# Tumor-Informed Circulating Tumor DNA Testing for Cancer Management

**Policy #** 00792
Original Effective Date: 07/11/2022
Current Effective Date: 07/11/2022

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically*

## Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers tumor-informed circulating tumor DNA testing (e.g., Signatera) for all indications to be **investigational.***

## Background/Overview

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.

**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.

## FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

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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 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 Breakthrough Device Designations covering new intended uses.

# Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

**Summary of Evidence**

For individuals with colorectal cancer (CRC) who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 3 noncomparative studies (N = 410) and 1 retrospective comparative study (N = 48). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. Nonrandomized studies have reported an association between ctDNA results measured at diagnosis, following surgery, during adjuvant therapy, and during surveillance after curative treatment and prognosis, but these studies are limited by a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations. No study reported management changes made in

response to ctDNA test results. A retrospective observational study found no advantage to surveillance with Signatera compared to standard surveillance conducted according to National Comprehensive Cancer Network (NCCN) guidelines (p>.99 for sensitivity and specificity compared to imaging). There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with breast cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 2 noncomparative studies (N = 133). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. One study evaluated Signatera testing for disease surveillance following primary treatment, and 1 reported the association of test results at different timepoints with response to neoadjuvant chemotherapy. Although the studies found an association of test results with prognosis, the studies are limited by a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with bladder cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 uncontrolled prospective cohort study (N = 68) and 1 retrospective subgroup analysis from a RCT (N = 581). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measure, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The prospective study reported an association between Signatera test results at diagnosis, during chemotherapy treatment, and during surveillance following cystectomy to prognosis. The retrospective analysis reported an association between test results and response to atezolizumab treatment. Study limitations, including a lack of comparison to tests used for the same purpose preclude drawing conclusions about clinical validity and usefulness. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence

is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-small cell lung cancer (NSCLC) who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 subgroup analysis of participants enrolled in a prospective observational study (N = 24). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. 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%). This study's small sample size and lack of a comparator preclude drawing conclusions about clinical validity. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with esophageal cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 noncomparative, retrospective study (N = 17). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measure, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. Patients who were ctDNA-positive before surgery had significantly poorer disease-free survival (DFS) ($p<.042$), with a median DFS of 32.0 months versus 63.0 months in ctDNA-negative preoperative patients. This study was limited by its small sample size and retrospective design. There is no direct evidence that the use of the test improves health outcomes. Due to the study's limitations and lack of additional supporting studies, the evidence is not sufficient to draw conclusions on clinical validity. Additionally, the management pathway for Signatera testing in esophageal cancer has not been clearly defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with solid tumors who receive tumor-informed ctDNA testing with Signatera to monitor response to immunotherapy, the evidence includes a subgroup analysis of individuals enrolled in a nonrandomized trial of pembrolizumab (N = 106). Relevant outcomes are overall

survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The subgroup analysis evaluated Signatera testing to monitor response to immunotherapy in individuals with advanced solid tumors who were enrolled in a Phase II clinical trial of pembrolizumab. Lower-than-median ctDNA levels at baseline were associated with improved overall survival (adjusted hazard ratio [HR] 0.49, 95% CI 0.29 to 0.83) and progression free survival (adjusted HR 0.54, 95% CI 0.34 to 0.85). The study was limited by a small sample size, variability in results across different tumor types, and lack of a comparison to standard methods of monitoring response to treatment. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. Additionally, the management pathway for Signatera testing for monitoring response to immunotherapy has not been clearly defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

# Supplemental Information

### Practice Guidelines and Position Statements

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

### National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines do not specifically address tumor-informed ctDNA testing for any of the cancer types included in this review. The guidelines on colon cancer state: "The panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy."

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

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

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT05212779 | Predicting the Risk of Ovarian Cancer Recurrence Using Circulating Tumor DNA to Assess Residual Disease | 45 | Dec 2024 |
| NCT04761783[a] | BESPOKE Study of ctDNA Guided Immunotherapy | 1539 | May 2025 |
| NCT04264702[a] | BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer | 2000 | Jan 2025 |
| NCT04786600[a] | A Phase II Randomized Therapeutic Optimization Trial for Subjects With Refractory Metastatic Colorectal Cancer Using ctDNA: Rapid 1 Trial | 78 | May 2025 |
| NCT05178576[a] | A Single Arm Phase II Study to Evaluate Treatment With Gevokizumab in individuals With Stage II/III Colon Cancer Who Are ctDNA-positive After Curative Surgery and Adjuvant Chemotherapy | 31 | Nov 2025 |
| NCT04920032[a] | Proof of Concept Study of ctDNA Guided Change in Treatment for Refractory Minimal Residual Disease in Colon Adenocarcinomas | 22 | Jun 2024 |
| NCT05060003[a] | A Phase II Randomized Study of Tiragolumab Plus Atezolizumab Versus Atezolizumab in the Treatment of Stage II Melanoma individuals Who Are ctDNA-positive Following Resection | 244 | Feb 2028 |

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|---|---|---|---|
| NCT05081024[a] | Establishing a ctDNA Biomarker to Improve Organ Preserving Strategies in individuals With Rectal Cancer | 50 | Sep 2024 |
| NCT05067842 | A Pilot Observational Study to Assess Feasibility of Tumor Response Assessment by Circulating Tumor DNA (ctDNA) in individuals With Locally Advanced Esophageal and GE Junction Adenocarcinoma Undergoing Treatment With Total Upfront Chemotherapy and Chemoradiation | 30 | Jan 2028 |
| NCT04670588 | A Prospective Observational Study to Determine the Feasibility of Tumor Response Assessment by Circulating Tumor DNA in individuals With Locally Advanced Rectal Cancer Undergoing Total Neoadjuvant Therapy | 30 | Dec 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 | Nov 2027 |
| NCT05174169[a] | Colon Adjuvant Chemotherapy Based on Evaluation of Residual Disease | 1912 | Jan 2030 |

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

# References

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# Policy History

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06/02/2022 Medical Policy Committee review
06/08/2022 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 06/2023

# Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2021 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|---|---|

| | |
|---|---|
| CPT | 81479 |
| HCPCS | No codes |
| ICD-10 Diagnosis | C15.3-C15.9, C18.0-C18.9, C19, C20, C21.0-C21.8, C34.00-C34.92, C50.011-C50.92, C67.0-C67.9 |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services

at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.