Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Policy #  00497
Original Effective Date:  07/20/2016
Current Effective Date:  08/14/2023

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

Note:  Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer is addressed separately in medical policy 00257.

Note:  Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer is addressed separately in medical policy 00272.

Note:  Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing is addressed separately in medical policy 00382.

Note:  Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management is addressed separately in medical policy 00403.

Note:  Molecular Panel Testing of Cancers to Identify Targeted Therapies is addressed separately in medical policy 00423.

Note:  Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy) is addressed separately in medical policy 00452.

Note:  Miscellaneous Genetic and Molecular Diagnostic Tests is addressed separately in medical policy 00577.

Note:  Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer is addressed separately in medical policy 00731.
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Note: Tumor-Informed Circulating Tumor DNA Testing for Cancer Management is addressed separately in medical policy 00792.

Note: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer is addressed separately in medical policy 00809.

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 the use of circulating tumor deoxyribonucleic acid DNA (ctDNA) panel testing (liquid biopsy panel testing) when coverage criteria are met to be eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for liquid biopsy panel testing will be considered when ALL of the following criteria are met:

- Individual was diagnosed with stage IIIB or IV non-small cell lung cancer (use medical policy 00452), metastatic castrate-resistant prostate cancer (use medical policy 00809), or progressive advanced or metastatic breast cancer (use medical policy 00731); AND
- Individual has not been previously tested using the same liquid biopsy panel, unless a new primary cancer diagnosis is made, and further cancer treatment is being considered; AND
- Liquid biopsy panel test must have a U.S. Food and Drug Administration (FDA) approved or cleared indication as an in vitro companion diagnostic for use in the individual’s cancer, i.e., FoundationOne Liquid CDx and Guardant360 CDx (see Policy Guidelines section); AND
- Tissue-based comprehensive somatic genomic profiling test is not feasible (i.e., quantity not sufficient for tissue-based profiling or invasive biopsy is medically contraindicated); AND
- Treatment is considered with genomic biomarker-linked therapies approved by regulatory agencies for individual’s cancer; AND

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- Follow-up tissue-based genotyping will be considered if no genetic alteration is detected by plasma genotyping, or if ctDNA is insufficient (not detected).

Note: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing (NGS), single available procedure code for the multi-gene panel test is to be utilized.

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 the use of circulating tumor deoxyribonucleic acid DNA (ctDNA) testing when patient selection criteria are not met to be investigational.*

Based on review of available data, the Company considers concurrent ctDNA (liquid biopsy) testing in addition to tumor based genomic profiling to be investigational.*

Based on review of available data, the Company considers the use of circulating tumor cells (CTCs) and/or ribonucleoprotein complexes to be investigational.*

Based on review of available data, the Company considers the use of urinary liquid biopsy (i.e., urine cell-free DNA or UcfDNA) and liquid biopsy testing on cerebrospinal fluid (CSF) samples for the screening, detection, diagnosis or monitoring of cancer to be investigational.*

Policy Guidelines
Liquid biopsies are becoming more popular as they provide an opportunity to genotype in a less invasive and expensive manner. However, the low sensitivity (between 60-80%) and higher number of false negative cases compared to traditional tissue biopsy are limitations associated with liquid biopsies.

Additional advanced or metastatic solid tumors not listed above may be considered if the test used is FDA-cleared or approved in vitro companion diagnostic for individual’s cancer or requested liquid
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biopsy testing is supported by most recent NCCN guidelines with category of evidence and consensus recommendation 2A or higher.

The link to the most recent list of FDA-cleared or approved in vitro companion diagnostics: List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) | FDA

Panel testing represents simultaneous testing of 5 or more genes.

This policy does not address the use of blood-based testing for "driver mutations" to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for detection or risk assessment of prostate cancer, the use of AR-V7 circulating tumor cells for metastatic prostate cancer.

**Background/Overview**

**Liquid Biopsy**

Liquid biopsy refers to the analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as methods of noninvasively characterizing tumors and tumor genome from the peripheral blood.

**Circulating Tumor DNA**

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

**Circulating Tumor Cells**

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs. Most assays detect CTCs through the use of surface epithelial
markers such as EpCAM and cytokeratins. The primary reason for detecting CTCs is prognostic, through quantification of circulating levels.

