


MEDICAL POLICY		Circulating Tumor Cell and DNA Assays For Cancer Management	
Effective Date: 1/1/2021		Section: LAB	Policy No: 151
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Medical Officer	Date		

See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

Note: This policy address cell-free DNA tests (also known as circulating tumor DNA tests or liquid biopsies) for non-small cell lung cancer.

I. The use of circulating tumor cells (CTCs) or circulating tumor/cell-free DNA (ctDNA or cfDNA), including but limited to the following (A.-Q.), are considered **investigational and not covered** in the management of patients with cancer.

- A. Cancer Intercept
- B. CellMax – First Sight CRC Colorectal Cancer Early Detection Test
- C. CellMax – LBx Liquid Biopsy
- D. CellMax – Prostate Cancer Test
- E. Cell Search

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<ul style="list-style-type: none"> F. Circulogene G. ClearID Biomarker Expression Assays H. ClearID Breast Cancer I. ClearID Lung Cancer J. ClearID Solid Tumor Panel K. Colvera L. FoundationACT (FoundationOne Liquid) M. IVDiagnostics N. LiquidGx O. OncoBEAM for Colorectal Cancer P. OncoBEAM for Melanoma Q. PlasmaSelect64 <p>Link to Policy Summary</p>
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CPT CODES

All Lines of Business	
Not Covered	
86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood)
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required
0229U	BCAT1(Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result

DESCRIPTION

Circulating Tumor Cells

Circulating tumor cells (CTCs) are found in the serum during the metastatic process of solid tumors when cells from a primary tumor invade, detach, disseminate, colonize and proliferate to a distant site. Detection of elevated CTCs during therapy has been suggested to be an indication of subsequent rapid disease progression and mortality in breast, colorectal, lung and prostate cancer. One example of this type of testing is the CellSearch® Circulating Tumor Cell Test, which is a circulating tumor cell kit with multiple components, reagents and devices for calculating CTCs levels based on a patient blood sample.

Circulating Tumor DNA

Cell-free DNA (also known as circulating tumor DNA (ctDNA)) refers to the small fragments of DNA that normal cells and tumor cells release into the blood by apoptosis, either from the primary tumor, metastases or CTC. Because mutations in ctDNA mirror the entire tumor genome, some have proposed their use as molecular biomarkers to track disease. “Liquid biopsy” refers to the analysis of ctDNA or CTCs to, purportedly, non-invasively determine changes in tumor burden.

REVIEW OF EVIDENCE

Numerous systematic reviews have been published which evaluate the use of circulating tumor cells (CTCs) or circulating tumor/cell-free DNA (ctDNA; cfDNA) to predict cancer prognosis or risk. However, the prediction of risk alone, does not establish the clinical utility of a test. Evidence from well-designed clinical trials is needed to determine if the use of CTCs in patient treatment decisions translate into improved quality of life, progression free survival or overall survival.¹⁻⁴ A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of detection and quantification of CTCs or ctDNA as tools for the management of cancer. Below is a summary of the available evidence identified through December 2019.

Systematic Reviews

In 2014, Hayes published a Health Technology Brief (updated in 2016; archived 2017), which evaluated the use of CTC in patients with metastatic breast cancer.⁵ Nine prospective trials were included in the evidence review and included 119-422 patients with a follow-up that ranged from 6-27 months. Overall, the evidence in support of the CellSearch test was given a C rating, indicating, “substantial uncertainty remains about safety and/or impact on health outcomes because of poor-quality studies, sparse data, conflicting study results, and/or other concerns.” In addition, the Hayes review noted the following insights:

- “Data from the CellSearch test may facilitate treatment selection; however, there is insufficient evidence regarding the best use for this test. Providers that adopt use of this test should audit internal outcomes or await the publication of evidence from well-designed clinical trials before widespread adoption.
- More evidence is needed to determine if CTC assays in general, and CellSearch Assay specifically, can accurately predict or detect response to treatment, and/or progression of disease. Currently it remains unclear whether this technology provides a benefit for clinical management of patients with breast cancer.”²

Additional systematic reviews were identified which evaluated the use of CTCs or ctDNA in the diagnosis of other cancers such as hepatocellular carcinoma,⁶ multiple myeloma,⁷ esophageal cancer,⁸ and others.⁹⁻¹⁶ While CTCs and ctDNA were associated with poor prognosis, studies indicated a high rate of false positive/negative results and no study evaluated the use of testing on changes in treatment management or improved overall outcomes. Studies which demonstrate the clinical utility of testing are needed in order to establish CTC and ctDNA as a useful test for diagnosing or managing patients with cancer.

