Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/25**
(See policy history boxes for previous effective dates)

Title: Circulating Tumor DNA and Circulating Tumor Cells for Selecting Targeted Therapy for Advanced Solid Cancers (Liquid Biopsy)

Description/Background

Liquid Biopsy

Liquid biopsy refers to analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as a method 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 (cfDNA). cfDNA 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.(1) Unlike apoptosis, necrosis is considered a pathologic process, and generates larger DNA fragments due to an 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.(1) Most assays detect CTCs through the use of surface epithelial markers such as epithelial cell adhesion molecules (EpCAM) and cytokeratins. The primary reason for in detecting CTCs is prognostic, through quantification of circulating levels.

DETECTING CTDNA AND CTCs

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed. Highly sensitive and specific methods have been developed to detect ctDNA, for both single-nucleotide mutations (e.g. BEAMing [which combines emulsion polymerase chain reaction [PCR] with magnetic beads and flow cytometry] and digital PCR) and copy-number changes. Digital genomic technologies allow for enumeration of rare mutant 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 (e.g., *EGFR* and *ALK* in non-small-cell lung cancer), or untargeted without knowledge of specific mutations present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either on the basis of biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.(1)

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA 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.

Information regarding FDA-approved companion diagnostic tests should be obtained from the FDA "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)" website. https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. For accuracy, the reader is advised to access the information directly from the FDA site. (This website is updated frequently)

U.S. Food & Drug Administration – Companion Diagnostics
A companion diagnostic is an FDA approved medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product.(2) The test helps a health care professional determine whether, for a specific patient, a particular therapeutic product's benefits outweigh any potential serious side effects or risks.

Companion diagnostics can:
- identify patients who are most likely to benefit from a particular therapeutic product;
- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or

- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

Medical Policy Statement

The clinical utility of circulating tumor DNA and circulating tumor cells for selecting targeted therapy for advanced solid cancers has been established when criteria are met.

The use of circulating tumor DNA and circulating tumor cell testing is considered investigational for all other indications related to solid tumors, including measurable residual disease (MRD) testing and cancer screening (e.g., Galleri).

Inclusionary and Exclusionary Guidelines

Inclusions:
The clinical utility of circulating tumor DNA and circulating tumor cells for selecting targeted therapy for advanced solid cancers has been established when **ALL** of the following criteria are met.

- May be considered established for guidance in the selection of appropriate targeted FDA therapeutic options for **ANY** of the following conditions:
    - Metastatic cancers
    - Inoperable locally advanced cancers
    - Refractory cancers
    - Recurrent cancers
    - Advanced cancer (stages III or IV); **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 **OR** individual is experiencing a relapse; **AND**
- There is clinical documentation that tissue-based testing cannot be performed (e.g., insufficient sample, inaccessible tumor or where there may be a delay in obtaining tumor sample) **OR** tissue-based testing is not required when there is an FDA-approved companion diagnostic device that is a circulating tumor test (liquid biopsy).

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Companion diagnostics can:
- identify patients who are most likely to benefit from a particular therapeutic product;

- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

FDA-Approved Companion Diagnostic Tests

FDA-approved companion diagnostic tests include:

- Tests which are billed with CPT* codes (most laboratories are able to process these)
- Proprietary laboratory analyses (PLA) tests (processed by one specific independent laboratory). Most PLA tests have billing codes that end in "U".

*CPT® is a registered trademark of the American Medical Association

Proprietary Laboratory Analyses (PLA) Testing

A PLA test is considered **established** when the following criteria are met:

- Biomarker confirmation is required by an FDA-approved or -cleared test prior to initiating treatment (as described in the FDA prescribing label of the therapeutic in the section "Indications and Usage"), **AND**
- The test is an FDA-approved companion diagnostic.
- Please refer to established codes for current coverage. A code may not be listed but could still be established if it is an FDA-approved companion diagnostic test.

  Information regarding FDA-approved companion diagnostic tests should be obtained from the FDA "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)" website. www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

  For accuracy, the reader is advised to access the information directly from the FDA site. (This website is updated frequently)

Exclusions:

- The use of circulating tumor DNA and circulating tumor cells is considered investigational when criteria above are not met.
- The use of circulating tumor DNA and circulating tumor cell testing is considered investigational for all other indications related to solid tumors, including measurable residual disease (MRD) testing and cancer screening (e.g., Galleri).

