MEDICAL POLICY	Circulating Tumor Cell and DNA Assays for Cancer Management (All Lines of Business Except Medicare)
Effective Date: 7/1/2022  Medical Officer Date	Medical Policy Number: 122 Technology Assessment Committee Approved Date: 5/08; 6/09; 6/11; 10/15 Medical Policy Committee Approved Date: 6/11; 11/11; 1/13; 3/14; 11/14; 12/16; 2/18; 5/19; 3/2020; 12/2020; 5/2021; 11/2021; 3/2022; 6/2022

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 except Medicare (*unless otherwise directed by a Medicare medical policy. Note that investigational services are considered "**not medically necessary**" for Medicare members.)*

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.

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making
  - Reason (indication) for performing test, including the suspected condition

- Existing signs and/or symptoms related to reason for current test request
- Prior test/laboratory results related to reason for current test request
- Family history, if applicable
- How results from current test request will impact clinical decision making

- All relevant CPT/HCPCS codes billed

POLICY CRITERIA

Notes:

- This policy does **not** address cell-free DNA tests (also known as circulating tumor DNA tests or liquid biopsies) for non-small cell lung cancer. Please refer to Medical Policy: "Non-Small Cell Lung Cancer Molecular Testing for Targeted Therapy" (see "Medical Policy Cross References" below).
- This policy does **not** address androgen receptor splice variant 7 (AR-V7) testing from circulating tumor cells (e.g. Oncotype DX® AR-V7 Nucleus Detect Test). Please refer to Medical Policy: "Prostate: Protein Biomarkers and Genetic Testing" (see "Medical Policy Cross References" below).

I. The use of circulating tumor cells (CTCs) or circulating tumor/cell-free DNA (ctDNA or cfDNA) may be considered **medically necessary** for assessing PIK3CA mutations in persons with **advanced or metastatic HR-positive/HER2-negative breast cancer**.

II. The use of circulating tumor cells (CTCs) or circulating tumor/cell-free DNA (ctDNA or cfDNA) via comprehensive molecular profiling panel (e.g. FoundationOne Liquid CDx, Guardant360 CDx) may be considered **medically necessary** when all of the following criteria are met (A.-C.):

A. The patient is a candidate for anti-cancer therapy (chemotherapy or immunotherapy); **and**
B. At least one of the following criteria are met (1.-3.):
    1. The patient is unable to undergo a tissue biopsy or an additional tissue biopsy due to documented medical reasons (i.e. invasive tissue sampling is contraindicated; **or**
    2. The patient does not have a biopsy-amendable lesion; **or**
    3. There is insufficient tumor tissue available for molecular analysis**; and**
C. The patient has a diagnosis for one of the following indications (1.3.):
    1. Metastatic or advanced esophageal or esophagogastric junction cancer; **or**
    2. Advanced gastric cancer; **or**
    3. Locally advanced or metastatic pancreatic adenocarcinoma.

III. The use of circulating tumor cells (CTCs) or circulating tumor/cell-free DNA (ctDNA or cfDNA), is considered **investigational and not covered** when criteria I.-II. above are not met., including but not limited to, the management of other indications with any of the following tests (A.-S.):

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
F. Circulogene
G. ClearID Biomarker Expression Assays
H. ClearID Breast Cancer
I. ClearID Lung Cancer
J. ClearID Solid Tumor Panel
K. Colvera
L. IVDiagnostics
M. LiquidGx
N. LungLB by LungLife AI
O. OncoBEAM for Colorectal Cancer
P. OncoBEAM for Melanoma
Q. PlasmaSelect64
R. RadTox cfDNA

Link to Policy Summary

CPT CODES

All Lines of Business Except Medicare	
Prior Authorization Required	
0155U	PIK3CA (phosphatidylinositol-hyphen4,5-hyphenbisphosphate 3-hyphenkinase, catalytic subunit alpha) (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y)
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-hyphen4,5-hyphenbisphosphate 3-hyphenkinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations

0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
81309	PIK3CA (phosphatidylinositol-hyphen4, 5-hyphenbiphosphate 3-hyphenkinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
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
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
0229U	BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
0285U	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
0317U	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm-generated evaluation reported as decreased or increased risk for lung cancer
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be **prior authorization is required.**	
81479	Unlisted Molecular Pathology

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 March 2022.

