PHP_2.04.141	Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)		
Original Policy Date:	March 1, 2026	**Effective Date:**	March 1, 2026
Section:	2.0 Medicine	**Page:**	Page 1 of 33

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

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)
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- Pathology: Molecular Pathology (path molec)

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.

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 Treatment Authorization Request (TAR) if medical necessity is established, as described in the TAR and Non-Benefit: Introduction to List section of the Provider Manual.

Biomarker Testing
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.

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.

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.

Requirements for CPT code 81462:
A TAR for CPT code 81462 requires documentation of the following criteria:

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

- Proprietary Laboratory Analyses (PLA) (prop lab)

Below is an excerpt of the PLA guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Requirements for PLA code 0242U:
The service requires a TAR.
A TAR requires documentation of the following numbered criteria:

1. The member has a diagnosis of either;
   - Non-small cell lung cancer, or
   - Hormone receptor-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative breast cancer
2. Treatment is contingent on the test result

Requirements for PLA code 0409U:
TAR requires documentation of the following criteria:

- 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

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 Statement

Any criteria that are not specifically addressed in the above APL and Provider Manuals, please refer to the criteria below.

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

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

Policy Guidelines

This policy does **not** address the use of blood-based testing (liquid biopsy) to select targeted treatment for breast cancer, metastatic colorectal cancer, non-small cell lung cancer, melanoma/glioma, ovarian cancer, pancreatic cancer, and prostate cancer, the use of liquid biopsy to select immune checkpoint inhibitor therapy, tumor-Informed circulating tumor DNA testing for cancer management, comprehensive genomic profiling for selecting targeted cancer therapies, the use of blood-based testing for detection or risk assessment of prostate cancer; or the use of AR-V7 circulating tumor cells for metastatic prostate cancer. Refer to the following related 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_2.04.111 - Gene Expression Profiling and Protein Biomarkers 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 Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Advanced Cancer
- PHP_2.04.153 - Tumor-Informed Circulating Tumor DNA Testing 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

Description

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as "liquid biopsy," have several potential uses for guiding therapeutic decisions in patients with cancer or being screened for cancer. This evidence review evaluates uses for liquid biopsies *not addressed in a separate review*. If a separate evidence review exists, then conclusions reached there supersede conclusions here.

Summary of Evidence

For individuals who have advanced cancer who receive testing of circulating tumor cells (CTCs) to select targeted treatment, the evidence includes observational studies. Relevant outcomes are OS, progression-free survival, recurrence-free survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs can replace variant analysis of tissue. The evidence is insufficient to determine 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 randomized clinical trials, systematic reviews with meta-analysis, and observational studies. Relevant outcomes are OS, progression-free survival, recurrence-free survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Numerous randomized clinical trials and systematic reviews identified an association with the detection of ctDNA or the kinetics of ctDNA and worse clinical outcomes for individuals with cancer, thus illustrating the clinical validity of testing for ctDNA. However, studies reporting clinical utility are lacking. Further studies are needed to establish a standardized definition for ctDNA molecular response and to illustrate how ctDNA testing can lead to different treatment regimens for cancer management. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to monitor treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cancer who receive testing of CTCs to monitor treatment response, the evidence includes a single randomized controlled trial (RCT), observational studies, and systematic reviews of observational studies. Relevant outcomes are OS, progression-free survival, recurrence-free survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. The available 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 randomized clinical trials, systematic reviews with meta-analysis, and observational studies. Relevant outcomes are OS, progression-free survival, recurrence-free survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Numerous randomized clinical trials and systematic reviews identified an association with the detection of ctDNA or the kinetics of ctDNA and worse clinical outcomes for individuals with

cancer, thus illustrating the clinical validity of testing for ctDNA. However, there were no studies assessing r clinical utility. Further studies are needed to distinguish the timing to assess ctDNA to accurately prognosticate the clinical outcomes for individuals with cancer and establish thresholds that lead to meaningful predictions for clinical outcomes. 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.

Additional Information
Not applicable

Related Policies

- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- 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
- Tumor-Informed Circulating Tumor DNA Testing for Cancer Management

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).