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81445	81455	81462	81463	81464	0239U
0242U	0326U				

Other codes (investigational, not medically necessary, etc.):

86152	86153	0091U	0338U	0485U	0486U
0487U	0491U	0492U			

Rationale

SELECTING TREATMENT IN ADVANCED SOLID CANCERS

Treatment selection is informed by tumor type, grade, stage, individual performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of liquid biopsy testing of individuals who have advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

Liquid biopsies are easier to obtain and less invasive than tissue biopsies. True-positive liquid biopsy test results lead to the initiation of appropriate treatment (e.g., targeted therapy) without tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival.

In individuals able to undergo tissue biopsy, negative liquid biopsies reflex to tissue testing. In individuals unable to undergo tissue biopsy, a negative liquid biopsy result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

Circulating Tumor DNA

The American Society of Clinical Oncology and College of American Pathologists jointly convened an expert panel to review the current evidence on the use of ctDNA assays.(3) The literature review included a search for publications on the use of ctDNA assays for solid tumors in March 2017 and covers several different indications for the use of liquid biopsy. The search identified 1338 references to which an additional 31 references were supplied by the expert panel. Seventy-seven articles were selected for inclusion. The summary findings are discussed in the following sections, by indication.

Merker (2018) concluded that while a wide range of ctDNA assays have been developed to detect driver mutations, there is limited evidence of the clinical validity of ctDNA analysis in tumor types outside of lung cancer and colorectal cancer (CRC).(3)

Since the end date of the searches conducted by Merker (2018), a number of observational studies have been published for various ctDNA tests. For example, two observational studies of the clinical validity of FoundationOne® Liquid (formerly FoundationACT®) in patients with various cancers compared liquid biopsy to tissue biopsy with FoundationOne® comprehensive genomic testing.(4, 5) Additional studies have assessed the validity of other tests, including the Guardant360 test (6,7) and OncoBEAM™ CRC assay(8-12). Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. Multiple high-quality studies are needed to

establish the clinical validity of a test.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. Merker (2018) concluded that no such trials have been reported for ctDNA tests.(3)

MONITORING TREATMENT RESPONSE IN CANCER

Monitoring of treatment response in cancer may be performed using tissue biopsy or imaging methods. Another proposed purpose of liquid biopsy testing in patients who have advanced cancer is to monitor treatment response, which could allow for changing therapy before clinical progression and potentially improve outcomes.

Circulating Tumor DNA

Merker et al (2018) identified several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes as well as studies demonstrating that ctDNA can identify the emergence of resistance variants.(3) However, they reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and concluded that clinical validity had not been established. Additionally, the authors concluded that there is no evidence that changing treatment before clinical progression, at the time of ctDNA progression, improves patient outcomes. Therefore, no inferences can be made about clinical utility.

Circulating Tumor Cells

Systematic reviews and meta-analyses describing an association between CTCs and poor prognosis have been reported for metastatic breast cancer,(12-15) CRC,(16,17) hepatocellular cancer,(18) prostate cancer,(19-21) head and neck cancer,(22) and melanoma.(23)

The clinical validity of each commercially available CTC test must be established independently, which has not been done to date.

PREDICTING RISK OF RELAPSE

Monitoring for relapse after curative therapy in individuals with cancer may be performed using imaging methods and clinical examination. Another proposed purpose of liquid biopsy testing in individuals who have cancer is to detect and monitor for residual tumor, which could lead to early treatment that would eradicate residual disease and potentially improve outcomes.

Circulating Tumor DNA

Merker et al (2018) identified several proof-of-principle studies demonstrating an association between persistent detection of ctDNA after local therapy and high risk of relapse.(3) However, current studies are retrospective and have not systematically confirmed that ctDNA is being detected before the metastatic disease has developed. They concluded that the performance characteristics had not been established for any assays.

