Tumor-Informed and Tumor-Agnostic (Plasma-Only) Circulating Tumor DNA Minimal Residual Disease (MRD) Detection for Cancer Management

Policy # 00792
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Current Effective Date: 12/11/2023

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

Note: Multi-gene Expression Assays for Predicting Recurrence in Colon Cancer is addressed separately in medical policy 00257.

Note: Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer is addressed separately in medical policy 00233.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider tumor-informed circulating tumor DNA (ct-DNA) testing (i.e., Signatera™)‡ to be **eligible for coverage**** when coverage criteria are met.

Patient Selection Criteria

Coverage eligibility for tumor-informed ctDNA testing (i.e., Signatera™)‡ will be considered when **ALL** of the following criteria are met:

- One of the following indications:
    - Individual with stage II or III colorectal cancer after curative treatment (including surgical resection) to inform decisions about adjuvant therapy and monitor for relapse; **OR**
    - Individual with stage IV metastatic colorectal cancer after surgical resection to inform decisions about adjuvant chemotherapy or targeted therapy; **OR**

  - Individual with advanced solid tumor treated with immune-checkpoint inhibitors [e.g., pembrolizumab (Keytruda), ipilimumab (Yervoy), nivilumab (Opdivo)] to monitor treatment response and inform subsequent treatment decisions; **OR**
  - Individual with metastatic breast cancer to diagnose disease progression, recurrence, or relapse following surgery and/or completion of adjuvant therapy; **OR**
  - Individual with localized, muscle invasive bladder cancer (MIBC) after radical cystectomy (node-positive or negative disease) for early detection of metastatic relapse to inform treatment decisions; **AND**
- The test must have a U.S. Food and Drug Administration (FDA) approval, clearance, or breakthrough device designation for use in the individual's cancer; **AND**
- Standard of care monitoring tests do not clearly demonstrate clinical, biological, or radiographical evidence of recurrence or progression of cancer; **AND**
- Frequency of testing does not exceed recommendations for monitoring noted in National Comprehensive Cancer Network (NCCN) guidelines:
  - For colorectal cancer initial ct-DNA test 4 to 6 weeks after surgery (or 2 to 4 weeks after completion of systemic therapy) to inform adjuvant decisions and thereafter every 3 to 6 months for first 2 years (not to exceed total of 4 tests per year), then every 6 to 12 months for the following 3 years (not to exceed total of 2 tests per year) to monitor for relapse
  - For monitoring treatment with immune-checkpoint inhibitors not more frequently than after every 3 cycles (not to exceed total of 4 tests per year for up to 5 years)
  - For breast cancer initial ct-DNA test 4-6 weeks after surgery or completion of adjuvant therapy and thereafter every 6-12 months for 4 years (not to exceed total of 2 tests per year) to monitor for relapse or recurrence (based on clinical study)
  - For MIBC initial ct-DNA test within 4 to 6 weeks after surgery to inform adjuvant decisions and thereafter every 3 to 6 months for first 2 years (not to exceed total of 4 tests per year), then annually for up to 10 years (not to exceed total of 1 test per year) for detection of metastatic relapse; **AND**
- Additional treatment is considered based on National Comprehensive Cancer Network (NCCN) or other nationally established guidelines **; AND**
- No other ctDNA minimal residual disease (MRD) testing was done or is planned (e.g., Guardant Reveal MRD).

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Note:
Initial Signatera testing includes tumor testing (tumor block or FFPE slides from surgery or biopsy) and whole-blood testing (to allow matching of whole exome sequencing of tumor and blood DNA). Initial Signatera tumor testing may not be performed more than once per patient per cancer diagnosis, unless there is clinical evidence of a priori change in genetic content.

Based on review of available data, the Company may consider tumor-agnostic (plasma-only) circulating tumor DNA (ctDNA) testing (i.e., Guardant Reveal™)‡ to be **eligible for coverage**** when coverage criteria are met.

Coverage eligibility for tumor-agnostic (plasma-only) ctDNA testing (i.e., Guardant Reveal™)‡ will be considered when ALL of the following criteria are met:

- Individual with stage II or III colorectal cancer after curative treatment (including surgical resection) to inform decisions about adjuvant therapy and monitor for disease progression, recurrence, or relapse; AND
- Standard of care monitoring tests do not clearly demonstrate clinical, biological, or radiographical evidence of recurrence or progression of cancer; AND
- Frequency of testing does not exceed recommendations for monitoring noted in National Comprehensive Cancer Network (NCCN) guidelines:
    - For colorectal cancer initial ct-DNA test 4 to 6 weeks after surgery (or 2 to 4 weeks after completion of systemic therapy) to inform adjuvant decisions and thereafter every 3 to 6 months for first 2 years (not to exceed total of 4 tests per year), then every 6 to 12 months for the following 3 years (not to exceed total of 2 tests per year) to monitor for relapse; AND
- Additional treatment is considered based on National Comprehensive Cancer Network (NCCN) or other nationally established guidelines; AND
- No other ctDNA minimal residual disease (MRD) testing was done or is planned (e.g., Signatera).

