al. Combined Analyses of Circulating Tumor DNA and Immunoscore in Patients With Stage III Colon Cancer: A Post Hoc Analysis of the PRODIGE-GERCOR IDEA-France/HORG-IDEA-Greece Trials. *J Clin Oncol.* May 2025; 43(13): 1564-1577. PMID 39903903
15. Mayadev J, Vázquez Limón JC, Ramírez Godínez FJ, et al. Ultrasensitive detection and tracking of circulating tumor DNA to predict relapse and survival in patients with locally advanced cervical cancer: phase III CALLA trial analyses. *Ann Oncol.* Sep 2025; 36(9): 1047-1057. PMID 40500687
16. Long GV, Tang H, Desai K, et al. Pretreatment and on-treatment ctDNA and tissue biomarkers predict recurrence in patients with stage IIIB-D/IV melanoma treated with adjuvant immunotherapy: CheckMate 915. *J Immunother Cancer.* Jul 11 2025; 13(7). PMID 40645660
17. Azaïs H, Brochard C, Taly V, et al. Prognostic value of circulating tumor DNA at diagnosis and its early decrease after one cycle of neoadjuvant chemotherapy for patients with advanced epithelial ovarian cancer. An ancillary analysis of the CHIVA phase II GINECO trial. *Gynecol Oncol.* Jan 2025; 192: 145-154. PMID 39671779
18. Shen T, Li T, Cao Y, et al. Circulating tumor DNA as a biomarker for progression and survival in esophageal cancer after neoadjuvant therapy and esophagectomy: a systematic review and meta-analysis. *Int J Surg.* Aug 12 2025; 111(11): 8515-22. PMID 40793951
19. Niu S, Sun T, Wang M, et al. Multiple time points for detecting circulating tumor DNA to monitor the response to neoadjuvant therapy in breast cancer: a meta-analysis. *BMC Cancer.* Jan 22 2025; 25(1): 115. PMID 39844103
20. Zhang D, Jahanfar S, Rabinowitz JB, et al. Role of circulating tumor DNA in early-stage triple-negative breast cancer: a systematic review and meta-analysis. *Breast Cancer Res.* Mar 12 2025; 27(1): 38. PMID 40075528
21. Leite da Silva LF, Saldanha EF, de Menezes JSA, et al. Plasma ctDNA kinetics as a predictor of systemic therapy response for advanced non-small cell lung cancer: a systematic review and meta-analysis. *Oncologist.* Feb 06 2025; 30(2). PMID 39998904
22. Kazemi-Harikandei SZ, Salmani Jelodar MR, Roshandel G, et al. The prognostic role of circulating DNA markers in patients with lung malignancies: a systematic review and meta-analysis. *Biomark Med.* Aug 2025; 19(16): 793-806. PMID 40825939