**Detecting Circulating Tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs)**

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

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

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

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

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

**FDA or Other Governmental Regulatory Approval**

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

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical
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Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

There are currently 2 FDA-cleared companion diagnostic liquid biopsy panel tests: FoundationOne® Liquid CDx (F1LCDx) and Guardant360® CDx.

For the most current list of FDA-cleared or approved companion diagnostic tests, go to link: List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) | FDA

F1LCDx is FDA-approved companion diagnostic used to identify patients who may benefit from treatment with select targeted therapies in accordance with the approved therapeutic product labeling, i.e., for patients with metastatic non-small cell lung cancer, metastatic castrate resistant prostate cancer, and progressive advanced or metastatic breast cancer.

As of June 2022, BRCA testing of tumor tissue (or cf-DNA) is no longer needed to qualify for treatment of ovarian cancer with Rubraca (rucaparib, PARP inhibitor). Rubraca is indicated for the maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

F1LCDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage; 75 genes are captured with increased sensitivity and have complete exonic (coding) coverage. The test also detects tumor fraction and the genomic signatures blood mutational burden (bTMB) and microsatellite instability high (MSI-H) status.

Guardant360® CDx is a next generation sequencing-based FDA-approved in vitro diagnostic device for detection of single nucleotide variants (SNVs), insertions and deletions (indels), copy number amplifications (CNAs), and fusions within 55 genes frequently mutated in cancer, using circulating cell-free DNA (cfDNA) from the plasma of peripheral whole blood.

Guardant360 CDx is intended to identify patients who may benefit from treatment with select targeted therapies in accordance with the approved therapeutic product labeling, i.e., in patients with
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locally advanced (stage IIIB) or metastatic non-small cell lung cancer considering treatment with osimertinib/Tagrisso, amivantamb/Rybrevant, or sotorasib (Lumakras).

Patients who test negative on liquid biopsy should be referred for (or "reflexed" to) routine biopsy with tissue testing for FDA-approved variants. Testing for T790M using plasma specimens is most appropriate for consideration in patients for whom a tumor biopsy cannot be obtained, as the efficacy of osimertinib has not been established in T790M plasma-positive, tissue-negative or unknown patient populations.

Liquid biopsy for NSCLC is further addressed in medical policy 00452 Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small Cell Lung Cancer.


Table 1. Companion Diagnostic Indications for F1 Liquid CDx

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Biomarker(s) Detected</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-small cell lung cancer (NSCLC)- plasma</td>
<td><strong>EGFR (HER1) exon 19 deletion or exon 21 L858R substitution mutation</strong>&lt;br&gt;<strong>EGFR (HER1) exon 20 insertion mutations</strong></td>
<td>Iressa®† (gefitinib), Tagrisso®‡ (osimertinib), or Tarceva®‡ (erlotinib) Exkivity (mobocertinib)</td>
</tr>
<tr>
<td>MET single nucleotide variants and indels that lead to MET exon 14 skipping</td>
<td></td>
<td>Tabrecta (capmatinib)</td>
</tr>
<tr>
<td>ALK rearrangements</td>
<td></td>
<td>Alecensa (alectinib)</td>
</tr>
<tr>
<td>ROS1 fusions</td>
<td></td>
<td>Rozlytrek (entrectinib)</td>
</tr>
<tr>
<td><strong>BRCA1 and BRCA2 alterations</strong></td>
<td></td>
<td>Rubraca (rucaparib)</td>
</tr>
</tbody>
</table>
Metastatic Castrate Resistant Prostate Cancer (mCRPC) - plasma

Breast cancer - plasma

Ovarian cancer - plasma

BRCA1, BRCA2, and ATM alterations

Lynparza (olaparib)


Piqray (alpelisib)

BRCA1 and BRCA2 alterations

Rubraca (rucaparib) - see June 2022 FDA label update (BRCA testing no longer required)

