Prior Authorization Review Panel
MCO Policy Submission

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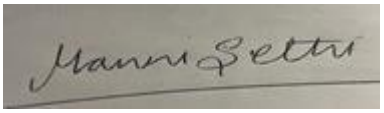
Plan: AmeriHealth Caritas Pennsylvania Community Health Choices	**Submission Date**: 8/1/2024
Policy Number: ccp.1516	**Effective Date:** 8/2022 **Revision Date:** July 1, 2024
Policy Name: Circulating tumor DNA and circulating tumor cells for cancer management (liquid biopsy)	
Type of Submission – Check all that apply: **New Policy** **x Revised Policy*** **Annual Review – No Revisions** **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Circulating tumor DNA and circulating tumor cells for cancer management (liquid biopsy)

Clinical Policy ID: CCP.1516

Recent review date: 7/2024

Next review date: 11/2025

Policy contains: Cancer, circulating tumor cells, circulating tumor DNA, liquid biopsy

AmeriHealth Caritas Pennsylvania Community HealthChoices has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania Community HealthChoices on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania Community HealthChoices will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are not guarantees of payment

Coverage policy

Liquid biopsy for circulating tumor deoxyribonucleic acid (ctDNA) and circulating tumor cells (CTCs) when testing for mutations in members with metastatic cancer is clinically proven and, therefore, may be medically necessary in the following situations:

Gastric, esophageal, esophagogastric junction, cervical, non-small cell lung, or ovarian cancers (National Comprehensive Cancer Network, 2024a, 2024b, 2024d, 2024k):

- If a member is medically unfit for invasive tissue sampling; or
- If there is insufficient material for molecular analysis; or
- If tissue biopsy is not feasible or tissue is not available; or
- For disease progression monitoring.

Central nervous system cancers (National Comprehensive Cancer Network, 2024e):

- When available, to increase sensitivity of tumor cell detection and assessment of response to treatment.

Breast cancer (National Comprehensive Cancer Network, 2024h):

- When tumor tissue or plasma-based circulating tumor DNA assays are used for diagnosis and disease progression, and if one specimen is negative for actionable biomarkers, testing on the alternative specimen can be considered.
- Metastatic breast cancer. In hormone receptor-positive, HER2-negative metastatic breast cancer patients who are candidates for alpelisib plus fulvestrant, testing for PIK3CA mutations using sequencing of tumor tissue or circulating tumor DNA is recommended to determine eligibility for treatment (Henry, 2022).

Prostate cancer (National Comprehensive Cancer Network, 2024j):

- In members for whom testing for androgen receptor splice variant 7 in circulating tumor cells can be considered to help guide therapy selection.

Limitations

Liquid biopsy for circulating tumor deoxyribonucleic acid and circulating tumor cells are investigational/not clinically proven and, therefore, not medically necessary for all other indications including pre-symptomatic cancer detection in members at increased hereditary risk for cancer, reporting or interpretation of germline variants, or routine monitoring of treatment response in metastatic breast cancer (Henry 2022, National Comprehensive Cancer Network, 2024i, National Comprehensive Cancer Network, 2024j).

Alternative covered services

Tissue biopsy.

Background

The emergence of targeted therapy for metastatic cancer if particular genetic mutations are present has increased the importance of accurately identifying tumor genomes. In addition, limitations in standard tissue biopsy tests, including risk to patients, inconsistent accuracy and high cost, have presented challenges to improving diagnosis.

Liquid biopsy for cancer patients is a recently developed approach that involves an analysis of circulating tumor deoxyribonucleic acid or circulating tumor cells. Blood is collected and sent to a laboratory, where it is spun and plasma is separated from the blood. Testing for genetic mutations follows.

Circulating tumor deoxyribonucleic acid in body fluids is one measurement that has potential to improve diagnostic accuracy and thus, treatment. In cancer patients, some deoxyribonucleic acid is released in the blood, and thus can be analyzed for mutations. Circulating tumor deoxyribonucleic acid has potential to be an early detection biomarker, especially for cancers with no accepted screening methodologies. Features for early detection include deoxyribonucleic acid fragment lengths, copy number variations, and associated patient phenotypic information (Campos-Carrillo, 2020).

