Circulating Tumor DNA for Cancer Management (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. 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. ctDNA 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 in detecting CTCs is prognostic, through quantification of circulating levels.

**Technologies for 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 (eg, Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single-nucleotide mutations (eg 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 (eg, *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.
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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.

Genomic Health plans to launch its first liquid biopsy test Oncotype SEQ™ in mid-2016. The test uses next-generation sequencing (NGS) to identify actionable genomic alterations for late-stage lung, breast, colon, melanoma, ovarian, and gastrointestinal cancers.

Circulogene’s (Theranostics) liquid biopsy uses a finger stick volume of blood and NGS to monitor known tumor mutations (=3000) in 50 cancer-associated genes for targeted therapy. The test uses a proprietary method to recover necrotic and apoptotic cell-death-associated cell-free DNA.

Pathway Genomics Cancer Intercept is a 96-gene mutation panel designed to detect mutations in 9 driver genes involved primarily in breast, ovarian, lung, and colorectal cancers, as well as melanoma.

Biocept Inc. offers assays that target mutations found in lung and breast cancers.

Foundation Medicine’s Foundation ACT detects mutations in over 60 genes for targeted therapy in metastatic cancer.

The CellSearch® System (Janssen Diagnostics, formerly Veridex) is the only FDA-approved device for monitoring patients with metastatic disease and circulating tumor cells. In January 2004, the CellSearch® System was cleared by FDA for marketing through the 510(k) process for monitoring metastatic breast cancer, in November 2007 for monitoring metastatic colorectal cancer, and in February 2008 for monitoring metastatic prostate cancer. The system uses automated instruments manufactured by Immucinon Corp. for sample preparation (CellTracks® AutoPrep) and analysis (CellSpotter Analyzer®), together with supplies, reagents, and epithelial cell control kits manufactured by Veridex.

***Note: This policy does not address the use of blood-based testing for EGFR mutations.

Related Policies:
Assays of Genetic Expression to Determine Prognosis in Patients with Breast Cancer
Gene Based Test for Screening, Detection and/or Management of Prostate Cancer
Molecular Analysis for Targeted Therapy for Non-Small Cell Lung Cancer (NSCLC)

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Circulating tumor DNA and circulating tumor cells for cancer management is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.
Circulating Tumor DNA for Cancer Management (Liquid Biopsy)

When Circulating Tumor DNA for Cancer Management (Liquid Biopsy) is covered

Not applicable.

When Circulating Tumor DNA for Cancer Management (Liquid Biopsy) is not covered

The use of circulating tumor DNA and circulating tumor cells for cancer management is considered investigational for all indications.

BCBSNC does not provide coverage for investigational services.

Policy Guidelines

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as “liquid biopsy,” potentially offer a noninvasive alternative to tissue biopsy for therapeutic decisions and clinical prognosis in patients with cancer.

For individuals who have cancer who receive molecular characterization of tumor using ctDNA, the evidence includes case series and systematic reviews of these case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Ultrasensitive methods to detect mutations from ctDNA have been developed, but there is limited evidence on the analytic validity of these methods. There is a need for further optimization and standardization of testing methods. Clinical validity consists of case series that report correlations between mutations detected in ctDNA with mutations detected in tumor tissue. Results have shown variable results for clinical sensitivity. Although some reports have suggested that clinical sensitivity may be high, this finding has not been consistent. Published studies have consistently reported high clinical specificity; however, most study population have consisted of small and heterogeneous, and it is not known to what degree mutations detected by ctDNA are representative of the primary tumor. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether mutation analysis by ctDNA can replace mutation analysis in tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer or are at high risk of developing cancer who receive identification and quantification of CTCs, the evidence includes case series and meta-analyses of these case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and test validity.

Published data on analytic validity are lacking. Most of the literature consists of reports of levels of CTCs and cancer prognosis, and have shown a correlation with survival in certain cancer types. However, the cutoff levels that should be used to signal a change in patient management are unknown, and there are no studies showing clinical utility and improved patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 86152, 86153
Circulating Tumor DNA for Cancer Management (Liquid Biopsy)

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


Sr. Medical Director review 5/2016


**Policy Implementation/Update Information**

7/1/16 New policy issued. The use of circulating tumor DNA and circulating tumor cells for cancer management is considered investigational for all indications. References added. Sr. Medical Director review 5/2016. (lpr)

11/22/16 Updated Description section: “This policy does not address the use of blood-based testing for EGFR mutations.” Reference added. No change to policy intent. (lpr)

4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.