23. Che S, Yu D. Predictive role of circulating tumor DNA based molecular residual disease for long-term outcomes in non-small cell lung cancer patients: a meta-analysis. *World J Surg Oncol*. Jun 13 2025; 23(1): 235. PMID 40514661
24. Zhang C, Zhao H, Shi Q. Postoperative Circulating Tumour DNA in Predicting Recurrence of Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis. *Clin Oncol (R Coll Radiol)*. Aug 2025; 44: 103892. PMID 40614309
25. Zhou Q, Chen X, Zeng B, et al. Circulating tumor DNA as a biomarker of prognosis prediction in colorectal cancer: a systematic review and meta-analysis. *J Natl Cancer Cent*. Apr 2025; 5(2): 167-178. PMID 40265088
26. Hoang T, Choi MK, Oh JH, et al. Utility of circulating tumor DNA to detect minimal residual disease in colorectal cancer: A systematic review and network meta-analysis. *Int J Cancer*. Aug 15 2025; 157(4): 722-740. PMID 40293388
27. Holz A, Paul B, Zapf A, et al. Circulating tumor DNA as prognostic marker in patients with metastatic colorectal cancer undergoing systemic therapy: A systematic review and meta-analysis. *Cancer Treat Rev*. Sep 2025; 139: 102999. PMID 40743933
28. Negro S, Pulvirenti A, Trento C, et al. Circulating Tumor DNA as a Real-Time Biomarker for Minimal Residual Disease and Recurrence Prediction in Stage II Colorectal Cancer: A Systematic Review and Meta-Analysis. *Int J Mol Sci*. Mar 11 2025; 26(6). PMID 40141130
29. Fiorica F, Mandarà M, Giuliani J, et al. Circulating DNA in Rectal Cancer to Unravel the Prognostic Potential for Radiation Oncologist: A Meta-analysis. *Am J Clin Oncol*. Feb 01 2025; 48(2): 83-91. PMID 39439084
30. Liu L, Hou S, Zhu A, et al. The prognostic value of circulating tumor DNA in malignant melanoma patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Front Immunol*. 2024; 15: 1520441. PMID 39896816
31. Noronha MM, da Silva LFL, Almeida LFC, et al. Prognostic and Predictive Value of ctDNA for Metastatic Uveal Melanoma: A Systematic Review and Meta-Analysis. *Pigment Cell Melanoma Res*. Sep 2025; 38(5): e70047. PMID 40799039
32. Zhao X, Hou S, Hao R, et al. Prognostic significance of circulating tumor DNA detection and quantification in cervical cancer: a systematic review and meta-analysis. *Front Oncol*. 2025; 15: 1566750. PMID 40255423
33. Yang R, Li T, Zhang S, et al. The effect of circulating tumor DNA on the prognosis of patients with head and neck squamous cell carcinoma: a systematic review and meta-analysis. *BMC Cancer*. Nov 21 2024; 24(1): 1434. PMID 39574043
34. Ma Q, Hou S, Ma H, et al. Prognostic significance of circulating tumor DNA in urothelial carcinoma patients undergoing immune checkpoint inhibitor therapy: a systematic review and meta-analysis. *Front Immunol*. 2025; 16: 1574449. PMID 40364842
35. Gao X, Qi W, Li J, et al. Prognostic and predictive role of circulating tumor DNA detection in patients with muscle invasive bladder cancer: a systematic review and meta-analysis. *Cancer Cell Int*. Mar 01 2025; 25(1): 75. PMID 40025568
36. Zulfiqar A, Liliana B, Mataho NL, et al. The Use of Circulating Tumor Cells in T1 Stage Non-muscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. *Urol Res Pract*. Apr 04 2025; 50(6): 343-350. PMID 40243380
37. Matheus GTFU, Ribeiro DM, Menegat ALRS, et al. Prognostic Significance of Circulating Tumor DNA Mutations in Gastrointestinal Stromal Tumors: A Systematic Review and Meta-analysis Based on Time-To-Event Data. *J Gastrointest Cancer*. Jul 15 2025; 56(1): 153. PMID 40665034
38. Sogbe M, Aliseda D, Sangro P, et al. Prognostic value of circulating tumor DNA in different cancer types detected by ultra-low-pass whole-genome sequencing: a systematic review and patient-level survival data meta-analysis. *Carcinogenesis*. Jan 20 2025; 46(1). PMID 39549302
39. Chiang AC, Madison RW, Assaf ZJ, et al. Real-World Validity of Tissue-Agnostic Circulating Tumor DNA Response Monitoring in Lung Cancers Treated With Chemotherapy, Immunotherapy, or Targeted Agents. *JTO Clin Res Rep*. Sep 2025; 6(9): 100829. PMID 40746669

