PHP_2.04.153	Tumor-Informed Circulating Tumor DNA Testing (Signatera™) for Cancer Management		
Original Policy Date:	March 1, 2026	**Effective Date:**	November 1, 2026
Section:	2.0 Medicine	**Page:**	Page 1 of 422

Policy Statement

I. Tumor-informed circulating tumor DNA testing (i.e., Signatera™) may be considered **medically necessary** when **all** of the following criteria are met:[34]
   A. The member is not receiving other molecular testing for minimal residual disease analysis concurrently with this test
   B. Identification of cancer recurrence, relapse, or progression will require a change in management
   C. Documentation of **one** of the following:
      1. Monitoring is needed to diagnose cancer recurrence, relapse, or progression and member has a diagnosis of **one** of the following:
         a. Merkel cell carcinoma
         b. Muscle-invasive bladder cancer
         c. Non-small cell lung cancer
         d. Stage II to IV breast cancer
         e. Stage II to IV colorectal cancer
         f. Stage II to IV ovarian cancer
      2. Monitoring of response is needed and member is receiving immune checkpoint inhibitor therapy for a diagnosis of any solid tumor
   D. Documentation of **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 (i.e. when there is no clinical, radiographical or other biological evidence that tumor cells remain post treatment and 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:

Blue Shield of California Promise Health Plan is an independent licensee of the Blue Shield Association

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

- 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

Coding
See the Codes table for details.

Description

This evidence review addresses the use of tumor-informed circulating tumor DNA (ctDNA) testing for cancer management. The purpose of tumor-informed ctDNA testing in individuals with cancer is to predict disease course to inform treatment decisions and to monitor for recurrence following treatment.

Coverage determinations under this policy reflect both the published clinical evidence and applicable federal and state coverage requirements. Tumor-informed circulating tumor DNA (ctDNA) testing has demonstrated prognostic value and clinical validity in selected cancer populations and intended uses. Although evidence demonstrating improved net health outcomes through ctDNA-directed management remains limited for many indications, coverage may be considered when the Policy Statement criteria are met and the intended use aligns with applicable coverage requirements and validated testing populations.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Summary of Evidence

Published studies demonstrate that postoperative and surveillance ctDNA results are strongly associated with recurrence risk and prognosis in patients with colorectal cancer. Evidence supporting ctDNA-guided management remains limited because few studies have evaluated management changes or health outcomes resulting directly from test use. Nevertheless, the available literature supports clinical validity for identifying patients at increased risk of recurrence within certain intended-use populations. Coverage determinations should be based on the clinical scenario, intended use, and applicable coverage requirements.

Available studies demonstrate an association between tumor-informed ctDNA detection and recurrence risk, prognosis, and treatment response in selected breast cancer populations. While direct evidence demonstrating improved health outcomes from ctDNA-guided management is limited, the literature supports the prognostic significance of ctDNA findings and their potential role in disease monitoring within validated intended-use populations. Coverage determinations should be based on applicable coverage requirements and clinical circumstances.

The available evidence demonstrates that detectable ctDNA is consistently associated with increased risk of recurrence and poorer survival outcomes in patients with muscle-invasive bladder cancer. Although studies evaluating management changes and health outcomes resulting directly from ctDNA-guided intervention remain limited, the literature supports the clinical validity and prognostic utility of tumor-informed ctDNA testing in appropriately selected patients. Coverage determinations should be based on validated intended-use populations and applicable coverage requirements.

Preliminary evidence suggests that tumor-informed ctDNA testing may identify molecular recurrence before clinical relapse in patients with non-small cell lung cancer. However, published evidence remains limited, and uncertainties persist regarding the impact of ctDNA-directed management on long-term outcomes. Available studies support the biologic and prognostic significance of ctDNA detection, while coverage determinations should remain limited to validated intended-use populations and applicable coverage criteria.

Available studies suggest that detectable ctDNA may be associated with recurrence risk and survival outcomes in patients with esophageal cancer. Although current evidence is limited by small sample sizes and the absence of studies evaluating ctDNA-directed management strategies, the findings support the potential prognostic value of tumor-informed ctDNA testing. Coverage determinations should be guided by validated intended-use populations and applicable coverage requirements.

Available evidence suggests that changes in ctDNA levels during immune checkpoint inhibitor therapy may correlate with treatment response, progression-free survival, and overall survival. While evidence demonstrating improved clinical outcomes from ctDNA-directed modifications in therapy remains limited, the literature supports the biologic and prognostic relevance of ctDNA monitoring in selected advanced solid tumors. Coverage determinations should be guided by validated intended-use populations and applicable coverage criteria.

Additional Information

Not applicable.

Related Policies

- Genetic Variant Testing (Including Liquid Biopsy) for Targeted Treatment in Advanced Cancer
- Tumor-Uninformed Circulating Tumor DNA and Circulating Tumor Cells (Guardant Reveal™) for Cancer Management (Liquid Biopsy)

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

- 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.

Signatera Regulatory Information
Signatera is a laboratory developed test regulated under CLIA. Signatera has been developed and its performance characteristics determined by Natera, the CLIA-certified laboratory performing the test. The test has not been cleared or approved by the US Food and Drug Administration (FDA), but has received 3 Breakthrough Device Designations from FDA:

- In May 2019, Signatera was granted a Breakthrough Device Designation (BDD) for the detection of ctDNA in localized or advanced colorectal cancer patients to optimize the use of chemotherapy alone or in combination with durvalumab.
- A March 2021 press release announced that FDA granted 2 additional BDDs covering new intended uses.[1]

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

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

The purpose of tumor-informed circulating tumor DNA (ctDNA) testing in individuals with cancer is to predict disease course to inform treatment decisions and to monitor for recurrence following treatment.

Signatera

Signatera is a tumor-specific ctDNA test. Tumor tissue obtained from either a diagnostic biopsy or surgically resected tissue is used to identify 16 single nucleotide variants found in the tumor but not in normal tissue and are likely to be present in all tumor cells regardless of tumor evolution. A custom assay of 16 tumor-specific clonal, somatic variants is generated for the individual and the resulting tumor signature can be monitored throughout the individual's disease course. When the test is used for detection of recurrence following curative treatment, plasma samples with 2 or more out of these 16 variants detected above a predefined confidence threshold are deemed to be ctDNA-positive. When the test is used to monitor treatment response, evaluation is based on whether ctDNA levels increase or decrease from a baseline measurement. The test is intended to be used in conjunction with radiological assessment.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. The first step in assessing a medical test is to formulate the clinical context and purpose of the test. 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.

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 individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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

In evaluating tumor-informed ctDNA testing, consideration is also given to applicable federal and state coverage requirements, evolving clinical practice patterns, and evidence demonstrating clinical validity and prognostic utility within specific intended-use populations. While demonstration of

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

improved net health outcomes remains the preferred evidentiary standard, coverage determinations may also reflect established coverage frameworks in circumstances where clinical validity and intended-use criteria have been recognized by applicable coverage authorities.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Colorectal Cancer

Clinical Context and Test Purpose

The purpose of Signatera testing in individuals who have colorectal cancer (CRC) is to inform treatment decisions and to monitor for recurrence following curative treatment.

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

Populations

The relevant populations of interest are individuals:

- With stage II or III CRC who have undergone surgical resection, or
- Who are being monitored for relapse following treatment for stage II or III CRC, or
- With metastatic (stage IV) CRC who have undergone surgical resection and are being evaluated for adjuvant chemotherapy and/or targeted therapy.

Interventions

The test being considered is circulating tumor DNA (ctDNA) testing with Signatera:

- Following surgery, to inform decisions about adjuvant chemotherapy or targeted therapy, or
- During disease surveillance after curative treatment, to identify metastatic relapse at an early timepoint, and aid in the selection of individuals who may benefit from early/adjuvant treatment.

Comparators

For individuals with stage II CRC, the current standard of care is not to routinely administer adjuvant chemotherapy. However, current National Comprehensive Cancer Network (NCCN) guidelines are that adjuvant chemotherapy can be considered in individuals with stage II CRC, using clinicopathologic characteristics to identify individuals who might benefit.

For individuals with stage III CRC, the current standard of care is to administer adjuvant chemotherapy routinely.

For individuals who are being monitored for relapse following treatment for stage II or III CRC, guidelines suggest monitoring carcinoembryonic antigen (CEA) every 3 to 6 months for 2 years, then every 6 months for a total of 5 years, as well as imaging every 6 to 12 months for 5 years.

For individuals with metastatic CRC who have undergone surgical resection, the current standard of care is routine individual checkups, periodic computed tomography scans, and monitoring of CEA level.

Outcomes

The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, recurrence-free survival (RFS), and overall survival at follow-up.

Given that the majority of CRC recurrences occur within the first 3 years after surgical resection of the primary tumor and approximately 95% in the first 5 years, the timepoint of interest to assess recurrence is 3 to 5 years following surgical resection.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

For individuals with stage II CRC who are being evaluated for adjuvant chemotherapy, given that the test will be used to *rule-in* stage II individuals for adjuvant chemotherapy, the performance characteristics of most interest are positive predictive value and specificity.

For individuals with stage III CRC who are being evaluated for adjuvant chemotherapy, given that the test will be used to *rule-out* individuals for adjuvant chemotherapy, the performance characteristics of most interest are negative predictive value and sensitivity. However, since the test would be used to select individuals who would not receive category 1 recommended treatment, direct evidence of improvement in outcomes is required. For individuals who are being monitored for relapse following treatment for CRC, recurrence at 3 to 5 years should be assessed.