<table>
<thead>
<tr>
<th>Tumor Type</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Non-small cell lung cancer (NSCLC) - plasma</td>
<td>EGFR (HER1) exon 19 deletion or EGFR exon 21 L858R, and T790M</td>
<td>Tagrisso®‡ (Osimertinib)</td>
</tr>
<tr>
<td></td>
<td>EGFR (HER1) exon 20 insertions</td>
<td>Rybrevant (amivantamab)</td>
</tr>
<tr>
<td></td>
<td>KRAS G12C</td>
<td>Lumakras (sotorasib)</td>
</tr>
<tr>
<td></td>
<td>ERBB2 activating mutations (SNVs and exon 20 insertions)</td>
<td>Enhertu (fam-trastuzumab deruxtecan-nxki)</td>
</tr>
</tbody>
</table>
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| Breast cancer- plasma | ESR1 missense mutations between codons 310 and 547 | Orserdu (elacestrant) |

**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.

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

**Summary of Evidence**
For individuals who have advanced cancer who receive testing of ctDNA to select targeted treatment, the evidence includes observational studies. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking for the indications covered in this review. The clinical validity of FoundationOne Liquid compared to tissue biopsy with FoundationOne comprehensive genetic profiling was evaluated in 4 industry-sponsored observational studies. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether variant analysis of ctDNA can replace variant analysis of tissue. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
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For individuals who have advanced cancer who receive testing of CTCs to select targeted treatment, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs can replace variant analysis of tissue. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cancer who receive testing of ctDNA to monitor treatment response, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to monitor treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cancer who receive testing of CTCs to monitor treatment response, the evidence includes a randomized controlled trial, observational studies, and systematic reviews of observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. The available randomized controlled trial found no effect on OS when patients with persistently increased CTC levels after first-line chemotherapy were switched to alternative cytotoxic therapy. Other studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to monitor treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have received curative treatment for cancer who receive testing of ctDNA to predict the risk of relapse, the evidence includes observational studies. Relevant outcomes are OS,
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Disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to predict relapse response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have received curative treatment for cancer who receive testing of CTCs to predict the risk of relapse, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to predict relapse response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at high-risk for cancer who receive testing of ctDNA to screen for cancer, no evidence was identified. Relevant outcomes are OS, disease-specific survival, test accuracy, and test validity. Published data on clinical validity and clinical utility are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at high-risk for cancer who receive testing of CTCs to screen for cancer, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy, and test validity. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The 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 (NCCN) states 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 (NCCN, 2022b) for disease assessment and monitoring.” However, assessment of the PIK3CA mutation may be performed through liquid biopsy if the tumor is HR-positive, HER2 negative, and if therapy with alpelisib plus fulvestrant is being considered (NCCN, 2022b).

For individuals with castrate-resistant metastatic prostate cancer, the NCCN specifies the use of circulating DNA for rucaparib treatment, stating that “the preferred method of selecting patients for rucaparib treatment is somatic analysis of BRCA1 and BRCA2 using a circulating tumor DNA sample” (NCCN, 2022a).

With regards to circulating tumor DNA (ctDNA) in colon cancer, the NCCN “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” (NCCN, 2021d).

NCCN guidelines for small cell lung cancer do not address use of CTCs or ctDNA for patient management (NCCN, 2021k).

For neuroendocrine tumors, NCCN notes that CTCs have been studied as prognostic markers, but state that more research is required. There is no single biomarker available that is satisfactory as a diagnostic, prognostic, or predictive marker (NCCN, 2021g).
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For pancreatic adenocarcinomas, the NCCN acknowledges that circulating cell-free DNA is being investigated as a biomarker for screening. The NCCN also notes that if tumor tissue is not available, cell-free DNA testing may be considered (NCCN, 2021i).

The NCCN does not comment on the usage of liquid biopsies, ctDNA, or CTCs for testing for hepatobiliary cancers (NCCN, 2021f).

For acute myeloid leukemia, the NCCN notes that “morphologically detectable,” circulating leukemic blasts from peripheral blood may be used to detect molecular abnormalities (NCCN, 2021a).

For bladder cancer, the NCCN mentions RT-PCR testing for FGFR2/3 gene alterations but does not specify whether this can be done through a liquid biopsy or cell-free DNA. The only comment made is that the laboratory should be CLIA-approved (NCCN, 2021b).