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.

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

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

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

Diagnostic Name (Manufacturer)	Indication	Biomarker	Drug Trade Name (Generic)	Related Evidence Opinion
			deruxtecan-nxki)	
	Breast Cancer	*ESR1* *ERB2*	Orserdu (elacestrant) ENHERTU (fam-trastuzumab deruxtecan-nxki)	2.04.151 In development for 2.04.151
therascreen PIK3CA RGQ PCR Kit (QIAGEN GmbH)	Breast Cancer	*PIK3CA*	Piqray (alpelisib)	2.04.151
xT CDx (Tempus Labs, Inc.)	Colorectal Cancer	*KRAS*	Erbitux (cetuximab	
	Colorectal Cancer	*KRAS* and *NRAS*	Vectibix (panitumumab)	

Source: FDA (2025)[2]
FDA: US 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) or circulating tumor cells (CTCs) as methods of noninvasively characterizing tumors and tumor genome from the peripheral blood.

Circulating Tumor DNA

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

Circulating Tumor Cells

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1 to 2 hours), and CTCs are cleared through extravasation into secondary organs.[1] Most assays detect CTCs through the use of surface epithelial

markers such as epithelial cell adhesion molecules (EpCAM) and cytokeratins. The primary reason for detecting CTCs is prognostic, through quantification of circulating levels.

Detecting Circulating Tumor DNA and Circulating Tumor Cells

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

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

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

Circulating tumor cell assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). Circulating tumor cells can then be detected using immunologic, molecular, or functional assays.[1]

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

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

This evidence review evaluates uses for liquid biopsies not addressed in other reviews. If a separate evidence review exists, then conclusions reached there supersede conclusions here. The main criterion for inclusion in this review is the limited evidence on clinical validity.

Selecting Treatment in Advanced Cancer

Clinical Context and Test Purpose

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

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

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

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

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

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

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

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

Review of Evidence

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

Circulating Tumor 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.

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

Monitoring Treatment Response in Cancer

Clinical Context and Test Purpose

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

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

Patients

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

Interventions

The test being considered is liquid biopsy using either ctDNA or CTCs. For ctDNA tests, the best unit for quantifying DNA burden has not been established.[3] 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 either ctDNA or CTCs. 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 *Active*	*Comparator*
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 tumor DNA (ctDNA) prior to and after one cycle of docetaxel.	Enzalutamide	Placebo
LaPelusa et al (2025)[6]	U.S.	1	Patients ≥18 years of age with locally advanced, histologically confirmed deficient mismatch repair/microsatellite	An exploratory analysis of a phase II clinical trial (NCT04082572) to investigate the ctDNA	Pembrolizumab	None

Study	Countries	Sites	Participants	Methods	Interventions *Active*	*Comparator*
			instability-high solid tumors.	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.		
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 *EGFR*-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 *EGFR* 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 *EGFR* variants and efficacy parameters.	Lazertinib	None
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	An exploratory analysis of the ADAURA phase III trial (NCT02511106) to investigate whether plasma-based, tumor-informed MRD analysis (ctDNA)	Osimertinib	Placebo

Study	Countries	Sites	Participants	Methods	Interventions *Active*	*Comparator*
			centrally confirmed *EGFR* mutation (Ex19del/L858R) and a World Health Organization performance status of 0 or 1.	could predict disease recurrence during and after adjuvant treatment in 220 patients with viable ctDNA during or after adjuvant therapy with Osimertinib.		
Syeda et al (2025)[11]	Global	210	Patients with completely resected, histologically confirmed, *BRAF* 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 metastatic recurrence in patients with TNBC.	docetaxel and carboplatin	Historical controls
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	A biomarker analysis from a multicenter, open-label, randomized phase II study (STAMP) of 89 patients. Longitudinal plasma samples (n =	Gemcitabine plus cisplatin	Capecitabine