Study Selection Criteria

For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Systematic Reviews

Chidharla et al (2023) published a systematic review of 23 studies (N = 3568) investigating the use of ctDNA as a biomarker for minimal residual disease in patients with CRC after curative-intent surgery; only 3 of the included studies used the Signatera ctDNA assay and are described in more detail in the section below (Henriksen et al [2022]; Loupakis et al [2021]; Kotani et al [2023]).[2] The results of this analysis demonstrated that ctDNA positivity after surgery was associated with a significantly higher risk of recurrence, with a pooled hazard ratio (HR) of 7.27 for all stages of CRC. Furthermore, post-adjuvant chemotherapy ctDNA positivity was associated with an even higher risk of recurrence (pooled HR, 10.59). Two additional systematic reviews by international author groups had similar findings.[3,4]

Nonrandomized Trials

Several nonrandomized studies, most of which were noncomparative, examined the association of Signatera testing to prognosis in individuals with CRC (Table 1). They differed in their study designs, populations (e.g., stage of disease), frequency and timing of standard care, outcome measures, and timing of follow up. Four studies evaluated the association between positive ctDNA results and prognosis in CRC (Table 2). These studies did not provide comparisons of ctDNA testing to standard methods of risk stratification for therapy selection, monitoring response to therapy, or early relapse detection. One retrospective study compared Signatera testing to other surveillance strategies in individuals with resected CRC.[5] There are no RCTs, and no studies in which Signatera testing was used to guide treatment decisions.

Reinert et al (2019) enrolled 125 individuals with stage I to III CRC in a validation study of the Signatera assay.[6] Plasma samples were collected before surgery, at 30 days following surgery, and every 3 months for up to 3 years. The recurrence rate at 3 years was 70% in individuals with a positive ctDNA test (7 of 10) compared to 11.9% (10 of 84) of those with a negative ctDNA test. In multivariate analyses, ctDNA status was associated with recurrence after adjusting for clinicopathological risk factors including stage, lymphovascular invasion, and microradical resection status.

Henriksen et al (2022) assessed the added benefit of serial ctDNA analysis; with samples taken at diagnosis, following surgery, during adjuvant therapy, and at follow up.[7]

Loupakis et al (2021) evaluated the association of ctDNA with Signatera on survival outcomes in 112 individuals who had undergone resection for metastatic (stage IV) CRC.[8] The study included an

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

analysis of the sensitivity of Signatera testing to digital droplet polymerase chain reaction (PCR) testing but not to standard methods to identify recurrence, such as CEA and imaging.

Fakih et al (2022) directly compared Signatera testing to other surveillance strategies in individuals with resected CRC in a retrospective observational study (Table 3).[5] This study was unique in that it used NCCN recommended guidelines for surveillance and ctDNA testing was performed at the same interval as standard surveillance with CEA and imaging. Test characteristics for Signatera were not significantly different from standard imaging techniques. Estimates were imprecise, with wide confidence intervals.

Kotani et al (2023) analyzed presurgical and postsurgical ctDNA levels in a large (N = 1039) prospective study that included patients with stage II to IV resectable CRC.[9] After a median follow-up of 16.74 months, postsurgical ctDNA positivity at 4 weeks after surgery was associated with a significantly higher risk of recurrence (HR, 10.0; 95% CI, 7.7 to 14; p<.0001), and identified patients with high-risk stage II or III CRC who derived a benefit from adjuvant chemotherapy (HR, 6.59; 95% CI, 3.53 to 12.3; p<.0001). For both outcomes, trends were observed across all pathological stages evaluated. An updated analysis was published with data through June 2024.[10] This analysis included patients with stage II to III colon cancer or stage IV CRC and had a median follow-up of 23 months. Similar to the previous analysis, ctDNA positivity at 4 weeks after surgery was associated with a significantly higher risk of recurrence (disease free survival [DFS] HR, 11.99; p<.0001), and identified patients with high-risk stage II or III CRC who derived a benefit from adjuvant chemotherapy (HR, 0.23; p<.0001).

Molinari et al (2024) analyzed post-neoadjuvant therapy and postsurgical ctDNA levels in a retrospective study of 33 patients with stage II to III rectal cancer.[11] After a median follow-up of 60 months, post-neoadjuvant therapy ctDNA positivity was associated with a significantly higher risk of recurrence (HR, 7.82), as was ctDNA positivity at 2 to 12 weeks post-surgery (HR, 19.65). Estimates were imprecise, with wide confidence intervals.

Slater et al (2024) prospectively analyzed ctDNA levels in patients with resectable stage I to III CRC before and after surgery, post-adjuvant chemotherapy, every 3 months for year 1 and every 6 months in years 2 and 3.[12] A total of 1203 patients were enrolled, of whom plasma samples were available for 214 patients; the median follow-up was 30.3 months. The 2-year RFS was 91.1% in patients with ctDNA not detected postoperatively and 50.4% in those with ctDNA detected (HR, 6.5; p<.0001). The negative predictive value, sensitivity, and specificity were 88.5%, 41.7%, and 90.8%, respectively. The TRACC Part C study is currently investigating the potential de-escalation of adjuvant chemotherapy in patients with undetectable postoperative ctDNA.

Study limitations are shown in Tables 4 and 5. Major limitations include a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations.

Table 1. Nonrandomized Studies of Signatera Testing in Colorectal Cancer - Study Characteristics

Study	Test Purpose	Study Population	Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Reinert et al (2019)[6]	1. Risk stratification 2. Monitoring response to adjuvant chemotherapy 3. Early relapse detection	130 individuals with stages I to III CRC; treated from May 1, 2014 to January 31, 2017	Multicenter, Denmark	CEA and CT imaging	2 or more variants detected out of 16	Before and after surgery, during and after adjuvant chemotherapy, and during surveillance Sample at Day	Yes

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Test Purpose	Study Population	Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
						30 following surgery; individuals were followed up for a median of 12.5 months	
Henriksen et al (2022)[7]	1. Risk stratification 2. Monitoring response to adjuvant chemotherapy 3. Early relapse detection Assessed added benefit of serial measurements	168 individuals with stage III CRC treated with curative intent between 2014 and 2019	Multicenter, Spain and Denmark	CEA analysis-thresholds set according to national guidelines and CT imaging	ctDNA detected-greater or equal to 2 variants detected out of 16	Median sampling 2 weeks after surgery (IQR, 2 to 4 weeks); postoperative plasma samples (within 2-4 weeks) prior. Plasma samples were also collected during and after adjuvant therapy; individuals were followed up for a median of 35 months.	Yes
Loupakis et al (2021)[8]	1. Risk stratification following surgery	112 individuals with stage IV CRC who had undergone resection with curative intent as part of the PREDATOR clinical trial	Italy	Radiological imaging	ctDNA detected-greater or equal to 2 variants detected out of 16	Plasma samples collected at the first time point and at the time of radiologic evidence of progressive disease or at the last follow-up; individuals were followed for a median of 10.7 months	Yes
Fakih et al (2022)[5]	1. Risk stratification following surgery	48 individuals with stage II to IV CRC who underwent surveillance with Signatera and underwent curative resections between	US, single center, retrospective	Confirmed recurrence, defined as a positive ctDNA finding or a finding on imaging confirmed by biopsy, CEA level elevation, or subsequent tumor	Any positive assay finding more than 4 weeks after definitive surgery	Standard surveillance strategy included ctDNA every 3 months for 2 years and then every 6 months for 3 years. CEA at the same interval as the ctDNA assay. Imaging	No

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Test Purpose	Study Population	Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
		2019 and 2021		radiographic dynamics		studies performed within NCCN guidelines and included yearly CT scans for 5 years for low-risk stage II disease and every 6 months for 2 years and then every year for 3 years for high-risk stage II and III disease. Imaging studies were performed every 3 months for 2 years and then every 6 months for 3 years for resected stage IV disease.	
Kotani et al (2023)[9] Nakamura et al (2024)[10]	1. Risk stratification 2. Monitoring response to adjuvant chemotherapy 3. Early relapse detection	1,039 individuals with stage II to IV or recurrent CRC who underwent surveillance with Signatera and underwent curative resections through June 2022 (Kotani et al [2023]) and updated analysis of 2,240 individuals with stage II to III resectable colon cancer or stage IV CRC through June 2024	Japan	NR	Any positive assay finding more than 4 weeks after definitive surgery	Samples collected 4 weeks after surgery, as well as 12 weeks after surgery for some patients	No

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Test Purpose	Study Population	Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
		(Nakamura et al [2024])					
Molinari et al (2024)[11]	1. Risk stratification following neoadjuvant therapy and following surgery	33 individuals with stage II to III rectal cancer, diagnosed between 2017 and 2021	Italy	NR	ctDNA detected-greater or equal to 2 variants detected out of 16	Samples collected after diagnostic biopsy, before surgery, and 2 to 12 weeks after surgery	No
Slater et al (2024); TRACC Part B study[12]	1. Risk stratification 2. Monitoring response to adjuvant chemotherapy 3. Early relapse detection	1,203 individuals with stage I to III resectable CRC from 2016 to 2022; plasma samples from 212 individuals were analyzed	UK	Radiological imaging	NR	Samples collected before and 3 to 12 weeks after surgery, after adjuvant chemotherapy, and every 3 months for year 1 and every 6 months in years 2 and 3	NR

CEA: carcinoembryonic antigen; CRC: colorectal cancer; CT: computerized tomography; ctDNA: circulating tumor DNA ; IQR: interquartile range; NCCN: National Comprehensive Cancer Network; NR: not reported; TRACC: TRAcking mutations in cell-free tumor DNA to predict relapse in early Colorectal Cancer

Table 2. Recurrence Rates by Risk Category in Nonrandomized Studies of Signatera in Colorectal Cancer