Circulating tumor cells are shed into the vasculature from a primary tumor. These cells can be seeds for cancer cell growth in distant sites and are detectable in certain cancers. Circulating tumor cells are very rare in healthy persons (Mavroudis, 2010). Testing for these cells is not a genetic analysis, but a calculation of the number of such cells (Aggarwal, 2013).

A survey found that in mid-2019, 38% (28 of 73) private insurers and 67% (8 of 12) Medicare Administrative Contractors covered circulating tumor deoxyribonucleic acid and circulating tumor cells for cancer patients. Just a few years prior, no insurer covered this service. However, coverage applied only to patients with advanced non-small cell lung cancer in 24 of 28 private insurers, and in 8 of 8 Medicare contractors (Douglas, 2020).

Findings

Guidelines

Circulating tumor deoxyribonucleic acid and circulating tumor cells are emphasized in multiple National Comprehensive Cancer Network guidelines from 2024, with indications for their use across various cancers.

In Gastric Cancer, liquid biopsy using circulating tumor deoxyribonucleic acid is recommended for patients with advanced disease or those unable to undergo a clinical biopsy. This method identifies genomic alterations and monitors disease progression, though negative results should be interpreted cautiously (National Comprehensive Cancer Network, 2024a).

For Esophageal and Esophagogastric Junction Cancers, circulating tumor deoxyribonucleic acid liquid biopsy is also recommended for similar reasons, offering an alternative to traditional biopsy for advanced disease monitoring (National Comprehensive Cancer Network, 2024b). In Colon Cancer, circulating tumor deoxyribonucleic acid is recognized as an emerging prognostic marker, but current evidence does not support its routine use outside clinical trials. The guidelines discourage care de-escalation based on circulating tumor deoxyribonucleic acid results and encourage trial participation (National Comprehensive Cancer Network, 2024c).

For Cervical Cancer, comprehensive genomic profiling via circulating tumor deoxyribonucleic acid assay is suggested if tissue biopsy is not feasible (National Comprehensive Cancer Network, 2024d). In Central Nervous System Cancers, circulating tumor deoxyribonucleic acid and circulating tumor cell assessments enhance tumor cell detection and treatment response evaluation when available (National Comprehensive Cancer Network, 2024e).

Biliary Tract Cancer guidelines indicate that cell-free deoxyribonucleic acid assays can detect some fusion breakpoints, albeit with lower sensitivity than tumor tissue testing (National Comprehensive Cancer Network, 2024f). For Ampullary Adenocarcinoma, circulating tumor deoxyribonucleic acid testing is considered if tissue testing is not feasible (National Comprehensive Cancer Network, 2024g).

In Breast Cancer, circulating tumor deoxyribonucleic acid assays may be used alongside tumor tissue assays, each having distinct advantages. If initial testing is negative for actionable biomarkers, alternative specimen testing is advised (National Comprehensive Cancer Network, 2024h). The Colorectal Cancer Screening guidelines mention an FDA-approved blood test detecting circulating methylated SEPT9 deoxyribonucleic acid for those refusing other screening modalities, though the retesting interval is unclear (National Comprehensive Cancer Network, 2024i).

The Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic cancers highlights circulating tumor deoxyribonucleic acid's potential for identifying somatic and germline variants. However, confirmatory

testing with a Clinical Laboratory Improvement Amendments-approved assay is recommended for suspected germline variants, and circulating tumor deoxyribonucleic acid testing should be limited to clinical trials due to undefined clinical utility and psychological impacts (National Comprehensive Cancer Network, 2024j).

Guidelines from the American Society of Clinical Oncology state that there is insufficient data to support its routine use to monitor response to therapy among patients with metastatic breast cancer, with low evidence quality and a moderate strength of recommendation. Similarly, for circulating tumor cell testing, the guideline also finds insufficient data to recommend its routine use for monitoring response to therapy in these patients, with intermediate evidence quality and a moderate strength of recommendation. These recommendations are based on the current lack of sufficient evidence demonstrating the clinical utility of these tests for monitoring treatment response in patients with metastatic breast cancer, leading to the conclusion that their routine use is not supported at this time (Henry, 2022).

Multiple large reviews support the prognostic accuracy of circulating tumor cells for patient outcomes, usually survival, of circulating tumor cells; high numbers of cells are associated with poor outcomes. These reviews include cancers of the bladder (Crupi, 2023; Jiang, 2021), breast (Lisencu, 2022), colon/rectum (Chang, 2023; Veyrune, 2021), esophagus (Zhang, 2020), head and neck (Xun, 2020), hepatocellular system (Cui, 2020), ovary (Huang, 2021), pancreas (Pang, 2021), prostate (Wang, 2011), and stomach (Gao, 2019).

