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

Policy # 00497
Original Effective Date: 07/20/2016
Current Effective Date: 01/01/2024

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.

Note: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer is addressed separately in medical policy 00810.

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 metastatic or advanced (stage III or IV) cancer; **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

Blood-based testing (liquid biopsy) to select targeted treatment and immunotherapy for breast cancer (MP 00731), colorectal cancer (MP 00233), melanoma or glioma (MP 00320), non-small cell lung cancer (MP 00452), ovarian cancer (MP 00810), prostate cancer (MP 00809), and tumor-informed or tumor-agnostic circulating tumor DNA minimal residual disease detection for cancer management (MP 00792) are also addressed in respective medical policies.

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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 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.

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

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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.

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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 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.

Certain liquid biopsy-based assays have been cleared or approved by the FDA as companion diagnostic tests (Table 1). These indication are addressed in other evidence opinions and are listed here for information only.

Table 1. FDA Cleared or Approved Liquid Biopsy Companion Diagnostic Tests

Diagnostic Name (Manufacturer)	Indication	Biomarker	Drug Trade Name (Generic)
Agilent Resolution ctDx FIRST assay	NSCLC	KRAS	Krazati (adagrasib)
cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	NSCLC	*EGFR* (*HER1*)	Tagrisso (osimertinib)
	NSCLC	*EGFR* (*HER1*)	Iressa (gefitinib)
	NSCLC	*EGFR* (*HER1*)	Tarceva (erlotinib)
	NSCLC	*EGFR* (*HER1*)	Gilotrif (afatinib)
FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NSCLC	*EGFR (HER1)*	Exkivity (mobocertinib)
	NSCLC	*EGFR (HER1)*	Iressa (gefitinib)

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	NSCLC	*EGFR (HER1)*	Tagrisso (osimertinib)
	NSCLC	*EGFR (HER1)*	Tarceva (erlotinib)
	NSCLC	*MET*	Tabrecta (capmatinib)
	NSCLC	*ROS1*	Rozlytrek (entrectinib)
	NSCLC	ALK	Alecensa (alectinib)
	Ovarian Cancer	*BRCA1* and *BRCA2*	Rubraca (rucaparib)
	Solid Tumors	*ROS1*	Rozlytrek (entrectinib)
	Breast Cancer	*PIK3CA*	Piqray (alpelisib)
	Metastatic Castrate Resistant Prostate Cancer	*BRCA1*, *BRCA2* and *ATM*	Lynparza (olaparib)
	Metastatic Castrate Resistant Prostate Cancer	*BRCA1 and BRCA2*	Rubraca (rucaparib)
Guardant360 CDx (Guardant Health, Inc.)	NSCLC	*EGFR* (*HER1*)	Tagrisso (osimertinib)
	NSCLC	*EGFR* (*HER1*)	Rybrevant (amivantamb)
	NSCLC	*KRAS*	Lumakras (sotorasib)

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	NSCLC	ERBB2	ENHERTU (fam-trastuzumab deruxtecan-nxki)
	Breast Cancer	*ESR1* *ERB2*	Orserdu (elacestrant) ENHERTU (fam-trastuzumab deruxtecan-nxki)
Therascreen PIK3CA RGQ PCR Kit (QIAGEN GmbH)	Breast Cancer	*PIK3CA*	Piqray (alpelisib)

Source: FDA (2023)
FDA: US Food and Drug Administration; NSCLC: non-small cell lung cancer

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

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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.

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

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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, 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

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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

There is no general National Comprehensive Cancer Network (NCCN) guideline on the use of liquid biopsy. Refer to treatment recommendations by cancer type for specific recommendations (and cancer specific BCBSLA medical policies for breast cancer, prostate cancer, colon cancer, non-small cell lung cancer, melanoma, and glioma).

NCCN guidelines for small cell lung cancer do not address use of CTCs or ctDNA for patient management (NCCN, 2.2024).

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, 1.2023).

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 can be considered (NCCN, 2.2023). Tumor/ somatic molecular profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy. Considered can be testing of potentially actionable somatic fusions (*ALK, NRG1, NTRK, ROS1, PGFR2,* and *RET*), mutations (*BRAF, BRCA1/2, KRAS,* and *PALB2*), amplifications (*HER2*), MSI, dMMR, or TMB via an FDA-approved and/or validated NGS-based assay. Testing on tumor tissue is preferred.