Study	Mean Recurrence Rate (95% CI)	
	ctDNA Positive	ctDNA Negative
Reinert et al (2019)[6]	7/10; 70% (34.2% to 93.1%)	10/84; 11.9% (6.3% to 20.1%)
HR for recurrence following surgery (95% CI)	7.2 (2.7 to 19.0); p<.001	
HR for recurrence following adjuvant chemotherapy (95% CI)	17.5 (5.4 to 56.5); p<.001	
Henriksen et al (2022)[7]	16/20 (80%)	22/120 (18%)
HR for RFS (95% CI)	7.0 (3.7 to 13.5); p<.001	
Loupakis et al (2021)[8]	59/61 (96.7%)	NR/51 Number with recurrences not reported; 49 of 51 were alive at data cutoff
HR for RFS (95% CI)	5.8 (3.5 to 9.7); p<.001	
HR for OS (95% CI)	16.0 (3.9 to 68.0); p<.001	
Kotani et al (2023)[9]	187/1039 (18.0%)	852/1,039 (82%)
HR for DFS (95% CI)	10 (7.7 to 14); p<.001	
HR for benefit with adjuvant chemotherapy (95% CI)	6.59 (3.53 to 12.3); p<.0001	
Nakamura et al (2024)[10]	336/2109 (15.93%)	1773/2109 (84%)
HR for DFS (95% CI)	11.99 (10.02 to 14.35); p<.0001	
HR for overall survival (95% CI)	9.68 (6.33 to 14.82); p<.0001	
Patients with stage II to III colon cancer	192/1,349 (14.23%)	1,157/1,349 (85.77%)
HR for benefit with adjuvant chemotherapy (95% CI)	0.23 (0.15 to 0.35); p<0.0001	

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Mean Recurrence Rate (95% CI)
Molinari et al (2024)[11]	At baseline, ctDNA detection rate was 90% (27/30) Post-neoadjuvant therapy, ctDNA was detected in 5 patients Post-surgery, ctDNA was detected in 3 patients
HR for DFS post-neoadjuvant therapy (95% CI)	7.82 (2.28 to 26.82); p<.001
HR for DFS post-surgery (95% CI)	19.65 (3.17 to 121.75); p<.001
Slater et al (2024)[12]	21/143 (14.7%) 122/143 (85.3%)
HR for RFS (95% CI)	6.5 (3 to 14.5); p<.0001

CI: confidence interval; ctDNA: circulating tumor DNA; DFS: disease-free survival; HR: hazard ratio; NR: not reported; OS: overall survival; RFS: recurrence-free survival.

Table 3. Retrospective Comparison of Signatera to Other Surveillance Strategies in Resected Colorectal Cancer

Study	Sensitivity	Specificity	PPV	NPV	Median Time to Recurrence, months
Fakih et al (2022)[5]					
Signatera Testing	53.3 (27.4 to 77.7)	100 (87.0 to 100)	100 (59.8 to 100)	82.5 (66.6 to 92.1)	14.3
Imaging	60.0 (32.9 to 82.5)	96.9 (82.5 to 99.8)	90.0 (54.1 to 99.5)	84.2 (68.1 to 93.4)	15.0
CEA	20.0 (5.3 to 48.6)	90.9 (74.5 to 97.6)	50.0 (13.9 to 86.1)	71.4 (55.2 to 83.8)	NA
CEA plus imaging	73.3 (44.8 to 91.1)	87.9 (70.9 to 96.0)	73.3 (44.8 to 91.1)	87.9 (70.9 to 96.0)	15.0
P-value	>.99	>.99	NA	NA	.45
Signatera vs. imaging	.55	.13			.79
Signatera vs. imaging plus CEA	.13	.25			NA
Signatera vs. CEA					

CEA: carcinoembryonic antigen; NA: not assessed; NPV: negative predictive value; PPV: positive predictive value.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Reinert et al (2019)[6]	1. Included individuals with stage I through III colorectal cancer		3. No comparator	1. Overall survival not assessed	1. Follow up for recurrence was under 3 years (median 12.5 months)
Henriksen et al (2022)[7]			3. No comparator		1. Follow up for recurrence was under 3 years (median 35 months)
Loupakis et al (2021)[8]			3. No comparator		1. Follow up for recurrence was under 3 years (median 10.7 months)
Fakih et al (2022)[5]				1. Survival outcomes not assessed	
Kotani et al (2023)[9]; Nakamura et al (2024)[10]			3. No comparator	1. Overall survival not assessed	1. Follow up for recurrence was under 3 years (median 16.74 months)
Molinari et al (2024)[11]			3. No comparator	1. Overall survival not assessed	
Slater et al (2024)[12]	1. Included individuals with stage I through		3. No comparator	1. Overall survival not assessed	1. Follow up for recurrence was under 3 years (median 30.3 months)

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
	III colorectal cancer				

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

Table 5. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Reinert et al (2019)[6]	1. individual selection not described					Multiple subgroup analyses, small numbers of individuals with positive ctDNA tests.
Henriksen et al (2022)[7]			2. Standard-of-care imaging frequency differed between the Spanish (every 6 months) and Danish (at month 12 and 36) cohort.			Small numbers of individuals with positive ctDNA tests.
Loupakis et al (2021)[8]						Small numbers of individuals with positive ctDNA tests.
Fakih et al (2022)[5]						
Kotani et al (2023)[9]; Nakamura et al (2024)[10]	1. individual selection not described					
Molinari et al (2024)[11]	1. individual selection not described					
Slater et al (2024)[12]	1. individual selection not described	1. blinding not described				

ctDNA: circulating tumor DNA.
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.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

[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: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Colorectal Cancer

Published studies demonstrate that postoperative and surveillance ctDNA results are strongly associated with recurrence risk and prognosis in patients with colorectal cancer. Evidence supporting ctDNA-guided management remains limited because few studies have evaluated management changes or health outcomes resulting directly from test use. Nevertheless, the available literature supports clinical validity for identifying patients at increased risk of recurrence within certain intended-use populations. Coverage determinations should be based on the clinical scenario, intended use, and applicable coverage requirements.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Breast Cancer

Clinical Context and Test Purpose

The purpose of Signatera testing in individuals with breast cancer is to predict disease course (e.g., aggressiveness, risk of recurrence, death) and inform treatment decisions, and to monitor for recurrence following curative treatment.

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

Populations

The population of interest is individuals with breast cancer, or those who have been treated for breast cancer and are being monitored for recurrence.

Interventions

The test being considered is ctDNA testing with Signatera:

- At diagnosis to inform decisions about neoadjuvant chemotherapy, or
- After surgery to inform decisions about adjuvant treatment, or
- Following curative treatment, to monitor for recurrence.

Comparators

- Decisions about neoadjuvant and adjuvant chemotherapy are based on clinicopathological risk factors.
- Guidelines for disease surveillance following breast cancer treatment recommend regular imaging and physical examinations, and additional testing upon presentation of symptoms.

Outcomes

The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

The specific outcomes of interest depend on the proposed purpose of testing in individuals with breast cancer.

- If used for risk stratification to *rule-out* individuals for neoadjuvant chemotherapy at diagnosis or adjuvant treatment following surgery, the performance characteristics of most interest are negative predictive value and sensitivity.
- If used for risk stratification to *rule-in* individuals for neoadjuvant chemotherapy at diagnosis or adjuvant treatment following surgery, the performance characteristics of most interest are positive predictive value and specificity.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

If used for disease surveillance following primary treatment, beneficial outcomes of a true positive test would be earlier detection of metastasis and initiation of treatment. Harmful outcomes of a false positive test would be undergoing unnecessary or incorrect treatment, and experiencing adverse effects of such treatment.

See also Blue Shield of California Promise Medical Policy: Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer for additional discussion of outcomes in breast cancer risk assessment studies.

Study Selection Criteria

For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Systematic Reviews

Zhang et al (2025) published a systematic review investigating the prognostic value of ctDNA in early-stage triple-negative breast cancer (TNBC).[13] Twenty publications were included in the analysis, though only 4 studies specifically investigated the Signatera assay. Results demonstrated that post-neoadjuvant (before or after surgery) ctDNA positivity was associated with increased risk of disease recurrence (HR, 4.12, 95% CI, 2.81 to 6.04; p<.00001) as well as worse overall survival (HR, 3.26; 95% CI, 1.88 to 5.63; p<.0001).

Nonrandomized Trials

Two noncomparative studies reported the association of Signatera testing with survival outcomes in breast cancer (Table 6). There are no RCTs, and no studies in which Signatera testing was used to guide treatment decisions.

Coombes et al (2019) evaluated Signatera for disease surveillance in 49 individuals who had received surgery and adjuvant therapy for stage I to III breast cancer of various subtypes.[14] Signatera detected ctDNA in 16 of 18 individuals who subsequently relapsed, and the presence of ctDNA test was associated with poorer prognosis (Table 7).

Magbanua et al (2021) evaluated ctDNA clearance as a predictor of response to neoadjuvant chemotherapy (NAC) in 84 individuals with nonmetastatic breast cancer who were enrolled in the I-SPY2 trial.[15] In the population as a whole, ctDNA positivity decreased during the course of NAC, from 73% before treatment (T0), to 35% at 3 weeks (T1), to 14% at the inter-regimen time point (T2), and down to 9% after NAC (T3). Hazard ratios for recurrence at each of these timepoints are shown in Table 7 and indicate that positive predictive value increased over time.

Study limitations are shown in Tables 8 and 9. Major limitations of both studies include a lack of comparison to standard methods of monitoring, and heterogeneity in the study populations.