Study	Countries	Sites	Participants	Methods	Interventions *Active*	*Comparator*
			randomization, and metastasis to at least one regional lymph node.	254) were prospectively collected post-surgery before ACT, and on-ACT at 12 and 24 weeks from cycle 1 day 1 (C1D1). ctDNA was evaluated using a personalized, tumor-informed, 16-plex PCR next-generation sequencing assay and was correlated with clinical outcomes.		
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 er 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-IIB node 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	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 levels with long-term clinical outcomes and patient baseline disease characteristics in the context of locally	Durvalumab with CRT	Placebo

Study	Countries	Sites	Participants	Methods	Interventions *Active*	*Comparator*
			RECIST version 1.1, and adequate organ and marrow function were enrolled.	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; C1D1: 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)[a,5]	ctDNA at baseline: 1.78 (1.20 to 2.64) ctDNA at C2D1: 1.95 (1.15 to 3.30)	NR	NR	NR	NR	p=.004 p=.019
LaPelusa et al (2025)[b,6]	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	Univariate analysis: HR=10.1 (3.0 to 33.8) Multivariate analysis	NR	NR	NR	Univariate analysis: PFS: p=.001

Study	PFS (HR, 95% CI)	OS (95% CI)	EFS (%, 95% CI)	DFS (HR, 95% CI)	RFS (HR, 95% CI)	p value
	analysis: 2.5 (1.1 to 5.9)[d] 5.8 (2.1 to 16.5)[e]	HR= 9.3 (1.9 to 45.2)[d] HR= 49.6 (4.5 to 544.5)[e]				OS: p<.001 Multivariate analysis: PFS: p=.004 OS: p=.006
Knutson et al (2024)[c,8]	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)[a,9]	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)[a,11]	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)[g] Persistently ctDNA(+): HR=4.0 (1.88 to 8.3)[g]	NR	MRD window: 1.8 (1.06 to 3.07)[a] post-surgery:3.81 (2.22 to 6.54)[a] 12wks after C1D1: 7.72 (4.09 to 14.56)[a] 24wks after C1D1: 5.24 (2.75 to 9.97)[a]	NR	OS: p =.002 & p<.001 DFS: p =.029 p<.001 p<.001 p<.001
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 er al (2025)[15]	ctDNA at baseline: 1.72 (0.99 to 3.00)[h] ctDNA at C3D1: 5.27 (2.95 to 9.40)[a]	NR	NR	NR	NR	PFS: p=.054 and p<.001

Study	PFS (HR, 95% CI)	OS (95% CI)	EFS (%, 95% CI)	DFS (HR, 95% CI)	RFS (HR, 95% CI)	p value
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,[21,22,23,24] colorectal cancer,[25,26,27,28,29] melanoma,[30,31] cervical cancer,[32] head and neck cancer,[33] bladder cancer,[34,35,36] 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	
Cohort A (n=450 patients)[a]	ctDNA detected	ctDNA not detected	ctDNA detected	ctDNA not detected	ctDNA detected	ctDNA not detected
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	
Cohort B (n=245 patients)[b]	<90% decrease/increase	≥90% decrease	<90% decrease/increase	≥90% decrease	<90% decrease/increase	≥90% decrease
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 ≥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 ≤50%.

Circulating Tumor Cells

Systematic reviews and meta-analyses describing an association between CTCs and poor prognosis have been reported for metastatic breast cancer,[40,41,42,43] CRC,[44,45] hepatocellular cancer,[46] prostate cancer,[47,48,49] head and neck cancer,[50] Multiple myeloma,[51] and melanoma.[52]

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.[53] 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,[54] CRC[55] bladder cancer,[56,57] liver cancer,[58] and esophageal cancer.[59]

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 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.[60] 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.[61]

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).[62]

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)[60]	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)[60]			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.

Circulating Tumor Cells

Chain of 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.

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 CTCs to guide early treatment before relapse.

No trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. Smerage et al (2014) reported on the results of an RCT of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after 1 cycle of first-line therapy could improve overall survival (OS; the primary study outcome).[63] 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 only one RCT with direct evidence that ctDNA to monitoring treatment response may improve the net health outcome compared with standard methods. However, there were some notable limitations from the RCTs that preclude any conclusions on whether testing for ctDNA leads to better net health outcomes compared to standard methods. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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.