40. Tie J, Cohen JD, Lahouel K, et al. Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. *N Engl J Med*. Jun 16 2022; 386(24): 2261-2272. PMID 35657320
41. Tie J, Wang Y, Lo SN, et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial. *Nat Med*. May 2025; 31(5): 1509-1518. PMID 40055522
42. Tie J, Wang Y, Loree JM, et al. ctDNA-guided adjuvant chemotherapy escalation in stage III colon cancer: Primary analysis of the ctDNA-positive cohort from the randomized AGITG dynamic-III trial (intergroup study of AGITG and CCTG). *J. Clin. Oncol.* 2025;43(16_suppl):3503, European Society for Medical Oncology (ESMO) Congress 2025, October 2025.
43. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. *J Clin Oncol*. Apr 10 2022; 40(11): 1231-1258. PMID 35175857
44. Centers for Medicare & Medicaid Services. 2020. National Coverage Determination: Next Generation Sequencing (90.2). <https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=372>. Accessed October 27, 2025.
45. Department of Healthcare Services Provider Manual Guideline. TAR and Non-Standard Benefits List: Codes 0001M thru 0999U. Accessed September 29, 2026, from https://mcweb.apps.prd.cammis.medi-cal.ca.gov/assets/AFECB45B-D2C9-46AD-93A8-5C614B0E79A5/tarandnoncd0.pdf?access_token=6UyVkJRRfByXTZEWlh8j8QaYyIPyP5ULO
46. Department of Healthcare Services Provider Manual Guideline. Proprietary Laboratory Analyses. Accessed September 29, 2026, from https://mcweb.apps.prd.cammis.medi-cal.ca.gov/assets/F9A3F413-CFE2-472F-85DA-CE264DE44979/proplab.pdf?access_token=6UyVkJRRfByXTZEWlh8j8QaYyIPyP5ULO
47. Department of Healthcare Services All Plan Letter. All Plan Letter APL 22-010: Cancer Biomarker Testing. Accessed September 29, 2026, from <https://www.dhcs.ca.gov/formsandpubs/Documents/MMCDAPLsandPolicyLetters/APL2022/APL22-010.pdf>

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
 - Clinical findings (i.e., pertinent symptoms and duration)
 - Comorbidities
 - Pertinent past procedural and surgical history
 - Past and present diagnostic testing and results
 - Prior conservative treatments, duration, and response
 - Treatment plan (i.e., surgical intervention)
- Radiology report(s) and interpretation (i.e., Magnetic Resonance Imaging [MRI], Computed Tomography [CT], Positron Emission Tomography [PET])
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

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®	0569U	Oncology (solid tumor), next-generation sequencing analysis of tumor methylation markers (>20,000 differentially methylated regions) present in cell-free circulating tumor DNA (ctDNA), whole blood, algorithm reported as presence or absence of ctDNA with tumor fraction, if appropriate <i>(Includes Guardant Reveal™, Guardant Health, Inc)</i>
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
03/01/2026	New policy.
06/01/2026	Administrative update. Definitions of Decision Determinations section updated.
11/01/2026	Annual review. Policy statement, state guideline resources, and literature review updated. Definitions of Decision Determinations section updated. Policy title changed from Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) to current one. Coding updated.

Definitions of Decision Determinations

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

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status

Blue Shield of California Promise Health Plan may use the following criteria and definitions to make decisions about procedures, treatments, supplies, devices, and equipment.

The following reference may be used to help guide determinations for members over 21 years of age and/or non-California Children's Services (CCS) Program members:

- California Code of Regulations. Title 22 § 51056.1. Experimental Services. Accessed September 9, 2026 from [https://govt.westlaw.com/calregs/Document/I542BE1835B6111EC9451000D3A7C4BC3?viewType=FullText&originationContext=documenttoc&transitionType=CategoryPageItem&contextData=\(sc.Default\)](https://govt.westlaw.com/calregs/Document/I542BE1835B6111EC9451000D3A7C4BC3?viewType=FullText&originationContext=documenttoc&transitionType=CategoryPageItem&contextData=(sc.Default))

The following reference may be used to help guide determinations for Medi-Cal members, as this framework has been approved by the Department of Health Care Services (DHCS) for use by California Children's Services (CCS):

- Department of Healthcare Services Numbered Letter 05-1020. Accessed September 9, 2026, from <https://www.dhcs.ca.gov/services/ccs/Documents/CCS-NL-05-1020-Experimental-and-Investigational-Services.pdf>

The following policy language applies to the California Children's Services (CCS) Program and the Genetically Handicapped Persons Program (GHPP) found in the above link for DHCS Numbered Letter 05-1020:

Policy

- A. The California Children's Services (CCS) Program and the Genetically Handicapped Persons Program (GHPP) will not provide coverage for experimental services unless specifically authorized by law.
- B. The CCS Program and GHPP may provide coverage for an investigational service if:
 1. It is approved by the FDA under any Investigational New Drug (IND) Application; or
 2. It is authorized for use under the State of California's Right to Try Act; and
 3. Its use is consistent with its FDA-approved IND Application or the State of California's Right to Try Act;
- C. Additional criteria that will be considered in the adjudication process include:
 1. Conventional therapy will not adequately treat the intended patient's condition;
 2. Conventional therapy will not prevent progressive disability or premature death;
 3. The provider of the proposed service has a record of safety and success with it or equivalent to that of other providers of the investigational services;
 4. Other criteria (e.g., cost and availability) may be considered in the adjudication of a given request in cases in which more than one investigational service is available;
 5. There is reasonable expectation that the investigational service will significantly prolong the patient's life or will maintain or restore a range of physical and social function suited to activities of daily living; and
 6. The service is not being performed as part of a research study protocol. For a beneficiary with cancer who participates in a clinical trial for cancer, California Health and Safety Code (HSC) § 1370.6 requires that all routine patient care costs related to the clinical trial be covered if the beneficiary's CCS-paneled treating physician recommends participation in the clinical trial after determining that participation in the clinical trial has a meaningful potential to benefit the enrollee. The coverage does not include investigational services that have not been approved by the FDA and that are associated with the clinical trial.

Feedback

Blue Shield of California Promise Health Plan 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 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/en/bsp/providers.

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

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan 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 of California Promise Health Plan reserves the right to review and update policies as appropriate

Appendix A

Policy Statement	
BEFORE Red font: Verbiage Removed	AFTER Blue font: Verbiage Changes/Additions
<p>Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) PHP_2.04.141</p> <p>State Guidelines: Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):</p> <ol style="list-style-type: none"> I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline: <ul style="list-style-type: none"> • N/A II. Department of Health Care Services (DHCS) Provider Manual Guideline: <ul style="list-style-type: none"> • <u>TAR and Non-Standard Benefits List: Codes 0001M thru 0999U (tar and non cd0)</u> • <u>TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)</u> • <u>Pathology: Molecular Pathology (path molec)</u> <p>Below is an excerpt of the Molecular Pathology guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.</p> <p>Biomarker and Pharmacogenetic Testing Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test. As such, the particular biomarker or pharmacogenomic test code may be covered with an approved TAR if medical necessity is established, as described in the TAR and Non-Benefit: Introduction to List section of the Provider Manual.</p> <p>Biomarker Testing</p>	<p>Tumor-Uninformed Circulating Tumor DNA (Guardant Reveal™) for Cancer Management (Liquid Biopsy) PHP_2.04.141</p> <p>Policy Statement:</p> <ol style="list-style-type: none"> I. The use of tumor-uninformed circulating tumor DNA (i.e., Guardant Reveal™) in individuals with colorectal cancer may be considered medically necessary when all of the following are met:⁴⁶ <ol style="list-style-type: none"> A. Member has a diagnosis of stage II to IV colorectal cancer and monitoring is needed to diagnose cancer recurrence, relapse, or progression B. Identification of cancer recurrence, relapse, or progression will require a change in management C. Member is not receiving other molecular testing for minimal residual disease analysis concurrently with this test D. One of the following: <ol style="list-style-type: none"> 1. Member is currently being treated for cancer, and the test has not been previously performed for this cancer diagnosis 2. Member is currently being treated for cancer and there is clinical suspicion that the molecular profile of the member's tumor has changed 3. Member is not currently being treated for their cancer (in other words, when there is no clinical, radiographical, or other biological evidence that tumor cells remain post treatment and subsequently the member is no longer being subjected to therapeutic interventions for cancer), and the test has not been performed in the last 12 months 4. Member is not currently being treated for their cancer, and now there is clinical suspicion for tumor recurrence. <p>Note: For individuals enrolled in health plans subject to the Biomarker Testing Law (Health & Safety Code Section 1367.667 and the Insurance</p>