Table 6. Nonrandomized Studies of Signatera Testing in Breast Cancer - Study Characteristics

Study	Test Purpose	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Coombes et al (2019)[14]	Relapse detection following	49 individuals with stage I to III breast cancer who	Prospective cohort, multicenter, UK	Cancer antigen 15-3 serum	2 or more variants detected out of 16	Plasma samples every 6 months for up to 4 years	Yes

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Test Purpose	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
	primary treatment	had undergone surgery and adjuvant chemotherapy; 34 HR–positive/HER2-negative, 8 HER2-positive, 7 TNBC		testing, CT imaging			
Magbanua et al (2021)[15]	Response to neoadjuvant chemotherapy	84 individuals with ≥ 2.5 cm nonmetastatic stage II/III breast cancer	Retrospective analysis of samples prospectively collected as part of the I-SPY2 TRIAL	Radiological imaging	2 or more variants detected out of 16	Plasma samples collected before, during, and after neoadjuvant chemotherapy	Yes

CT: computerized tomography; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; TNBC: triple-negative breast cancer.

Table 7. Nonrandomized Studies of Signatera Testing in Breast Cancer - Study Results

Study	Initial N	Final N	Excluded Samples	Recurrence Rate	Median Time to Recurrence, months (range)	Clinical Validity			
						Sensitivity	*Specificity*	*PPV*	*NPV*
Coombes et al (2019)[14]	197	49	148	18/49 (36.7%)	8.9 (0.5 to 24.0)	16/18 (89%)	31/31 (100%)	NR	NR
HR (95% CI) for RFS (first postsurgical sample)	11.8 (4.3 to 32.5), p<.001								
HR (95% CI) for RFS (any follow up sample)	35.8 (7.9 to 161.3), p<.001								
Magbanua et al (2021)[15]	84	75	9	NA	NA	NR	NR	4/6 (67%)	50/54 (93%)
HR (95% CI) for recurrence (T0, baseline)	4.11 (0.52 to 32.4)								
HR (95% CI) for RFS (T1, 3 weeks after therapy initiation)	4.5 (1.2 to 17.4)								
HR (95% CI) for RFS (T2, between regimens)	5.4 (1.3 to 22.5)								
HR (95% CI) for RFS (T3, after neoadjuvant chemotherapy)	11.5 (2.9 to 46.1)								

CI: confidence interval; HR: hazard ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RFS: recurrence-free survival.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Coombes et al (2019)[14]	2. Study population included a mix of individuals with stage I to III breast cancer		3. Not compared to tests used for the same purpose		
Magbanua et al (2021)[15]			3. Not compared to tests used for the same purpose		

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

Table 9. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Coombes et al (2019)[14]						1. Confidence intervals for test characteristics not reported; small number of positive ctDNA tests
Magbanua et al (2021)[15]	2. Retrospective analysis					1. Confidence intervals for test characteristics not reported; small number of positive ctDNA tests

ctDNA: circulating tumor DNA.
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: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Breast Cancer

Available studies demonstrate an association between tumor-informed ctDNA detection and recurrence risk, prognosis, and treatment response in selected breast cancer populations. While direct evidence demonstrating improved health outcomes from ctDNA-guided management is limited, the literature supports the prognostic significance of ctDNA findings and their potential role

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

in disease monitoring within validated intended-use populations. Coverage determinations should be based on applicable coverage requirements and clinical circumstances.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Bladder Cancer

Clinical Context and Test Purpose

The purpose of Signatera testing in individuals with bladder cancer is to predict disease course to inform treatment decisions and to monitor for recurrence following curative treatment.

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

Populations

The relevant population of interest is individuals with bladder cancer, or those who have been treated for bladder cancer and are being monitored for recurrence.

Interventions

The test being considered is ctDNA testing with Signatera:

- At diagnosis, to identify individuals at low risk of recurrence after cystectomy who may be eligible for cystectomy without neoadjuvant chemotherapy, or
- After chemotherapy before cystectomy, to determine treatment response and inform treatment decisions (e.g., additional cycles of chemotherapy or other therapeutic strategies), or
- During disease surveillance after cystectomy, to identify metastatic relapse after cystectomy at an early time point, and aid in the selection of individuals who may benefit from early/adjuvant treatment. For individuals with bladder cancer who are being evaluated for adjuvant chemotherapy, given that the test will be used to *rule-in* individuals for adjuvant chemotherapy, the performance characteristics of most interest are positive predictive value and specificity.

Comparators

- Urine testing, cystoscopy, and radiographic imaging are used for disease monitoring in individuals with bladder cancer.
- Detection of relapse and monitoring of response to treatment in the metastatic setting is performed by standard computed tomography scan.

Outcomes

The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

If used to *rule in* individuals with bladder cancer who would be likely to benefit from adjuvant chemotherapy, the performance characteristics of most interest are positive predictive value and specificity.

If used to *rule out* patients with bladder cancer who could forego adjuvant chemotherapy, the performance characteristics of most interest are negative predictive value and sensitivity. However, since the test would be used to select individuals who would not receive category 1 recommended treatment, direct evidence of improvement in outcomes is required.

Study Selection Criteria

For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Nonrandomized Trials

Severa nonrandomized studies have reported an association between Signatera testing and prognosis in bladder cancer (Tables 10 and 11).

Christensen et al (2019) assessed the association of ctDNA with prognosis in 68 individuals with localized advanced bladder cancer who were receiving neoadjuvant chemotherapy before cystectomy (median follow-up of 21 months).[16] Data from a 68-month follow-up of this cohort were reported by Lindskrog et al (2023).[17] Additionally, Lingskrog et al (2023) reported on the association of ctDNA with prognosis in a separate cohort of 102 patients who did not receive neoadjuvant chemotherapy and had ctDNA testing before and after cystectomy (median follow-up of 72 months). Results demonstrated that ctDNA was prognostic regardless of whether or not patients received neoadjuvant chemotherapy before cystectomy.

Powles et al (2021) reported the association of a positive Signatera test to treatment response in 581 individuals who had undergone surgery for urothelial cancer and were enrolled in a RCT of atezolizumab versus observation.[18] Study participants who were positive for ctDNA had improved disease-free survival (DFS) and overall survival in the atezolizumab arm versus the observation arm (DFS HR, 0.58 [95% CI, 0.43 to 0.79]; p=.0024 and overall survival HR, 0.59 [95% CI, 0.41 to 0.86]). No difference in DFS or overall survival between treatment arms was noted for patients who were negative for ctDNA. At 2-year follow up, ctDNA status remained prognostic and no relapses were observed in the ctDNA-negative patients at baseline and after neoadjuvant therapy.[19]

Ben-David et al (2024) retrospectively assessed whether ctDNA status before cystectomy and during surveillance is predictive of recurrence in patients with bladder cancer.[20] A total of 112 patients were included with a median follow-up of 8 months. Detectable ctDNA before surgery was found in 59 patients, and was associated with worse prognosis (Kaplan-Meier analysis, p<.0001). Additionally, patients with undetectable ctDNA before surgery had comparable RFS regardless of whether they received neoadjuvant therapy before surgery. Patients with detectable ctDNA that remained persistently detectable after surgery had the worst prognosis, with RFS rates of 33% at 6 months and 16% at 12 months.

Sfakianos et al (2025) retrospectively assessed whether ctDNA status before cystectomy and during surveillance is predictive of recurrence in patients with bladder cancer.[21] A total of 167 patients were included with a median follow-up of 10 months. Detectable ctDNA before surgery was found in 26 of 65 patients (40%) with available plasma samples. Among those receiving upfront surgery, patients with detectable ctDNA had shorter DFS (HR, 10.61; 95% CI, 1.01 to 1434; p=.03). Likewise, detectable ctDNA during the window of 1 to 12 weeks after surgery was associated with shorter DFS (HR, 6.93; p<.001) as well as during surveillance (more than 12 weeks after surgery if no adjuvant therapy was administered or 2 or more weeks after the completion of adjuvant therapy; HR, 23.02; p<.001).

The major limitation of these studies was lack of comparison to other tests used for the same purpose (Tables 12 and 13).

Table 10. Nonrandomized Studies of Signatera Testing in Bladder Cancer - Study Characteristics

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Sfakianos et al (2025)[21]	167 individuals with stage I to IV bladder cancer	Retrospective, multicenter in the US	Radiological imaging	Greater or equal to 2 variants	Blood samples collected before and after	NR

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
	who underwent cystectomy between 2016 and 2023			detected out of 16	cystectomy. Median follow-up of 10 months	
Ben-David et al (2024)[20]	112 individuals with bladder cancer who underwent cystectomy between 2021 and 2023	Retrospective, one hospital in the US	Radiological imaging	NR	Blood samples collected after completion of neoadjuvant therapy (if applicable) and before and after cystectomy. Median follow-up of 8 months.	No
Lindskrog et al (2023)[17]	102 individuals with muscle-invasive bladder cancer who underwent cystectomy between 2001 and 2014 and did not receive neoadjuvant chemotherapy	Retrospective, one University Hospital, Denmark	Radiological imaging	Greater or equal to 2 variants detected out of 16	Surveillance according to European Guidelines. Blood samples collected before and after cystectomy. Median follow-up of 72 months after cystectomy.	NR
Powles et al (2021)[18]	581 individuals with urothelial cancer from a randomized Phase III trial of adjuvant atezolizumab vs. observation who had undergone surgery and were evaluable for ctDNA	Retrospective	Radiological imaging	Greater or equal to 2 variants detected out of 16	Post-surgical plasma samples were collected and tested at baseline and 6 weeks after randomization and individuals were followed up for a median of 23 months	No
Christensen et al (2019)[16,17]	68 individuals with muscle-invasive bladder cancer who were receiving neoadjuvant chemotherapy before cystectomy between 2013 and 2017	Prospective, one University Hospital, Denmark	Radiological imaging	Greater or equal to 2 variants detected out of 16	Surveillance according to European Guidelines. Blood samples collected at uniformly scheduled clinical visits and before each chemotherapy cycle. Median follow-up of 21 months after cystectomy	Yes

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
					(published by Christensen et al [2019]). Median follow-up of 68 months after cystectomy (published by Lindskrog et al [2023]).	

ctDNA: circulating tumor DNA; NR: not reported.