Chidambaram et al (2022) conducted a systematic review and meta-analysis of the clinical utility of circulating tumor DNA testing in esophageal cancer.(24) Four retrospective studies (N=233, N range 35 to 97) provided data to assess ctDNA for monitoring for recurrence after

treatment. The pooled sensitivity was 48.9% (range, 29.4% to 68.8%) and specificity was 95.5% (range, 90.6% to 97.9%).

Circulating Tumor Cells

Rack et al (2014) published results of a large multicenter study in which CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy using the CellSearch System.(25) After chemotherapy, 22% of patients were CTC-positive, and CTC positivity was negatively associated with prognosis.
Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer,(26) CRC,(27) bladder cancer,(28,29) liver cancer,(30) and esophageal cancer.(31)

Merker et al (2018) concluded that there is no evidence that early treatment before relapse, based on changes in ctDNA, improves patient outcomes.(3) Similarly, no trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes.

SCREENING FOR CANCER IN ASYMPTOMATIC INDIVIDUALS

It has also been proposed that liquid biopsies could be used to screen asymptomatic individuals for early detection of cancer, which could allow for initiating treatment at an early stage, potentially improving outcomes.

For individuals who are being screened for cancer who receive multicancer early detection (MCED) testing with Galleri, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome. No clinical utility studies have been published; estimates of changes in cancer-specific mortality, quality of life, functional outcomes and rates of overdiagnosis and overtreatment are unknown.

Circulating Tumor DNA

Merker et al (2018) reported that there is no evidence of clinical validity for the use of ctDNA in asymptomatic individuals.(3)

Circulating Tumor Cells

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer.(32,33) Reported sensitivity was low in both cancers (42% and 35%) overall. Sensitivity was lower in patients with early-stage cancer, suggesting that the test would not be useful as an initial screen.

SUMMARY

Although there is limited evidence regarding the clinical utility of circulating tumor DNA (ctDNA) and circulating tumor cell testing in individuals with cancer, this testing may help to determine eligibility for selecting FDA approved targeted cancer treatments for advanced solid cancers. Therefore, this testing may be considered established when policy criteria are met.

There is not enough research to show that plasma-based testing for variants in circulating tumor DNA (ctDNA) to select targeted treatment improves health outcomes when policy criteria are not met. This includes ctDNA testing as an adjunct to, or replacement for tumor

tissue testing, when tumor tissue is possible, or testing when there is no FDA-approved targeted treatment for the indication. Plasma-based ctDNA testing is generally less sensitive than tumor tissue testing and may identify changes that are not associated with the tumor Therefore, this testing is considered investigational when medical necessity criteria are not met.

There is not enough research to show that testing for circulating tumor/cell-free DNA (ctDNA or cfDNA) or circulating tumor cells (CTCs) for purposes other than targeted treatment selection can improve overall health outcomes for people with solid tumors. Various ctDNA and CTC tests have been proposed to detect the presence or recurrence of solid tumor cancers. However, the impact such testing on health outcomes has not been clearly demonstrated in prospective studies. In addition, no clinical practice guidelines based on research recommended routine use of this type of testing in patient management. Therefore, CTC and ctDNA testing that is not for the purpose of selecting a targeted treatment is considered investigational.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society of Clinical Oncology
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.(34) The Opinion addressed cfDNA 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 systematic review conducted by Merker et al (2018) (3) 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."

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.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently ongoing trials that might influence this review are listed in the Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06090214	Circulating Tumor Cells for the Diagnosis of Intestinal-type Adenocarcinoma of the Ethmoid: a Pilot Study	42	Dec 2025
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	April 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

Government Regulations
National:

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:(35)

"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:

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, results provided to the treating physician for management of the patient using a report template to specify treatment options."

Local:

MolDX: OncoCee™ Billing and Coding Guidelines – A55245; Original date 2/16/17; Revision date: 7/24/21, **retired 7/24/21**

The MolDX Contractor has completed a preliminary review of Biocept's OncoCee, Circulating Tumor Cell (CTC) Assay to detect metastatic disease for breast, prostate, lung, and colon cancer. To date, the assays have insufficient evidence to support reasonable and necessary criteria for Medicare reimbursement. Therefore, we will deny these CTC assay services.