Policy Statement	
BEFORE	AFTER
<p>Red font: Verbiage Removed</p> <p>Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.</p> <p>When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.</p> <p>Pharmacogenomic Testing Pharmacogenomic testing is defined as a laboratory genetic testing that includes, but is not limited to, a panel test to identify how a person's genetics may impact the efficacy, toxicity and safety of medications. Medically necessary pharmacogenomic testing is covered subject to utilization controls and evidence-based clinical practice guidelines.</p> <p>Requirements for CPT code 81462: A TAR for CPT code 81462 requires documentation of the following criteria:</p>	<p>Blue font: Verbiage Changes/Additions</p> <p>Code Section 10123.209), Centers for Medicare & Medicaid Services (CMS) National and Local Coverage Determinations (NCDs or LCDs) may also apply. Please refer to the Medicare National and Local Coverage section of this policy. LCD selection is contingent upon the location of the servicing provider (i.e., laboratory).</p> <p>State Guideline Resources: Applicable State Guideline resources as of the effective date of this policy:</p> <ol style="list-style-type: none"> I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline: <ul style="list-style-type: none"> • N/A II. Department of Health Care Services (DHCS) Provider Manual Guideline: <ul style="list-style-type: none"> • TAR and Non-Standard Benefits List: Codes 0001M thru 0999U (tar and non cd0) • Proprietary Laboratory Analyses (PLA) (prop lab) III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline: <ul style="list-style-type: none"> • APL 22-010 – Cancer Biomarker Testing <p>Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.</p> <p>For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals</p>

Policy Statement	
BEFORE	AFTER
<p>Red font: Verbiage Removed</p> <ol style="list-style-type: none"> 1. The member has a diagnosis of non-small cell lung cancer, and 2. The member is medically unable to undergo invasive biopsy or tumor tissue testing is not feasible, and 3. Management is contingent on the test results <ul style="list-style-type: none"> • Proprietary Laboratory Analyses (PLA) (prop lab) <p>Below is an excerpt of the PLA guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.</p> <p>Requirements for PLA code 0242U: The service requires a TAR. A TAR requires documentation of the following numbered criteria:</p> <ol style="list-style-type: none"> 1. The member has a diagnosis of either; <ul style="list-style-type: none"> o Non-small cell lung cancer, or o Hormone receptor-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative breast cancer 2. Treatment is contingent on the test result <p>Requirements for PLA code 0409U: TAR requires documentation of the following criteria:</p> <ul style="list-style-type: none"> • The member has a diagnosis of non-small cell lung cancer, and • The member is medically unable to undergo invasive biopsy or tumor tissue testing is not feasible, and • Management is contingent on the test results <p>III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:</p> <ul style="list-style-type: none"> • APL 22-010 – Cancer Biomarker Testing <p>Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.</p>	<p>Blue font: Verbiage Changes/Additions</p> <p>with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.</p> <p>Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:</p> <ul style="list-style-type: none"> • Advanced or metastatic stage 3 or 4 cancer. • Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer. <p>MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.</p>

Policy Statement	
BEFORE <u>Red font: Verbiage Removed</u>	AFTER <u>Blue font: Verbiage Changes/Additions</u>
<p>For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.</p> <p>Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:</p> <ul style="list-style-type: none"> • Advanced or metastatic stage 3 or 4 cancer. • Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer. <p>MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.</p> <p>Policy Statement: <u>Any criteria that are not specifically addressed in the above APL and Provider Manuals, please refer to the criteria below.</u></p> <p>I. The use of circulating tumor DNA and/or circulating tumor cells is considered investigational for all indications reviewed herein (see Policy Guidelines). <i>(Per Medi-Cal guidelines and for Medi-Cal members only: coverage for the use of circulating tumor DNA and/or circulating tumor cells may be approved based on criteria listed in the State Guidelines section above.)</i></p>	

Policy Statement	
BEFORE	AFTER
<u>Red font: Verbiage Removed</u>	<u>Blue font: Verbiage Changes/Additions</u>
<p>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 <u>Medicare National and Local Coverage</u> section of this policy, to <u>MolDX: Plasma-Based Genomic Profiling in Solid Tumors</u>, and to <u>MolDX: Minimal Residual Disease Testing for Cancer</u> for reference.</p>	