Table 11. Recurrence Rates by Risk Category in Nonrandomized Studies of Signatera in Bladder Cancer

Study	Mean Recurrence Rate (95% CI)	
	ctDNA Positive	ctDNA Negative
Sfakianos et al (2025)[21]		
Before cystectomy	26/65 (40%)	39/65 (60%)
DFS	Median, 7.98 months	Not reached
HR for DFS (95% CI)	10.61 (1.01 to 1434) p=.035	
1 to 12 weeks after cystectomy	24/100 (24%)	76/100 (76%)
Recurrence	8/18 (44%)	6/76 (8%)
HR for DFS (95% CI)	HR, 6.93 (2.4 to 20.05); p<.001	
12 weeks after cystectomy if no adjuvant therapy or 2 or more weeks after the completion of adjuvant therapy	52/117 (44%)	65/117 (56%)
DFS	Median, 14.1 months	Not reached
HR for DFS (95% CI)	23.02 (5.51 to 96.17); p<.001	
Ben-David et al (2024)[20]		
Before cystectomy	59/112 (53%)	53/112 (47%)
RFS at 6 months	64%	98%
RFS at 12 months	35%	95%
RFS at 15 months	35%	76%
Lindskrog et al (2023)[17]		
At diagnosis before cystectomy	44/96 (46%)	52/96 (54%)
Adjusted HR (95% CI) for recurrence at 72-month follow-up	3.4 (1.7 to 6.8); p=.0005	
After cystectomy	15/34 (44%)	19/34 (56%)
Adjusted HR (95% CI) for recurrence at 72-month follow-up	17.8 (3.9 to 81.2); p=.0002	
Christensen et al (2019)[16,17]		
At diagnosis before chemotherapy	11/24 (46%)	1/35 (3%)
Adjusted HR for recurrence at 21-month follow-up	29.1; p=.001	
Adjusted HR (95% CI) for recurrence at 68-month follow-up	15.6 (3.5 to 69); p=.0003	
After chemotherapy before cystectomy	6/8 (75%)	6/55 (11%)
Adjusted HR for recurrence at 21-month follow-up	12.0; p<.001	
Adjusted HR (95% CI) for recurrence at 68-month follow-up	15.2 (5 to 46.8); p<.0001	
During disease surveillance after cystectomy	13/17 (76%)	0/47 (0%)
Adjusted HR for recurrence at 21-month follow-up	129.6; p<.001	
Adjusted HR (95% CI) for recurrence at 68-month follow-up	37.7 (8.5 to 167.1); p<.0001	

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Mean Recurrence Rate (95% CI)
Powles et al (2021)[18]	
Following surgery (cycle 1 day 1)	
HR (95% CI) for DFS	6.3 (4.45 to 8.92); p<.0001
6 weeks after randomization (cycle 3 day 1)	
HR (95% CI) for DFS	8.65 (5.67 to 13.18); p<.0001

CI: confidence interval; ctDNA: circulating tumor DNA; DFS: disease-free survival; HR: hazard ratio; NR: not reported; RFS: recurrence-free survival.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Sfakianos et al (2025)[21]			3. Not compared to tests used for the same purpose		Short follow-up of 10 months
Ben-David et al (2024)[20]			3. Not compared to tests used for the same purpose		Short follow-up of 8 months
Lindskrog et al (2023)[17]			3. Not compared to tests used for the same purpose		
Powles et al (2021)[18]	.		3. Not compared to tests used for the same purpose		
Christensen et al (2019)[16]			3. Not compared to tests used for the same purpose		

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

Table 13. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Sfakianos et al (2025)[21]						
Ben-David et al (2024)[20]						
Lindskrog et al (2023)[17]		Blinding not described.				
Powles et al (2021)[18]						
Christensen et al (2019)[16]						1. Confidence intervals for hazard ratios not reported.

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.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

[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: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Bladder Cancer
The available evidence demonstrates that detectable ctDNA is consistently associated with increased risk of recurrence and poorer survival outcomes in patients with muscle-invasive bladder cancer. Although studies evaluating management changes and health outcomes resulting directly from ctDNA-guided intervention remain limited, the literature supports the clinical validity and prognostic utility of tumor-informed ctDNA testing in appropriately selected patients. Coverage determinations should be based on validated intended-use populations and applicable coverage requirements.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Non-Small Cell Lung Cancer
Clinical Context and Test Purpose
The purpose of Signatera testing in individuals with non-small cell lung cancer (NSCLC) is to predict disease course to inform treatment decisions and to monitor for recurrence following surgical resection.

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

Populations
The relevant population of interest is individuals with NSCLC, or those who have been treated for NSCLC and are being monitored for recurrence.

Interventions
The test being considered is ctDNA testing with Signatera following surgical resection, to identify metastatic relapse at an early time point, and aid in the selection of individuals who may benefit from early/adjuvant treatment.

Adjuvant platinum-based chemotherapy is not the standard of care following surgery for NSCLC; treatment improves cure rates after surgery in only 5% of patients, and 20% of patients receiving chemotherapy experience acute toxicities. Signatera testing is proposed to select patients who are very likely to relapse post-operatively and who might benefit from adjuvant treatment.

Comparators
Radiographic imaging is used for disease monitoring in individuals with NSCLC. Detection of relapse and monitoring of response to treatment in the metastatic setting is performed by standard computed tomography scan, with frequency and type of imaging depending on primary treatment and stage. For patients with stage I-II NSCLC following completion of definitive therapy, NCCN guidelines recommend history and physical and chest computed tomography every 6 months for 2 to 3 years, then annually. For patients with primary treatment that included radiotherapy, surveillance is recommended every 3 to 6 months for 3 years, and every 6 months for 2 years, then annually. Treatment options following recurrence include resection and/or systemic therapy.

Outcomes
The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Beneficial outcomes of a true positive test would be an individual undergoing potentially beneficial additional treatment such as chemotherapy at an earlier time point than if a relapse were identified clinically.

Harmful outcomes of a false positive test would be undergoing unnecessary or incorrect treatment, and experiencing adverse effects of such treatment.

Nonrandomized Trial

The evidence for the use of Signatera to detect relapse in NSCLC following surgery is limited to a subgroup analysis of 24 individuals enrolled in TRACERx, a longitudinal cohort study of tumor sampling and genetic analysis in individuals with NSCLC.[22] Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test (defined as at least 2 single-nucleotide variants detected). Of 10 individuals with no relapse after a median follow up of 775 days, (range 688 to 945 days), 1 had a positive ctDNA test (10%).

Study limitations are shown in Tables 15 and 16. Major limitations include no comparison to standard surveillance methods and imprecise estimates due to the small sample size. Additionally, the commercially available Signatera has been updated since this publication.

Table 14. Nonrandomized Study of Signatera Testing in Non-Small Cell Lung Cancer

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Main Results
Abbosh et al (2017)[22]	24 individuals with early-stage NSCLC	Prospective, subgroup of patients enrolled in the TRACERx Study	Clinical assessment and chest radiograph	Greater or equal to 2 variants detected out of 16	Every 3 months for 2 years, then every 6 months thereafter; individuals were followed up for a median of 775 days	Yes	Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test. Of 10 individuals with no relapse after a median follow up of 775 days (range 688 to 945 days), 1 had a positive ctDNA test (10%). Median interval between ctDNA detection and NSCLC relapse confirmed by CT imaging indicated by clinical and chest radiograph follow-up (lead time) was 70 days (range, 10 to 346 days).

CT: computed tomography; ctDNA: circulating tumor DNA; NSCLC: non-small cell lung cancer.

Table 15. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Abbosh et al (2017)[22]			3. No comparison to standard methods of monitoring for relapse	1. Health outcomes not assessed	

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

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

Table 16. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Abbosh et al (2017)[22]	2. Subgroup analysis, subset of the first 100 participants enrolled in the study; unclear if selection was consecutive		2. Timing of ctDNA testing unclear			1. No comparison to imaging, no confidence intervals

ctDNA: circulating tumor DNA.
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: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Non-Small Cell Lung Cancer

Preliminary evidence suggests that tumor-informed ctDNA testing may identify molecular recurrence before clinical relapse in patients with non-small cell lung cancer. However, published evidence remains limited, and uncertainties persist regarding the impact of ctDNA-directed management on long-term outcomes. Available studies support the biologic and prognostic significance of ctDNA detection, while coverage determinations should remain limited to validated intended-use populations and applicable coverage criteria.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Esophageal Cancer

Clinical Context and Test Purpose

The purpose of Signatera testing in individuals with esophageal cancer is to detect minimal residual disease following surgical resection and to monitor for disease recurrence.

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

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Populations
The relevant population of interest is individuals with esophageal cancer who have undergone surgical resection.

Interventions
The test being considered is ctDNA testing with Signatera:

- Following surgical resection, to detect minimal residual disease and aid in the selection of individuals who may benefit from early/adjuvant treatment, or
- For disease monitoring after curative treatment, to identify metastatic relapse at an early time point, and aid in the selection of individuals who may benefit from early/adjuvant treatment.

Comparators
Recommendations on surveillance and monitoring following esophageal cancer treatment include periodic upper endoscopy, laboratory tests, and imaging as indicated. Specific recommendations depend on tumor classification.

Outcomes
The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

Beneficial outcomes of a true positive test would be an individual undergoing potentially beneficial additional treatment at an earlier time point than if a relapse were identified clinically.