Randomized Controlled Trials

A single randomized controlled trial (RCT) was identified, which evaluated the use CTCs levels to direct chemotherapy and improve overall survival in patients with metastatic breast cancer.¹⁷ This trial included 595 patients with persistent increases in CTC's tested whether changing chemotherapy after once cycle of a first-line chemotherapy agent would improve overall survival (OS). There were 3 arms of this study; arm A included patients (n=276) with no increase in CTCs after 21 days of therapy; arm B included patients (n=165) with an initial increase in CTC's after 21 days of therapy and remained on the initial therapy. Those patients with persistently increased CTCs (n=123) after the 21 days of therapy were randomly assigned to either a group to continue the initial therapy (arm C1) or a group changed to an alternative chemotherapy agent (arm C2). The results indicated that CTCs were strongly prognostic of overall survival; however, no differences were observed between arm C1 and C2.

CLINICAL PRACTICE GUIDELINES

Breast Cancer

National Comprehensive Cancer Network (NCCN)

The 2019 NCCN breast cancer guidelines indicated the following regarding the clinical utility of CTC's in patients with metastatic breast cancer:¹⁸

“The clinical use of circulating tumor cells (CTC) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer for disease assessment and monitoring. Patients with persistently increased CTC after 3 weeks of first-line chemotherapy have a poor progression-free survival (PFS) and overall survival (OS). In spite of its prognostic ability, CTC count has failed to show a predictive value. A prospective, randomized, phase 3 trial (SWOG S0500) evaluated the clinical utility of serial enumeration of CTC in patients with metastatic breast cancer. According to the study results, switching to an alternative cytotoxic therapy after 3 weeks of first-line chemotherapy in patients with persistently increased CTC did not affect either PFS or OS.”¹⁸

No other NCCN guidelines were identified which address the use of CTC's.^{19,20}

American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP)

In 2018, ASCO and CAP assembled a joint expert panel to conduct a literature review on the use of ctDNA analysis in patients with cancer.²¹ On the basis of findings across 77 publications, authors concluded that evidence of clinical validity and utility were “insufficient” for the majority of ctDNA assays in advance cancer. The panel also noted a lack of clinical utility and clinical validity of ctDNA assays in early-stage cancer, treatment monitoring or residual disease detection.

American Society of Clinical Oncology (ASCO)

In 2017, ASCO strongly recommended against the use of circulating tumor cell biomarkers to guide decisions on adjuvant systemic therapy for women with early stage invasive breast cancer. This recommendation was based on intermediate-quality evidence.⁸

In 2015, ASCO issued a moderate strength recommendation against the use of altering therapy for patients with metastatic breast cancer on the basis of circulating biomarker results.²²

Colorectal Cancer

American Society of Clinical Pathology, College of American Pathologist, Association for Molecular Pathology, and American Society of Clinical Oncology (ASCP/CA/AMP/ASCO)

In 2017, the ASCP/CA/AMP/ASCO issued a joint guideline addressing molecular biomarkers for the evaluation of colorectal cancer.²³ On the basis of expert opinion, authors concluded that the “clinical application of liquid biopsy assays awaits robust validation and further studies to determine their clinical utility.”²³

CENTERS FOR MEDICARE & MEDICAID

As of January 14, 2020, three Centers for Medicare & Medicaid (CMS) coverage guidance documents were identified which address circulating tumor cell assays.²⁴⁻²⁶ Local Coverage Determination (LCD): MoLDx: Circulating Tumor Cell Marker Assays (L34066) states the following:

“This is a NON-coverage policy for the circulating tumor cell (CTC) assays. This policy does not address tests for circulating free or circulating tumor DNA (cfDNA; ctDNA)... [a]lthough the detection of elevated CTCs during therapy is a definitive indication of subsequent rapid disease progression and mortality in breast, colorectal and prostate cancer, no data has been forthcoming to demonstrate improved patient outcomes, or that the assay changes physician management to demonstrate improved patient outcomes.”²⁴

POLICY SUMMARY

There is insufficient evidence regarding the use of circulating tumor cells (CTCs) and/or circulating tumor/cell-free DNA (ctDNA or cfDNA) in the diagnosis or management of patients with cancer. There is a lack of studies which demonstrate the clinical utility of testing, or how testing may alter treatment decisions or improve health outcomes. No evidence-based clinical practice guidelines recommend the use of CTCs or ctDNA in the management of any cancer. Therefore, the use of CTCs or ctDNA is considered investigational to diagnose or manage patients with cancer.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days’ notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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