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The NCCN Guidelines for Hepatocellular Carcinoma (v. 2.2023) note that to date, there are no treatments with differential benefit for specific molecularly defined subgroups of HCC and there is no established indication for routine molecular profiling in HCC. Evidence remains insufficient for definitive recommendations regarding specific criteria to guide genetic risk assessment in hepatobiliary cancers or for universal germline testing in these tumors. There is no established role for MSI, MMR, TMB, or PD-L1 testing in HCC at this time.

The NCCN Guidelines on Biliary Tract Cancers (3.2023) note for molecular testing in unresectable or metastatic biliary tract cancers that a cell-free DNA (cfDNA) test may be considered for identifying gene mutations (*NTRK* gene fusion, MSI-H/dMMR, TMB-H, *BRAF* V600E mutation, *FGFR2* fusion or rearrangement, *IDH1* mutation, *HER2 (ERBB2)* overexpression and/or amplification, *RET* gene fusion) if tissue is too scant or not available and repeat biopsy is not feasible, however, it may not reliably identify gene fusions or rearrangements depending on the panel used and the specific partner gene.

For acute myeloid leukemia, the NCCN notes that "morphologically detectable," circulating leukemic blasts from peripheral blood may be used to detect molecular abnormalities (NCCN, 6.2023). A variety of gene mutations are associated with specific prognoses (category 2A) and may guide medical decision-making (category 2B).

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, v. 3.2023). The panel recommends that molecular/genomic testing be performed for stages IVA and IVB bladder cancer (may be considered for stage IIIB). The therascreen FGFR RGQ RT-PCR Kit has been approved as a companion diagnostic for erdafitinib.

American Society of Clinical Oncology (ASCO)
In 2022, the American Society of Clinical Oncology (ASCO) published a Provisional Clinical Opinion on somatic genetic testing in individuals with metastatic or advanced cancer. The Opinion addressed circulating tumor DNA (ctDNA) testing under additional topics but did not include a specific statement with a strength of recommendation rating. The panel noted, "There is a growing body of evidence on the clinical utility of genomic testing on cfDNA in the plasma," citing the

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systematic review conducted by Merker et al (2018) The panel also noted that ASCO will update that systematic review over the next few years.

The discussion also included the following points:

- "In patients without tissue-based genomic test results, treatment may be based on actionable alterations identified in cfDNA."
- "Testing is most helpful when genomic testing is indicated, archival tissue is unavailable, and new tumor biopsies are not feasible."
- "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."

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 specifically for liquid biopsy. The national coverage determination on next generation sequencing (NCD 90.2) would apply to liquid biopsy tests meeting the criteria below:

"Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:
    i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
    ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
    iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
b. The diagnostic laboratory test using NGS must have:

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i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
iii. results provided to the treating physician for management of the patient using a report template to specify treatment options."

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study	15254	Mar 2024
NCT03957564	Liquid Biopsy in Monitoring the Neoadjuvant Chemotherapy and Operation in Patients With Resectable or Locally Advanced Gastric or Gastro-oesophageal Junction Cancer	40	May 2024
NCT05582122	SURVEILLE-HPV: National, Multicenter, Open-label, Randomized, Phase II Study Evaluating HPV16 Circulating DNA as Biomarker to Detect the Recurrence, in Order to Improve Post Therapeutic Surveillance of HPV16-driven Oropharyngeal Cancers	420	Mar 2031
NCT05764044	Adjuvant Chemotherapy in Cell-free Human Papillomavirus Deoxyribonucleic Acid (cfHPV-DNA) Plasma Positive Patients: A Biomarker In Locally Advanced Cervical Cancer (CC)	50	Dec 2023

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

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Policy History

Original Effective Date: 07/20/2016
Current Effective Date: 01/01/2024

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

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07/19/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Added a reference to Policy Guidelines at the end of the investigational statement. Added a Policy Guidelines section. Coverage eligibility unchanged.
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.
09/20/2023	Coding update
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Added a Note to cross reference medical policy *00810 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian*

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Cancer. Revised the 1st criteria bullet for clarity. Revised the Policy Guidelines, the FDA, and the Supplemental Information sections. New codes effective 01/01/2024 added to policy.

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

Policy # 00497
Original Effective Date: 07/20/2016
Current Effective Date: 01/01/2024

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

Code Type	Code
CPT	0239U, 0242U, 0326U, 0356U, 81449, 81451, 81456, 81479, 86152, 86153 Delete codes effective 1/1/2023: 0177U, 0229U Add code effective 10/01/2023: 0409U Add codes effective 01/01/2024: 81462, 81463, 81464
HCPCS	No codes
ICD-10 Diagnosis	C561-C569, C61, D400

*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:

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

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

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

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

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.

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