Harmful outcomes of a false positive test would be undergoing unnecessary or incorrect treatment and experiencing adverse effects of such treatment.

Study Selection Criteria
For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Nonrandomized Trial
One prospective cohort study and one noncomparative retrospective study reported the association of Signatera testing measured before and after surgery with relapse and recurrence (Tables 17 and 18).

Mukherjee et al (2025) examined the association between ctDNA and prognosis in a Phase II study of 22 patients with localized esophageal or gastroesophageal junction adenocarcinoma treated with induction chemotherapy and preoperative chemoradiation.[23] With a median follow-up of 15.8 months, ctDNA data were available for 10 patients, and 7 were eligible for survival analysis. Among them, patients who cleared ctDNA post-surgery (n=5) had significantly better overall survival (25.9 vs. 10.1 months; p=.012) and progression-free survival (PFS; 25.9 vs. 7.6 months; p=.0082) than those with persistent ctDNA (n=2).

Ococks et al (2021) assessed data from 17 individuals with esophageal adenocarcinoma. Patients who were ctDNA-positive before surgery had significantly poorer DFS (p<.042), with a median DFS of 32.0 months vs. 63.0 months in ctDNA-negative preoperative patients. This study was limited by the very small number sample size, and its retrospective design (Tables 19 and 20).

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Table 17. Nonrandomized Study of Signatera Testing to Predict Relapse in Esophageal Cancer - Study Characteristics

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Mukherjee et al (2025)[23]	22 individuals with localized esophageal or gastroesophageal junction adenocarcinoma treated with induction chemotherapy and preoperative chemoradiation followed by surgery	Prospective	Radiological imaging	2 or more variants detected out of 16	Blood samples were collected at baseline, after induction chemotherapy, after chemoradiation, and after surgery, and patients were followed up for a median of 15.8 months	No
Ococks et al (2021)[24]	17 individuals with esophageal adenocarcinoma who had undergone surgery	Retrospective	Radiological imaging	2 or more variants detected out of 16	Blood samples were collected before and after surgical treatment and patients were followed up for a median of 43.4 months.	Yes

Table 18. Recurrence Rates by Risk Category in Nonrandomized Studies of Signatera in Resected Esophageal Cancer

Study			
	Overall survival	**PFS**	
Mukherjee et al (2025)[23]			
ctDNA status following surgery	ctDNA positive: n=2 ctDNA negative: n=5	ctDNA positive: n=2 ctDNA negative: n=5	
ctDNA clearance vs no clearance following surgery	median, 25.9 vs. 10.1 months; p=.012	median, 25.9 vs. 7.6 months; p=.0082	
	Median DFS		
	ctDNA Positive	**ctDNA Negative**	**p for comparison**
Ococks et al (2021)[24]			
ctDNA status before surgery			
Recurrence rate	5/11	0/6	
Median DFS	32.0 months	63.0 months	.042
ctDNA status following surgery			
Recurrence rate	4/4	1/13	NR
Median DFS	14.2 months	51.2 months	NR

ctDNA: circulating tumor DNA; DFS: disease-free survival; NR: not reported; PFS: progression-free survival.

Table 19. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Mukherjee et al (2025)[23]	4. The study included 54.5% of patients with gastroesophageal junction adenocarcinoma and 45.5% of patients with esophageal adenocarcinoma		3. No comparison to tests used for the same purpose		1. Short follow-up of approximately 16 months

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Ococks et al (2021)[24]		2. Unclear if the test used was the commercially available version	3. No comparison to tests used for the same purpose		

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

Table 20. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Mukherjee et al (2025)[23]						Imprecise estimates due to small sample size
Ococks et al (2021)[24]					Excluded individuals who did not undergo surgery	Imprecise estimates due to small sample size

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: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Esophageal Cancer

Available studies suggest that detectable ctDNA may be associated with recurrence risk and survival outcomes in patients with esophageal cancer. Although current evidence is limited by small sample sizes and the absence of studies evaluating ctDNA-directed management strategies, the findings support the potential prognostic value of tumor-informed ctDNA testing. Coverage determinations should be guided by validated intended-use populations and applicable coverage requirements.

Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Solid Tumors Receiving Immunotherapy

Clinical Context and Test Purpose

The purpose of Signatera testing in individuals with solid tumors who have received immunotherapy is to monitor treatment response and inform subsequent treatment decisions. Signatera is proposed

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

as a method to stratify patients according to their likelihood of response to immunotherapy, to guide treatment decisions.

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

Populations
The relevant population of interest is individuals with solid tumors who have received immune checkpoint inhibitor (ICI) therapy.

Interventions
The test being considered is ctDNA testing with Signatera.

Comparators
For individuals with solid tumors receiving immunotherapy, treatment response is monitored by repeated radiographic evaluation of the tumor.

Outcomes
The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, RFS, and overall survival at follow-up.

If the test is used to *rule-in* individuals with solid tumors who are likely to respond to immunotherapy, the performance characteristics of most interest are positive predictive value and specificity.

If the test is used to *rule-out* individuals with solid tumors who are unlikely to respond to immunotherapy, the performance characteristics of most interest are negative predictive value and sensitivity.

Study Selection Criteria
For the evaluation of clinical validity of the Signatera test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Systematic Review
Valenza et al (2025) published a systematic review evaluating ctDNA as a predictive biomarker of pathologic complete response in patients with solid tumors who are treated with neoadjuvant immune checkpoint inhibitor (ICI) therapy.[25] Thirteen trials (N = 380) were included, of which only 2 trials specifically evaluated Signatera. Among the 380 patients, 74 received ICI monotherapy and 306 received an ICI in combination with chemotherapy or targeted therapy. Overall, 144 of 380 (38%) patients achieved pathologic complete response after neoadjuvant treatment, and 262 of 380 (73%) had ctDNA clearance after neoadjuvant ICI therapy. The estimated sensitivity of ctDNA clearance for pathologic complete response was 0.98 (95% CI, 0.86 to 1.00), and the estimated specificity of ctDNA persistence for lack of pathologic complete response was 0.53 (95% CI, 0.37 to 0.69).

Nonrandomized Trial
Bratman et al (2020) evaluated Signatera to predict treatment response in 106 individuals receiving pembrolizumab for solid tumors, including squamous cell cancer of head and neck, triple negative breast cancer, high-grade serous ovarian cancer, malignant melanoma, and mixed solid tumors (Tables 21 and 22).[26]

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Lower-than-median ctDNA levels at baseline were associated with improved overall survival (adjusted HR, 0.49; 95% CI, 0.29 to 0.83) and PFS (adjusted HR, 0.54; 95% CI, 0.34 to 0.85). Among participants with at least 2 ctDNA measurements, any rise in ctDNA levels during surveillance above baseline was associated with rapid disease progression and poor survival (median overall survival, 13.7 months), whereas among 12 patients whose ctDNA cleared during treatment, overall survival was 100% at a median follow up of 25.4 months (range, 10.8 to 29.5 months) following the first clearance.

Study limitations are shown in Tables 23 and 24. This single-center study is limited by its small sample size and variability in results across different tumor types. The study did not include a comparison of monitoring with ctDNA to standard methods of monitoring response such as repeat imaging.

Table 21. Nonrandomized Study of Signatera Testing to Predict Response to Immunotherapy in Individuals with Solid Tumors - Study Characteristics

Study	Study Population	Study Design and Setting	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Bratman et al (2020)[26]	106 individuals with advanced solid tumors who were enrolled in a Phase II clinical trial of pembrolizumab (NCT02644369)	Prospective, single center	TMB, PD-L1 testing, radiological imaging	Greater or equal to 2 variants detected out of 16	Baseline sample obtained and after every 3 cycles; individuals were followed up for a median of 25 months	Yes

PD-L1: programmed death ligand-1; TMB: tumor mutational burden.

Table 22. Overall Survival by Risk Category in a Nonrandomized Study of Signatera to Monitor Response to Immunotherapy

	Overall Survival
Bratman et al (2020)[26]	
Lower than median ctDNA at baseline	adjusted HR, 0.49 (95% CI, 0.29 to 0.83)
ctDNA increased (n = 45)	13.7 months
ctDNA decreased but still detectable (n = 16)	23.8 months
ctDNA cleared (n = 12)	25.4 months (range 10.8 to 29.5 months)

CI: confidence interval; ctDNA: circulating tumor DNA; HR: hazard ratio.

Table 23. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Bratman et al (2020)[26]	1, 2. Unclear what management changes would be implemented based on test results.		No comparison to standard surveillance methods	3. Clinical validity outcomes not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

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 24. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Bratman et al (2020)[26]						2. Comparison to other tests not reported

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: Tumor-Informed Circulating Tumor DNA Testing with Signatera in Individuals with Solid Tumors Receiving Immunotherapy

Available evidence suggests that changes in ctDNA levels during immune checkpoint inhibitor therapy may correlate with treatment response, progression-free survival, and overall survival. While evidence demonstrating improved clinical outcomes from ctDNA-directed modifications in therapy remains limited, the literature supports the biologic and prognostic relevance of ctDNA monitoring in selected advanced solid tumors. Coverage determinations should be guided by validated intended-use populations and applicable coverage criteria.