When 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 other uses of tumor-informed and tumor-agnostic ctDNA minimal residual disease detection to be **investigational***, including but not limited to using other tests, when coverage criteria noted above are not met, and for individuals with **any** of the following conditions:

- Pregnancy
- Active hematological or other concurrent malignancy
- History of allogeneic bone marrow/ stem cell transplant
- History of blood transfusions within three months of testing.

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.

Tumor-informed assays require knowledge of the tumor genomic profile of the patient, based on whole-exome or targeted sequencing of the primary tumor (e.g., SignateraTM, SafeSeqS). These assays are personalized and designed for each patient to detect patient-specific genomic alterations via the targeted sequencing of the plasma DNA.

Tumor-informed assays have several advantages, including a high level of analytical sensitivity down to a variant allele frequency of 0.01% and a low probability of false-positive results secondary to clonal hematopoiesis of indeterminate potential (CHIP). However, tumor-informed assays require a longer turnaround time and incur additional costs for tumor sequencing. Tumor sequencing may not capture all MRD relevant alterations due to intratumoral heterogeneity, and may not detect emerging mutations arising from treatment-related changes.

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.

Tumor-agnostic assays are broad panel-based sequencing assays performed without prior knowledge of the patient's tumor mutational profile and designed to look for genomic alterations and aberrant DNA methylation patterns known to occur in a given tumor type (e.g., Guardant REVEAL).

Tumor-agnostic assays have several advantages that include fast turnaround time, logistical simplicity, ability to perform the test when tumor tissue is not available, and the potential of detecting MRD even after clonal evolution of the micrometastatic tumor cells.

Guardant Reveal
Guardant Reveal is the first liquid-only test to detect minimal residual disease in colorectal cancer and first MRD assay to leverage ctDNA methylation analysis in addition to genomic alterations. Aberrant DNA methylation is often an early step in the carcinogenesis of CRC and was shown to improve sensitivity of the assay.

One of the primary concerns with plasma-only assays is that specificity and sensitivity might be limited if the assay is not guided by specific alterations identified in the resected tumor. The loss of specificity is a critical concern, as noncancer-derived mutations are frequently present in the blood which could lead to false positives. Further analysis of larger cohorts is needed as high specificity of MRD detection will remain critical if MRD assays are to be used to select individuals for additional or more intensive therapy. This would avoid situations in which individuals who are cured are erroneously identified as MRD positive and subjected to potentially unnecessary therapy.

The Guardant Reveal test is currently being utilized in several prospective clinical trials to assess the impact of ctDNA-guided adjuvant therapy. Ongoing prospective interventional studies will further evaluate the performance of this assay for MRD detection and to help guide treatment decisions.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 individuals 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. The two designations will allow to develop Signatera, via phase III clinical trials, as a companion diagnostic to two different cancer therapies.

The Guardant Reveal test was developed, and its performance characteristics determined, by the Guardant Health Clinical Laboratory in Redwood City, CA, which is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. Guardant Reveal refers to Guardant Reveal Laboratory Developed Test (LDT). This test has not been cleared or approved by the US FDA.

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.

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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 colorectal cancer (CRC) who receive tumor-agnostic ctDNA testing with Guardant Reveal, the evidence includes single-institution prospective, observational study of 103 individuals with stages I-IV colorectal cancer treated with curative intent between August 2016 and May 2019. Of 103 individuals, 84 had evaluable plasma draw after completion of definitive therapy (surgery only in 39 or adjuvant therapy in 45 individuals). Using “landmark” plasma draw 1-month after definitive therapy and > 1 year follow-up, 15 individuals had detectable ctDNA and all 15 had cancer recurrence with reported positive predictive value 100% (HR 11.28, p<0.0001). Of 49 individuals without detectable ctDNA at the landmark timepoint, 12 (24.5%) recurred. Landmark recurrence sensitivity and specificity were 55.6% and 100%. Integrating epigenomic signatures (DNA methylation) increased sensitivity by 25-30% versus genomic tumor alterations alone. CEA antigen levels did not predict recurrence (HR, 1.84, p=0.18, PPV 53.9%). Study limitations include modest sample size, a more focused study and analysis is needed to understand performance in specific patient populations, and study did not systematically incorporate serial longitudinal draws for all individuals. Although incorporation of longitudinal and surveillance draws available for some individuals did improve overall sensitivity from 55.6% to 69% and 91%, the lack of systematic

longitudinal and surveillance draws across all individuals precluded a comprehensive assessment. Guardant Reveal test is currently being utilized in several prospective clinical trials to assess the impact of ctDNA-guided adjuvant therapy. Ongoing interventional studies will further evaluate the performance of this assay for MRD detection and to help guide treatment decisions. 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. Individuals 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 individuals. 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.