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. Furthermore, the RCTs that assessed the clinical validity of ctDNA testing have demonstrated that ctDNA levels correlate with worse clinical outcomes, but further studies are needed to established threshold metrics for predicting the risk of relapse for individuals with cancer. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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.

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.[64] 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."

In 2022, ASCO published a guideline update on biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer.[65] The following recommendations were issued:
Circulating tumor DNA

- "If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use ctDNA to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong)."

Circulating tumor cells

- "If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use circulating tumor cells (CTC) to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong)"

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 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:[66]

"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 2.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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

NCT No.	Trial Name	Planned Enrollment	Completion Date
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
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.

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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., MRI, CT, 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®	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 ***(Includes FirstSightCRC™, CellMax Life)***
	0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements ***(Includes Guardant360® CDx, Guardant Health Inc)***
	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

Type	Code	Description
		biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood ***(Includes CELLSEARCH® HER2 Circulating Tumor Cell (CTC-HER2) Test, Menarini Silicon Biosystems, Inc)***
	0409U	Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability ***(Includes LiquidHALLMARK®, Lucence Health, Inc)***
	0486U	Oncology (pan-solid tumor), next-generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction ***(Includes Northstar Response™, BillionToOne Laboratory, BillionToOne, Inc)***
	0490U	Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular-weight melanoma-associated antigen, CD34 and CD45 protein biomarkers, peripheral blood ***(Includes CELLSEARCH® Circulating Melanoma Cell (CMC) Test, Menarini Silicon Biosystems Inc)***
	0491U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker-expressing cells, peripheral blood ***(Includes CELLSEARCH® ER Circulating Tumor Cell (CTC-ER) Test, Menarini Silicon Biosystems Inc)***
	0492U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker-expressing cells, peripheral blood ***(Includes CELLSEARCH® PD-L1 Circulating Tumor Cell (CTC-PD-L1) Test, Menarini Silicon Biosystems Inc)***
	0498U	Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation ***(Includes OptiSeq™ Colorectal Cancer NGS Panel, DiaCarta, Inc)***
	0501U	Oncology (colorectal), blood, quantitative measurement of cell-free DNA (cfDNA) ***(Includes QuantiDNA™ Colorectal Cancer Triage Test, DiaCarta, Inc)***
	0507U	Oncology (ovarian), DNA, whole-genome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected ***(Includes Avantect Ovarian Cancer Test, ClearNote® Health)***
	0560U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments

Type	Code	Description
		(Includes Haystack MRD™ Baseline, Quest Diagnostics®)
	0561U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD ***(Includes Haystack MRD™ Monitoring, Quest Diagnostics®)***
	0562U	Oncology (solid tumor), targeted genomic sequence analysis, 33 genes, detection of single-nucleotide variants (SNVs), insertions and deletions, copy-number amplifications, and translocations in human genomic circulating cell-free DNA, plasma, reported as presence of actionable variants ***(Includes PGDx elio™ plasma focus Dx, Personal Genome Diagnostics Inc)***
	0571U	Oncology (solid tumor), DNA (80 genes) and RNA (10 genes), by next-generation sequencing, plasma, including single-nucleotide variants, insertions/deletions, copy-number alterations, microsatellite instability, and fusions, reported as clinically actionable variants ***(Includes LiquidHALLMARK® ctDNA and ctRNA, Lucence Health, Inc)***
	0585U	Targeted genomic sequence analysis panel, solid organ neoplasm, circulating cell-free DNA (cfDNA) analysis from plasma of 521 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, and microsatellite instability, report shows identified mutations, including variants with clinical actionability ***(Includes Labcorp® Plasma Complete™, Labcorp, Laboratory Developed Test) (Code effective 10/1/2025)***
	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion

Type	Code	Description
		variants of >50 exons, sequence analysis of multiple genes on one platform)
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
	81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements
	81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability
	81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
	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
03/01/2026	New policy.

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

In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

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.