Summary of Evidence

Tumor-informed ctDNA testing has demonstrated prognostic value and clinical validity in multiple cancer types and clinical settings, including recurrence monitoring and assessment of therapeutic response. The strength of evidence varies by indication, and studies directly demonstrating improved health outcomes resulting from ctDNA-directed management remain limited. Accordingly, coverage under this policy is restricted to specific intended-use populations, clinical circumstances, and coverage criteria that are consistent with applicable federal and state coverage requirements. Coverage outside these defined circumstances remains unsupported by the available 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

The American Society of Clinical Oncology (ASCO) 2022 guideline update on biomarkers for systemic therapy in metastatic breast cancer (MBC) does not recommend the use of circulating tumor DNA (ctDNA) as a biomarker to monitor the response to therapy (Type of recommendation: informal

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

consensus-based; Quality of evidence: low; Strength of recommendation: moderate). The guidelines also provide the following recommendations:

- "Patients with locally recurrent unresectable or metastatic hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase inhibitor and hormonal therapy should undergo testing for PIK3CA mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine their eligibility for treatment with the phosphatidylinositol 3-kinase inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with PIK3CA mutations (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)."
- "There are insufficient data at present to recommend routine testing for ESR1 mutations to guide therapy for hormone receptor-positive, HER2-negative MBC. Existing data suggest reduced efficacy of aromatase inhibitors (AIs) compared with the selective estrogen receptor degrader fulvestrant in patients who have tumor or ctDNA with ESR1 mutations (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate)."
- "There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)."

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines either do not specifically address tumor-informed ctDNA testing for the cancer types included in this review, or do not provide specific recommendations for use.

The guidelines on colon and rectal cancer state: "Circulating tumor (ctDNA) is a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care and treatment decision-making are not recommended based on ctDNA results. Participation in clinical trials is encouraged."[27,28]

The guideline on breast cancer makes several statements regarding ctDNA assays as noted below. The relevant discussion for these recommendations is pending an update.[29]

- For recurrent/stage IV disease: "Tissue or plasma-based circulating tumor DNA (ctDNA) assays may be used and each of these have benefits and limitations for diagnosis and disease progression. Tissue-based assays have greater sensitivity for some alterations, but ctDNA may reflect tumor heterogeneity more accurately. If one specimen is negative for actionable biomarkers, testing on the alternative specimen can be considered."
- In HR-positive/HER2-negative breast cancer: "Some plasma-based ctDNA assays include a measure of tumor fraction (TF), which can aid in identification of low ctDNA content. Samples with low TF, especially <1%, should be interpreted with caution. Tests have varying sensitivities at low TF. Additional sampling from current tumor sample or future plasma can be considered."
- In HR-positive/HER2-negative breast cancer with ESR1 mutation: "Assess for ESR1 mutations at progression following prior lines of endocrine therapy (ctDNA preferred)."
- In recurrent unresectable (local or regional) or stage IV breast cancer: "Tissue biopsy is more sensitive than ctDNA (liquid biopsy) at detecting homozygous copy loss of PTEN or TMB-H."

The guideline on bladder cancer states the following regarding muscle-invasive bladder cancer/resectable: "The Panel recognizes that some ultrasensitive circulating tumor DNA (ctDNA) assays may have prognostic value after cystectomy. However, to date, the Panel has concluded that there are insufficient data for ctDNA results to determine the course of surveillance or therapy after complete surgical resection." For advanced disease, the guideline notes the following: "Studies have

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

demonstrated that ultrasensitive ctDNA assays may track the response to therapy and progression. However, there are insufficient data that changes in therapy based on ctDNA significantly improve outcomes. Additionally, there are no data to date that ctDNA clearance should be used to make decisions to alter or discontinue therapy."[30]

The guideline on esophageal and esophagogastric junction cancers states: "The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." The detection of mutations/alterations or fusions in DNA shed from esophageal or EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, when limited tissue is available or for patients who have metastatic or advanced esophageal/esophagogastric cancers who are not able to undergo a traditional biopsy, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor."[31]

The guideline on non-small cell lung cancer (NSCLC) states the following in their section on molecular and biomarker analysis:[32]

- "ctDNA testing should not be used in lieu of a histologic tissue diagnosis.
- ctDNA is not routinely recommended in settings other than advanced/metastatic disease. For stages I–III, tissue-based testing is preferred. Metastatic disease confined to the thorax may have a higher yield with tissue-based testing.
- Studies have demonstrated ctDNA and tissue testing to have very high specificity. Both ctDNA and tissue testing have appreciable false-negative rates, supporting the complementarity of these approaches, and data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.
- Limitations of ctDNA testing that can impact interpretation include:
  - Low tumor fraction/ctDNA; some assays include a measure of ctDNA fraction, which can aid in identification of situations in which low ctDNA fraction might suggest compromised sensitivity.
  - The presence of mutations from sites other than the target lesion, most commonly clonal hematopoiesis of indeterminate potential (CHIP) or post-chemotherapy marrow clones. KRAS and TP53 can be seen in either of these circumstances
  - The inherent ability of the assay to detect fusions or other genomic variation of relevance."

U.S. Preventive Services Task Force Recommendations
Not applicable.

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

Ongoing and Unpublished Clinical Trials
Some unpublished trials that might influence this review are listed in Table 25.

Table 25. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06854939	A Prospective Study Investigating the Relationship Between Minimal Residual Disease Detection, Monitoring Frequency, and Prognosis in Non-small Cell Lung Cancer Patients Eligible for Curative Treatment. (MRDSEEKER)	350	Sept 2029

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT06666439	Longitudinal Tumor Burden Quantification Using Circulating Tumor DNA in Metastatic Lobular Breast Cancer (LBC-Monitor)	20	Oct 2026
NCT06663787	Personalized Detection of CtDNA for Patients with HER2-Positive Metastatic Breast Cancer Who Achieved Durable Response by Anti-HER2 Treatment (HER2 CR) (HER2 CR)	50	Dec 2025
NCT05987241	Testing the Role of DNA Released From Tumor Cells Into the Blood in Guiding the Use of Immunotherapy After Surgical Removal of the Bladder, Kidney, Ureter, and Urethra for Urothelial Cancer Treatment, MODERN Study	992	Sept 2030
NCT06450314	Decreasing Treatment for Metastatic HER2-Positive Breast Cancer With Undetectable Cancer Levels in Blood Tests. (HEROES)	170	Dec 2029
NCT05212779	Predicting the Risk of Ovarian Cancer Recurrence Using Circulating Tumor DNA to Assess Residual Disease	45	Dec 2024
NCT04264702[a]	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	2000	Sept 2025
NCT04920032[a]	Proof of Concept Study of ctDNA Guided Change in Treatment for Refractory Minimal Residual Disease in Colon Adenocarcinomas	22	Dec 2026
NCT05081024[a]	Establishing a ctDNA Biomarker to Improve Organ Preserving Strategies in individuals With Rectal Cancer	50	Sep 2025
NCT04929015	Peritoneal Carcinomatosis Leveraging ctDNA Guided Treatment in GI Cancer Study (PERICLES Study)	30	Nov 2024
NCT05058183[a]	Safe De-escalation of Chemotherapy for Stage 1 Breast Cancer	400	Dec 2028
NCT05174169[a]	Colon Adjuvant Chemotherapy Based on Evaluation of Residual Disease	1912	Mar 2030
NCT05965479	Developing ctDNA Guided Adjuvant Therapy for Gastroesophageal Cancer (DECIPHER)	25	Apr 2028
NCT05914792	Longitudinal ctDNA Surveillance for Older Women With ER+ Breast Cancer Who Omit Surgery	40	July 2026
Completed			
NCT04761783[a]	BESPOKE Study of ctDNA Guided Immunotherapy	1539	Mar 2024

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

References

1. Natera. FDA Grants Two New Breakthrough Device Designations for Nateras Signatera MRD Test. March 24, 2021. https://www.natera.com/company/news/fda-grants-two-new-breakthrough-device-designations-for-nateras-signatera-mrd-test/. Accessed July 13, 2025
2. Chidharla A, Rapoport E, Agarwal K, et al. Circulating Tumor DNA as a Minimal Residual Disease Assessment and Recurrence Risk in Patients Undergoing Curative-Intent Resection with or without Adjuvant Chemotherapy in Colorectal Cancer: A Systematic Review and Meta-Analysis. Int J Mol Sci. Jun 16 2023; 24(12). PMID 37373376
3. 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
4. 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
5. Fakih M, Sandhu J, Wang C, et al. Evaluation of Comparative Surveillance Strategies of Circulating Tumor DNA, Imaging, and Carcinoembryonic Antigen Levels in Patients With Resected Colorectal Cancer. JAMA Netw Open. Mar 01 2022; 5(3): e221093. PMID 35258578