Circulating tumor deoxyribonucleic acid testing has had mixed results as a diagnostic, screening, and monitoring tool in metastatic cancer. In particular, sensitivity rates were low, including 63.7% for colorectal cancer detection (Xie, 2019); 48.9% for esophageal cancer (Chidambaram, 2022); 67% and 73,8% for lung cancer (Passiglia, 2018; Zaman, 2023); 28% for pancreatic cancer (Creemers, 2017); and 62% for stomach cancer (Gao, 2017). Specificity rates are much higher.

For most cancers, treatments based on these markers have not demonstrated improved patient outcomes. Future studies are needed to document modified therapy due to circulating tumor deoxyribonucleic acid changes before progression improves survival (Garcia-Pardo, 2022).

A study of patients with metastatic lung, breast, and colorectal cancer (n = 178) that received liquid biopsy resulted in 22 patients with (and 44 patients without) targeted therapy. Average progression-free survival in the targeted treatment group was significantly greater (12 versus 5 months, *P* =.029), but overall survival was not (15 versus 13 months, *P* =.087) (Choicair, 2022).

A study of metastatic breast cancer (n = 341) divided subjects into those with alpelisib or placebo, both in addition to fulvestrant; liquid biopsy can identify those with PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutations that respond to targeted treatment. Median overall survival was 7.9 months greater after combination treatment, an insignificant difference (Andre, 2021). Overall treatment effect, which included quality of life, was not different between two groups (Ciruelos, 2021).

For metastatic non-small cell lung cancer, a systematic review of 38 studies (n = 1,141) confirmed a limited role for targeted next-generation sequencing of liquid biopsy (versus tissue-based biopsy) in detecting clinically relevant mutations. Percent agreement ranged from 53.6% to 67.8%, depending on the gene (Esagian, 2020).

Among newly-diagnosed non-small cell lung cancer patients (n = 282), cell-free deoxyribonucleic acid increased detection of targetable mutations from 60 to 89 patients over standard tissue biopsy (Leighl, 2019). Among 323 patients, 94 had plasma testing alone, and 31 (33.0%) had a targetable mutation detected; 85.7% (36/42) receiving targeted therapy based on the plasma result achieved a complete or a partial response or stable disease (Aggarwal, 2019).

A study (n = 124) of patients diagnosed with various cancers by tissue biopsy showed liquid biopsy detected at least one tumor-derived mutation in 84% of the subjects. Sensitivity varied for breast cancer (95%), colorectal cancer (82%), and non-small cell lung cancer (76%) (Razavi, 2019).

A systematic review of eight studies documented 79% of liquid biopsy samples showed somatic mutations. When both liquid biopsy samples and tissue samples are evaluated, the sensitivity to detect targetable mutations in non-small cell lung cancer increases (Saarenheimo, 2021).

In 2024, we updated coverage criteria based on new guidelines from both the American Society of Clinical Oncology (Henry, 2022) and the National Comprehensive Cancer Network. We also found a new systematic review and meta-analysis that was conducted to evaluate the effectiveness of circulating tumor DNA obtained from cerebrospinal fluid in identifying genetic changes in leptomeningeal metastasis compared to circulating tumor DNA derived from plasma. The study encompassed six studies (n = 226), and the findings indicated that cerebrospinal fluid-derived circulating tumor DNA has a superior diagnostic capacity for detecting genetic alterations in leptomeningeal metastasis, with a relative risk of 1.46. The included studies identified shared genetic modifications in cerebrospinal fluid, such as STK11, TP53, and ATM, and the agreement rate between cerebrospinal fluid and tissue samples for genomic alterations in circulating tumor DNA varied from 71% to 88.9%. The study concluded that comprehending molecular alterations in circulating tumor DNA can substantially enhance its prognostic value, aiding in the prediction of tumor aggressiveness, invasiveness, and resistance to therapy (Wijaya, 2023).

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On June 12, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “cancer,” “circulating tumor cells,” “circulating tumor deoxyribonucleic acid,” and “liquid biopsy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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7/2023: Policy references updated.

7/2024: Policy references updated.