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: 07/10/2023

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™) 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
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: 07/10/2023

- Individual with advanced solid tumor treated with immune-checkpoint inhibitors [e.g., pembrolizumab (Keytruda), ipilimumab (Yervoy), nivolumab (Opdivo)] to monitor treatment response and inform subsequent treatment decisions; 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 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).

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.

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
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: 07/10/2023

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

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
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: 07/10/2023

- 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-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: 07/10/2023

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.

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:
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: 07/10/2023

- 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.

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,
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: 07/10/2023

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
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: 07/10/2023

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.
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: 07/10/2023

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.
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**

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.
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: 07/10/2023

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 established 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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT05212779</td>
<td>Predicting the Risk of Ovarian Cancer Recurrence Using Circulating Tumor DNA to Assess Residual Disease</td>
<td>45</td>
<td>Dec 2024</td>
</tr>
<tr>
<td>NCT04761783</td>
<td>BESPOKE Study of ctDNA Guided Immunotherapy</td>
<td>1539</td>
<td>May 2025</td>
</tr>
<tr>
<td>NCT04264702</td>
<td>BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer</td>
<td>2000</td>
<td>Jan 2025</td>
</tr>
<tr>
<td>NCT04786600</td>
<td>A Phase II Randomized Therapeutic Optimization Trial for Subjects With Refractory Metastatic Colorectal Cancer Using ctDNA: Rapid 1 Trial</td>
<td>78</td>
<td>May 2025</td>
</tr>
<tr>
<td>NCT05178576</td>
<td>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</td>
<td>31</td>
<td>Nov 2025</td>
</tr>
<tr>
<td>NCT04920032</td>
<td>Proof of Concept Study of ctDNA Guided Change in Treatment for Refractory Minimal Residual Disease in Colon Adenocarcinomas</td>
<td>22</td>
<td>Jun 2024</td>
</tr>
<tr>
<td>NCT05060003</td>
<td>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</td>
<td>244</td>
<td>Feb 2028</td>
</tr>
<tr>
<td>NCT05081024</td>
<td>Establishing a ctDNA Biomarker to Improve Organ Preserving Strategies in individuals With Rectal Cancer</td>
<td>50</td>
<td>Sep 2024</td>
</tr>
</tbody>
</table>
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: 07/10/2023

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Study Description</th>
<th>NCT</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT05067842</td>
<td>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</td>
<td>30</td>
<td>Jan 2028</td>
</tr>
<tr>
<td>NCT04670588</td>
<td>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</td>
<td>30</td>
<td>Dec 2025</td>
</tr>
<tr>
<td>NCT04929015</td>
<td>Peritoneal Carcinomatosis Leveraging ctDNA Guided Treatment in GI Cancer Study (PERICLES Study)</td>
<td>30</td>
<td>Nov 2024</td>
</tr>
<tr>
<td>NCT05058183a</td>
<td>Safe De-escalation of Chemotherapy for Stage 1 Breast Cancer</td>
<td>400</td>
<td>Nov 2027</td>
</tr>
<tr>
<td>NCT05174169a</td>
<td>Colon Adjuvant Chemotherapy Based on Evaluation of Residual Disease</td>
<td>1912</td>
<td>Jan 2030</td>
</tr>
<tr>
<td>NCT04068103</td>
<td>Circulating Tumor DNA Testing in Predicting Treatment for Individuals With Stage IIA Colon Cancer After Surgery</td>
<td>1408</td>
<td>April 30, 2027</td>
</tr>
<tr>
<td>NCT03803553</td>
<td>Identification and Treatment Of Micrometastatic Disease in Stage III Colon Cancer</td>
<td>500</td>
<td>February 1, 2023</td>
</tr>
<tr>
<td>NCT04259944</td>
<td>The PEGASUS trial: Post-surgical liquid biopsy-guided treatment of stage III and high-risk stage II colon cancer individuals.</td>
<td>140</td>
<td>October 15, 2024</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.  
* Denotes industry-sponsored or cosponsored trial.
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: 07/10/2023

References
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: 07/10/2023

15. Minimal Residual Disease Detection using a Plasma-only Circulating Tumor DNA Assay in Patients with Colorectal Cancer | Clinical Cancer Research | American Association for Cancer Research (aacrjournals.org)
16. Using Circulating Tumor DNA in Colorectal Cancer: Current and Evolving Practices Midhun Malla, MD, MS1; Jonathan M. Loree, MD, MS2; Pashtoon Murtaza Kasi, MD, MS3; and Aparna Raj Parikh, MD4. July 2022
17. Minimal Residual Disease Detection using a Plasma-only Circulating Tumor DNA Assay in Patients with Colorectal Cancer | Clinical Cancer Research | American Association for Cancer Research (aacrjournals.org)

**Policy History**
Original Effective Date: 07/11/2022
Current Effective Date: 07/10/2023
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

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
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: 07/10/2023


Next Scheduled Review Date: 06/2024

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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.
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:  07/10/2023

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

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0340U, 81479</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related Diagnoses</td>
</tr>
</tbody>
</table>

*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

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
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:  07/10/2023

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.