The NCCN guidelines for melanoma (v.3.2020) reference papers on circulating tumor DNA in the discussion of molecular characteristics of metastatic disease with the statement, ‘A number of tests have been developed for detecting BRAF and KIT mutations common in metastatic melanoma. The sensitivity and accuracy of these tests vary, and improved assays are in development.’

American Society of Clinical Oncology (ASCO)
It is noted in ASCO 2022 Provisional Clinical Opinion (PCO) that “in patients without tissue-based genomic test results, treatment may be based on actionable alterations identified in cfDNA. Genomic testing on cfDNA is most helpful when genomic testing is indicated, archival tissue is unavailable, and new tumor biopsies are not feasible. cfDNA is more commonly reported with mutant allelic fractions of individual mutations, compared with solid tumor panels, thus facilitating assessment of clonality. cfDNA testing has the additional advantage of capturing tumor heterogeneity because of pooling in the blood of DNA from throughout the tumor or from multiple tumors and is a promising tool for assessing genomic mechanisms of acquired resistance. Furthermore, cfDNA levels themselves may be prognostic, and early cfDNA dynamics may serve as an early predictor of therapy response or resistance. Ongoing studies are expected to better delineate the clinical utility of serial liquid biopsies. However, longitudinal monitoring of mutant allele fractions may inform therapeutic efficacy and identify potential resistance conferring mutations.”
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Liquid biopsy testing of urine or cerebrospinal fluid samples is not mentioned in 2022 ASCO POC.

**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.

**Ongoing and Unpublished Clinical Trials**
Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT02889978(^a)</td>
<td>The Circulating Cell-free Genome Atlas Study</td>
<td>15254</td>
<td>Mar 2024</td>
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<tr>
<td>NCT04168931</td>
<td>Efficacy of Adding Trastuzumab to Standard Chemotherapy in Patients With Advanced HER2-negative Gastric Cancer and HER2 Positive Expression in Circulating Tumor Cells</td>
<td>85</td>
<td>Jan 2025</td>
</tr>
<tr>
<td>NCT03957564</td>
<td>Liquid Biopsy in Monitoring the Neoadjuvant Chemotherapy and Operation in Patients With Resectable or Locally Advanced Gastric or Gastro-oesophageal Junction Cancer</td>
<td>40</td>
<td>May 2024</td>
</tr>
</tbody>
</table>

\(^a\)Denotes industry sponsored or co-sponsored trial.

NCT: national clinical trial.
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References

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Current Effective Date: 08/14/2023
06/30/2016    Medical Policy Committee review
07/20/2016    Medical Policy Implementation Committee approval. New Policy.
01/01/2017    Coding update: Removing ICD-9 Diagnosis codes
07/06/2017    Medical Policy Committee review
07/19/2017    Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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07/05/2018 Medical Policy Committee review
07/03/2019 Medical Policy Committee review
07/18/2019 Medical Policy Implementation Committee approval. Clarifying edit to the INV statement, added ‘reviewed herein’ to stress that other indications are reviewed in separate policies. Coverage eligibility unchanged.
07/02/2020 Medical Policy Committee review
07/08/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2021 Medical Policy Committee review
07/14/2021 Medical Policy Implementation Committee approval. Added Guardant 360 to FDA section. Liquid biopsy to select targeted treatment for breast cancer was removed from the Policy Guidelines. Coverage eligibility unchanged.
07/07/2022 Medical Policy Committee review
07/13/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/01/2022 Medical Policy Committee review
09/14/2022 Medical Policy Implementation Committee approval. Extensive revisions made to the coverage section and throughout the policy.
12/07/2022 Coding update
07/06/2023 Medical Policy Committee review
07/12/2023 Medical Policy Implementation Committee approval. Added a reference to see medical policy 00809 to the Patient Selection Criteria bullet for an individual diagnosed with metastatic castrate-resistant prostate cancer. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2024

Coding
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descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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

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<th>Code Type</th>
<th>Code</th>
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<td></td>
<td>Delete codes effective 1/1/2023: 0177U, 0229U</td>
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<td></td>
<td>Add code effective 1/1/2023: 0356U, 81449, 81451, 81456</td>
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<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>C61, D400</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

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Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Policy #  00497
Original Effective Date:  07/20/2016
Current Effective Date:  08/14/2023

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.
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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.