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

6. Reinert T, Henriksen TV, Christensen E, et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer. JAMA Oncol. Aug 01 2019; 5(8): 1124-1131. PMID 31070691
7. Henriksen TV, Tarazona N, Frydendahl A, et al. Circulating Tumor DNA in Stage III Colorectal Cancer, beyond Minimal Residual Disease Detection, toward Assessment of Adjuvant Therapy Efficacy and Clinical Behavior of Recurrences. Clin Cancer Res. Feb 01 2022; 28(3): 507-517. PMID 34625408
8. Loupakis F, Sharma S, Derouazi M, et al. Detection of Molecular Residual Disease Using Personalized Circulating Tumor DNA Assay in Patients With Colorectal Cancer Undergoing Resection of Metastases. JCO Precis Oncol. Jul 2021; 5. PMID 34327297
9. Kotani D, Oki E, Nakamura Y, et al. Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer. Nat Med. Jan 2023; 29(1): 127-134. PMID 36646802
10. Nakamura Y, Watanabe J, Akazawa N, et al. ctDNA-based molecular residual disease and survival in resectable colorectal cancer. Nat Med. Nov 2024; 30(11): 3272-3283. PMID 39284954
11. Molinari C, Marisi G, Laliotis G, et al. Assessment of circulating tumor DNA in patients with locally advanced rectal cancer treated with neoadjuvant therapy. Sci Rep. Nov 28 2024; 14(1): 29536. PMID 39604448
12. Slater S, Bryant A, Aresu M, et al. Tissue-Free Liquid Biopsies Combining Genomic and Methylation Signals for Minimal Residual Disease Detection in Patients with Early Colorectal Cancer from the UK TRACC Part B Study. Clin Cancer Res. Aug 15 2024; 30(16): 3459-3469. PMID 38864835
13. 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
14. Coombes RC, Page K, Salari R, et al. Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence. Clin Cancer Res. Jul 15 2019; 25(14): 4255-4263. PMID 30992300
15. Magbanua MJM, Swigart LB, Wu HT, et al. Circulating tumor DNA in neoadjuvant-treated breast cancer reflects response and survival. Ann Oncol. Feb 2021; 32(2): 229-239. PMID 33232761
16. Christensen E, Birkenkamp-Demtröder K, Sethi H, et al. Early Detection of Metastatic Relapse and Monitoring of Therapeutic Efficacy by Ultra-Deep Sequencing of Plasma Cell-Free DNA in Patients With Urothelial Bladder Carcinoma. J Clin Oncol. Jun 20 2019; 37(18): 1547-1557. PMID 31059311
17. Lindskrog SV, Birkenkamp-Demtröder K, Nordentoft I, et al. Circulating Tumor DNA Analysis in Advanced Urothelial Carcinoma: Insights from Biological Analysis and Extended Clinical Follow-up. Clin Cancer Res. Dec 01 2023; 29(23): 4797-4807. PMID 37782315
18. Powles T, Assaf ZJ, Davarpanah N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. Nature. Jul 2021; 595(7867): 432-437. PMID 34135506
19. Szabados B, Kockx M, Assaf ZJ, et al. Final Results of Neoadjuvant Atezolizumab in Cisplatin-ineligible Patients with Muscle-invasive Urothelial Cancer of the Bladder. Eur Urol. Aug 2022; 82(2): 212-222. PMID 35577646
20. Ben-David R, Tillu N, Cumarasamy S, et al. Longitudinal Tumor-informed Circulating Tumor DNA Status Predicts Disease Upstaging and Poor Prognosis for Patients Undergoing Radical Cystectomy. Eur Urol Oncol. Oct 2024; 7(5): 1105-1112. PMID 38521660
21. Sfakianos JP, Basu A, Laliotis G, et al. Association of Tumor-informed Circulating Tumor DNA Detectability Before and After Radical Cystectomy with Disease-free Survival in Patients with Bladder Cancer. Eur Urol Oncol. Apr 2025; 8(2): 306-314. PMID 39013741
22. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature. Apr 26 2017; 545(7655): 446-451. PMID 28445469

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

23. Mukherjee S, Fujiwara Y, Fountzilas C, et al. Trifluridine/Tipiracil and Oxaliplatin as Induction Chemotherapy in Resectable Esophageal and Gastroesophageal Junction Adenocarcinoma: A Phase II Study. Cancer Med. Apr 2025; 14(7): e70835. PMID 40200573
24. Ococks E, Sharma S, Ng AWT, et al. Serial Circulating Tumor DNA Detection Using a Personalized, Tumor-Informed Assay in Esophageal Adenocarcinoma Patients Following Resection. Gastroenterology. Nov 2021; 161(5): 1705-1708.e2. PMID 34284036
25. Valenza C, Saldanha EF, Gong Y, et al. Circulating tumor DNA clearance as a predictive biomarker of pathologic complete response in patients with solid tumors treated with neoadjuvant immune checkpoint inhibitors: a systematic review and meta-analysis. Ann Oncol. Jul 2025; 36(7): 726-736. PMID 40187491
26. Bratman SV, Yang SYC, Iafolla MAJ, et al. Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab. Nat Cancer. Sep 2020; 1(9): 873-881. PMID 35121950
27. National Comprehensive Cancer Network. Guidelines on Colon Cancer. Version 4.2025. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed July 16, 2025.
28. National Comprehensive Cancer Network. Guidelines on Rectal Cancer. Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed July 15, 2025.
29. National Comprehensive Cancer Network. Guidelines on Breast Cancer Version 4.2025. www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 17, 2025.
30. National Comprehensive Cancer Network. Guidelines on Bladder Cancer Version 1.2025. www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 14, 2025
31. National Comprehensive Cancer Network. Guidelines on Esophageal and Esophagogastric Junction Cancers Version 3.2025. www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed July 18, 2025.
32. National Comprehensive Cancer Network. Non-small cell lung cancer. Version 7.2025. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed July 13, 2025.
33. Department of Healthcare Services Provider Manual Guideline. TAR and Non-Standard Benefits List: Codes 0001M thru 0999U. Accessed September 14, 2026, from https://mcweb.apps.prd.cammis.medi-cal.ca.gov/assets/AFECB45B-D2C9-46AD-93A8-5C614B0E79A5/tarandnoncd0.pdf?access_token=6UyVkRRfByXTZEWIh8j8QaYylPyP5ULO
34. Department of Healthcare Services Provider Manual Guideline. Proprietary Laboratory Analyses. Accessed September 14, 2026, from https://mcweb.apps.prd.cammis.medi-cal.ca.gov/assets/F9A3F413-CFE2-472F-85DA-CE264DE44979/proplab.pdf?access_token=6UyVkRRfByXTZEWIh8j8QaYylPyP5ULO
35. Department of Healthcare Services All Plan Letter. All Plan Letter APL 22-010: Cancer Biomarker Testing. Accessed September 14, 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)
  - Activity and functional limitations
  - Family history, if applicable
  - Reason for procedure/test/device, when applicable (e.g., routine screening, suspected recurrence or progression, etc.)
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results, including previous MRD testing
  - Prior treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

  - Specific anticipated change in management based on a positive or negative test result
  - Cancer type, stage, treatment status, and intended use of testing, including recurrence monitoring or therapeutic-response monitoring
  - Performing laboratory and the applicable coverage authority, when coverage depends on laboratory location
  - Other concurrent MRD or molecular surveillance testing, including the clinical reason for any confirmatory or additional testing
- Radiology report(s) and interpretation (i.e., Magnetic Resonance Imaging [MRI], Computed Tomography [CT], Positron Emission Tomography [PET])

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
	0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate ***(Includes Signatera™, Natera, Inc)***
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	Policy statement, state guideline resources, and literature review updated. Definitions of Decision Determinations section updated. Policy title changed from Tumor-Informed Circulating Tumor DNA Testing for Cancer Management 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

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

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)

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

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

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.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Appendix A

Policy Statement	
BEFORE **Red font: Verbiage Removed**	**AFTER** **Blue font: Verbiage Changes/Additions**
Tumor-Informed Circulating Tumor DNA Testing for Cancer Management PHP_2.04.153 **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) • 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 0340U:** A TAR requires documentation of all of the following criteria (1 thru 3): 1. The member is not receiving other molecular testing for minimal residual disease analysis concurrently with this test, and 2. One of the following criteria must be met (a or b), and: a. Monitoring is needed to diagnose cancer recurrence, relapse or progression and member has a diagnosis of one of the following: muscle-invasive bladder cancer, stage II to IV ovarian cancer, stage II to IV breast cancer, non-small cell lung cancer, Merkel cell carcinoma, or stage II to IV colorectal cancer, or	**Tumor-Informed Circulating Tumor DNA Testing (Signatera™) for Cancer Management PHP_2.04.153** **Policy Statement:** I. Tumor-informed circulating tumor DNA testing (i.e., Signatera™) may be considered **medically necessary** when **all** of the following criteria are met:[34] A. The member is not receiving other molecular testing for minimal residual disease analysis concurrently with this test B. Identification of cancer recurrence, relapse, or progression will require a change in management C. Documentation of **one** of the following: 1. Monitoring is needed to diagnose cancer recurrence, relapse, or progression and member has a diagnosis of **one** of the following: a. Merkel cell carcinoma b. Muscle-invasive bladder cancer c. Non-small cell lung cancer d. Stage II to IV breast cancer e. Stage II to IV colorectal cancer f. Stage II to IV ovarian cancer 2. Monitoring of response is needed and member is receiving immune checkpoint inhibitor therapy for a diagnosis of any solid tumor D. Documentation of **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 (i.e. when there is no clinical, radiographical or other biological evidence that tumor cells remain post treatment and the member is no longer being subjected to therapeutic

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Policy Statement	
BEFORE **Red font: Verbiage Removed**	**AFTER** **Blue font: Verbiage Changes/Additions**
b. Monitoring of response is needed and member is receiving immune checkpoint inhibitor therapy for a diagnosis of any solid tumor 3. One of the following criteria must be met (a thru d): a. Member is currently being treated for cancer and the test has not been previously performed for this cancer diagnosis, or b. Member is currently being treated for cancer and there is clinical suspicion that the molecular profile of the member's tumor has changed, or c. Member is not currently being treated for their cancer (i.e. when there is no clinical, radiographical or other biological evidence that tumor cells remain post treatment and the member is no longer being subjected to therapeutic interventions for cancer) and the test has not been performed in the last 12 months, or d. Member is not currently being treated for their cancer and now there is clinical suspicion for tumor recurrence 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.	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). **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

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.

Policy Statement	
BEFORE Red font: Verbiage Removed	**AFTER** Blue font: Verbiage Changes/Additions
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 Manual, please refer to the criteria below. I. Tumor-informed circulating tumor DNA testing (e.g., Signatera) is considered **investigational** for all indications. ***(Per Medi-Cal guidelines and for Medi-Cal members only: tumor-informed circulating tumor DNA testing coverage may be approved based on specific 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 and to MolDX: Minimal Residual Disease Testing for Cancer for reference.	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.

Reproduction without authorization from Blue Shield of California Promise Health Plan is prohibited.