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 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 guideline on colon cancer states: "There is currently insufficient evidence to recommend use of circulating tumor DNA (ctDNA) assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results. Participation in clinical trials is encouraged."

The guideline on breast cancer states that for recurrent/stage IV disease: "Tissue or plasma-based circulating tumor DNA (ctDNA) assays may be used. Tissue-based assays have greater sensitivity, but ctDNA may reflect tumor heterogeneity more accurately." Additionally, "For HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or liquid biopsy to

identify candidates for alpelisib plus fulvestrant. PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended." It is also noted that the clinical use of Circulating Tumor Cells (CTC) or circulating DNA (ctDNA) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer (v. 4.2023) for disease assessment and monitoring. The relevant discussion for these recommendations is pending an update.

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." Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced esophageal/esophagogastric cancers who may be unable to undergo a traditional biopsy or for disease progression monitoring, 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 mutations or amplifications."

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

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

Medicare Local Coverage
"The reviewed evidence supports that minimal residual disease (MRD) testing can be used to accurately predict disease recurrence or progression before clinical or radiographical evidence is evident (establishing molecular recurrence) and performs better than other stablished methods for disease surveillance such as serial CEA monitoring, physical exams, imaging or flow cytometry. Although this is a logical progression of our understanding of the development and evolution of

cancer (that tumor cells grow and shed DNA at proportional levels until such a time there is macroscopic disease in organs or bone marrow), the evidence presented above clearly establishes that MRD testing can demonstrate acceptable clinical validity in the determination of disease recurrence; a condition whose identification has pre-established utility as it is an event that in the proper clinical context requires altering or modifying patient management. Current medical practice, including as defined in the NCCN guidelines, clearly advocate for changing or re-establishing treatment when such a diagnosis is rendered. As such, determining molecular recurrence before there is clinical or radiographical evidence of it is likely to further improve patient outcomes and is consistent with current guidelines that advocate for early detection of and treatment for recurrence. Furthermore, additional uses of MRD have been established, such as for monitoring treatment response, although it is based on the same principle. The studies described above again demonstrate the clinical validity of molecular progression as predictive of failure to respond to treatment and demonstrate futility in continued therapy. The utility of such testing in maintenance therapy monitoring to improve patient outcomes is therefore similarly inherent; preclusion of potentially hazardous compounds that are not likely to have clinical benefit and prevention of adverse events have demonstrated improved patient outcomes.

This remains a rapidly evolving field, and we anticipate that new evidence may emerge either showing limitations of the clinical utility underlying MRD testing or additional strengths and new applications. Additionally, this coverage decision is based heavily on paradigm for care which was not developed for MRD testing. In summary, we anticipate future revisions to this coverage decision as the science and standard of care evolves, which may further limit or expand coverage for MRD testing."

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	Feb 2026
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	Feb 2027
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	Nov 2028
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	30	Jan 2028

	Advanced Esophageal and GE Junction Adenocarcinoma Undergoing Treatment With Total Upfront Chemotherapy and Chemoradiation		
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	Dec 2028
NCT05174169[a]	Colon Adjuvant Chemotherapy Based on Evaluation of Residual Disease	1912	Mar 2030
NCT05757843	Using Circulating Tumor DNA to Personalize Duration of Consolidation Durvalumab	56	Dec 2025
NCT05965479	Developing ctDNA Guided Adjuvant Therapy for Gastrooesophageal Cancer (DECIPHER)	25	Oct 2027
NCT05914792	Longitudinal ctDNA Surveillance for Older Women With ER+ Breast Cancer Who Omit Surgery	40	Dec 2028

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

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Policy History

Original Effective Date: 07/11/2022
Current Effective Date: 12/11/2023

06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. New policy.
09/20/2022	Coding update
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Coverage changed from investigational to eligible for coverage with criteria due to senate bill update.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. Added coverage for Guardant Reveal. Title changed from Tumor-Informed Circulating Tumor DNA Testing for Cancer Management to Tumor-Informed and Tumor-Agnostic (Plasma-Only) Circulating Tumor DNA Minimal Residual Disease (MRD) Detection for Cancer Management.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Added “Individual with metastatic breast cancer to diagnose disease progression, recurrence, or relapse following surgery and/or completion of adjuvant therapy” and “For breast cancer initial ct-DNA test 4-6 weeks after surgery or completion of adjuvant therapy and thereafter every 6-12 months for 4 years (not to exceed total of 2 tests per year) to monitor for relapse or recurrence (based on clinical study)” to the coverage criteria section. Supplemental information and references updated.

Next Scheduled Review Date: 11/2024

Tumor-Informed and Tumor-Agnostic (Plasma-Only) Circulating Tumor DNA Minimal Residual Disease (MRD) Detection for Cancer Management

Policy # 00792
Original Effective Date: 07/11/2022
Current Effective Date: 12/11/2023

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 2022 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	0340U, 81479 Add code effective 12/01/2023: 81445
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

*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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.