To receive a CTC assay service denial, please submit the following claim information:

- Select the appropriate CPT code for the service rendered:
  - **86152**-Cell enumeration using immunologic selection and identification in fluid specimen (eg, CTC in blood)
  - **86153**-CTC, physician interpretation and report

Circulating Tumor Cell Marker Assays - L32218; revision effective date 10/1/2014, **retired 9/30/15**

Coverage Indications Limitations and/or Medical Necessity
This is a coverage policy for the CellSearch (Veridex) circulating tumor cell (CTC) assay. All other methods for circulating tumor cell detection, including reverse-transcription polymerase chain reaction PCR (RTPCR) Assays, are non-covered.

CTCs represent the point in the metastatic process of solid tumors when cells from a primary tumor invade, detach, disseminate, colonize and proliferate in a distant site. Detection of elevated CTCs during therapy is an accurate indication of subsequent rapid disease progression and mortality in breast, colorectal and prostate cancer. Therefore, CTC will be limited to metastatic breast, colorectal and prostate cancer. CTC testing for all other malignant diagnoses will be denied as not reasonable and necessary.

The CellSearch assay, an independent predictor of progression-free survival and overall survival in patients with metastatic breast, colorectal and prostate cancer, involves the automated immunomagnetic selection of CTCs based on an anti-EpCAM antibody cell capture. To perform this assay, a 7.5 ml aliquot of blood is incubated with EpCAM antibody-covered ferroparticles (nanotechnology). Circulating epithelial cells that express EpCAM are isolated in a magnetic field without centrifugation.

The supernatant containing unbound cells is removed. The enriched cell samples are labeled with a fluorescent nuclei acid dye and two monoclonal antibodies (CD 45 and Cytokeratin 8, 18, 19), each tagged with distinct fluorescent compounds. The stained cells are then analyzed on a fluorescence microscope. Digital fluorescent images are screened by a qualified technician for CTCs; the cell has a nucleus, expresses keratin (EpCAM and CK) and does not express CD45.

The assay findings are verified by a pathologist and issued in a report as a numerical result where more than 5 cells per 7.5 ml of whole blood predicts worse prognosis in patients with known recurrent breast and prostate cancer, and more than 3 cells are predictive of shorter progression free survival (PFS) and overall survival (OS) in metastatic colorectal cancer.

Utilization Guidelines
Services performed for excessive frequency are not medically necessary. Patients should be treated on an individual basis as indicated by the response to treatment. The intent of the following guidelines is to provide the maximum amount of tests required to adequately follow disease progression or treatment response.

WPS Medicare expects physicians to limit CTC testing to only times when the CTC information may change treatment. Documentation maintained in the patient record must support medical necessity and be available upon request.

Frequency:

- Baseline – limited to once prior to initiation of tumor-type specific chemotherapy
- Follow-up during chemotherapy treatment - repeat every 4-6 weeks
- Surveillance with no chemotherapy treatments - repeat every 4-6 months

A rapid rise in the CTC value usually indicates aggressive disease and impending adverse

outcome. WPS Medicare would expect to see no further CTC testing after the transition to palliative/hospice care.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Prostate Cancer Early Detection: Biomarkers Prior to Biopsy
- Genetic Testing – Next-Generation Sequencing of Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions
- Somatic Biomarker Testing (including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS,BRAF, MMR/MSI, HER2, and TMB)
- Genetic Testing - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)
- Genetic Testing—BRAF Mutation in Selecting Melanoma Patients for Targeted Therapy Including Liquid Biopsy
- Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 13, 2024 the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/09	12/1/08	10/13/08	Joint policy established
3/1/12	12/13/11	12/21/11	Routine maintenance; references updated
9/1/12	6/12/12	6/19/12	Codes updated. No change in policy status.
7/1/13	4/16/13	4/22/13	Codes updated. Medicare and Medicaid information updated to reflect CMS coverage of CellSearch (Veridex) circulating tumor cell (CTC) assay.
11/01/14	8/19/14	8/25/14	Routine maintenance; references updated
1/1/16	10/13/15	10/27/15	Routine maintenance
1/1/17	10/11/16	10/11/16	Policy extensively revised and title changed to “Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy).” Mirrors BCBSA
1/1/18	10/19/17	10/19/17	• Routine maintenance • Added note: policy does not address the use of blood-based testing for epidermal growth factor receptor mutations.
1/1/19	10/16/18	10/16/18	Routine maintenance
11/1/19	8/20/19		• Routine maintenance • Disclaimer added to MPS regarding what this policy does NOT cover
5/1/20	2/18/20		• Routine maintenance
5/1/21	2/16/21		• Routine maintenance • Added note: the indication for liquid biopsy to select targeted treatment for breast cancer was removed from this policy. Per BCBSA this indication will be added to a new policy to be developed on gene expression profiling and circulating

			tumor DNA testing for breast cancer management. • Added 0239U code to Investigational, not medically necessary.
5/1/22	2/15/22		• Routine maintenance • No references added • Policy statement unchanged • 3/23/22 the below paragraph was removed from under the Description/Background and MPS. This policy does not address the use of blood-based testing for driver mutations to select therapy in non-small-cell lung cancer (i.e. EGFR) or metastatic colorectal cancer, blood-based testing for use of liquid biopsy for detection or risk assessment of prostate cancer or AR-V7 circulating tumor cells for metastatic prostate cancer, or liquid biopsy to select targeted treatment for breast, ovarian, or pancreatic cancer.
5/1/23	2/21/23		• Routine maintenance • Added 0388U as E/I • Vendor Review: NA (ky)
1/1/24	10/25/23		• Routine maintenance • Updated reference, policy status **changed from E/I to MIXED.** Medical Policy Statement updated and Inclusionary and Exclusionary Guidelines added to reflect policy status change. **This would be a divergent from BCBSA.** • Added codes 0242U and 0326U to EST. Moved code 0239U from E/I to EST. Added code 0091U to E/I. • Add codes 81445, 81450, and 81455 to the policy under EST as currently are the relevant codes

			for cell-free (liquid biopsy) they are just not cell-free (liquid biopsy) specific. • Title changed **to** Circulating Tumor DNA and Circulating Tumor Cells for Selecting Targeted Therapy for Advanced Solid Cancers (Liquid Biopsy) **from** Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) • Vendor: NA Post JUMP: • Add codes 81445, 81450, and 81455 to the policy under EST as currently are the relevant codes for cell-free (liquid biopsy) they are just not cell-free (liquid biopsy) specific. • Updated the first sentence after Inclusions section to the highlight: The clinical utility of circulating tumor DNA and circulating tumor cells for selecting targeted therapy for advanced solid cancers has been established when ALL of the following criteria are met. • Added the below to the Inclusion section: FDA-Approved Companion Diagnostic Tests FDA-approved companion diagnostic tests include: • Tests which are billed with CPT* codes (most laboratories are able to process these) • Proprietary laboratory analyses (PLA) tests (processed by one specific independent laboratory). Most PLA tests have billing codes that end in “U”. *CPT® is a registered trademark of the American Medical Association

			Proprietary Laboratory Analyses (PLA) Testing A PLA test is considered established when the following criteria are met: • Biomarker confirmation is required by an FDA-approved or -cleared test prior to initiating treatment (as described in the FDA prescribing label of the therapeutic in the section "Indications and Usage"), AND • The test is an FDA-approved companion diagnostic Information regarding FDA-approved companion diagnostic tests should be obtained from the FDA "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)" website. www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools For accuracy, the reader is advised to access the information directly from the FDA site. (This website is updated frequently) (ky)
3/1/24	12/19/23		• Code Informational-update: added new codes: 81462, 81463, and 81464 eff 1/1/24 under EST to policy. • Updated nomenclature of codes 81445 and 81455 effective 1/1/24. • Code 81450 removed from this JUMP policy because the test is for hematolymphoid neoplasm and the liquid biopsy policy is on solid tumors.

			• Vendor: N/A (ky)
1/1/25	10/15/24		• Routine maintenance. • Code Informational-update: added new codes 0485U, 0486U, 0487U, 0491U, and 0492U under E/I to policy. • Vendor: N/A (ky)

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR SELECTING TARGETED THERAPY FOR ADVANCED SOLID CANCERS (LIQUID BIOPSY)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.