Systematic Reviews

- In 2018 (updated 2021), Hayes published a review of the Guardant360 test and its ability to identify actionable alterations across all solid tumor sites.[5] Actionable alterations were defined as "alterations, for which NCCN guidelines exist… which identifies FDA-approved treatments and clinical trials to help guide treatment decisions." In 3 studies evaluated, 8.9% to 28.4% of patients with NSCLC, breast cancer or diverse cancers received a matched targeted therapy based on variant(s) identified by Guardant360, with one retrospective data review study reporting that 26% of NSCLC patients had a change in targeted treatment after Guardant360 results. This study was also limited by its small sample size (n=116), lack of concordance comparison with tissue next generation sequencing, and investigators' financial conflicts of interest with Guardant Health. In 3 studies, the objective response rate ranged from 43% to 85.7% in patients with NSCLC or different solid tumors. One study reported a longer median progression-free survival in patients with NSCLC who received matched therapy based on Guardant360 results (14.7 months) compared with patients who never received matched therapy (7.8 months), although this difference was not statistically significant.

  Investigators concluded that, taken collectively, the 7 evaluated studies provided low-quality evidence in support of the clinical utility of the Guardant360 test, only 1 of which was a prospective study evaluating NSCLC. Hayes ultimately assigned Guardant360 a "C" rating ("potential but unproven benefit") as a tool to identify actionable alterations in solid tumors, based on very low quality evidence of clinical validity and utility.

- In 2020, ECRI conducted a genetic test assessment evaluating the clinical validity and utility of Guardant360 in informing management of advanced solid tumor cancers.[6] Searching the literature through May 2020, 4 studies on clinical validity and 10 studies on clinical utility were identified. Among studies assessing clinical validity for indications other than non-small cell lung cancer, 4 studies reported Guardant360 sensitivity of 47% to 85% for detecting actionable genetic alterations (AGAs) in solid tumors and 87% for detecting microsatellite instability-high status. Three cohort studies assess clinical utility compared Guardant-guided and nontargeted therapy. One study reported that progression-free survival and overall survival did not differ statistically between Guardant (n = 17) and nontargeted therapy (n = 18) groups with advanced colorectal cancer. Another study reported a higher response rate (RR) with Guardant-guided therapy (42%, n = 12) than with nontargeted therapy (7.1%, n = 28) in patients with advanced solid tumors. In patients with head and neck cancer, authors reported 50% and 57% risk ratios (RRs) for Guardant-guided and nontargeted therapy groups, respectively. Collectively, 5 cohort studies (n = 2,327) reported that Guardant360 identified AGAs in 7% to 68% of patients, and 1% to 13% among patients that received test-guided therapy. Three of these studies reported 13% to 67% RRs in evaluable patients (n = 26) who received Guardant-guided therapy. Investigators concluded that evidence supporting the clinical validity and utility of Guardant360 is "somewhat favorable," but noted that studies conducted to date report too few data to determine the test's impact on overall survival or progression-free survival. Additionally, studies included for review suffered from retrospective designs and a lack of comparator groups.

- In 2018 (updated 2021), Hayes published a molecular test assessment evaluating the clinical validity and utility of the Colvera test (Clinical Genomics Pathology Inc.).[7] In total, 3 studies were included for review, evaluating men and women with primary colorectal cancer (CRC). Sample sizes ranged from 122 to 172 patients. Collectively, these three "very low quality" studies were determined to provide preliminary evidence supporting the analytical validity and clinical validity of Colvera to accurately identify residual disease or recurrence in patients with previously treated stage I through IV primary CRC. No studies were identified that evaluated the clinical utility. Investigators assigned a "D2" rating (insufficient evidence) for the Colvera test.

- 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.[8] 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,[9] multiple myeloma,[10] esophageal cancer,[11] and others.[12-19] 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.[20] This trail 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.

Nonrandomized Controlled Trials

Two recent nonrandomized controlled trials assessed the clinical validity of Colvera.[21,22] Mixed results and significant limitations undermined the validity of results reported. Both studies called for large, randomized studies with long-term follow-up to better establish the test's clinical validity and utility.

CLINICAL PRACTICE GUIDELINES

Breast Cancer

National Comprehensive Cancer Network (NCCN)

The 2.2022 NCCN breast cancer guidelines indicated the following regarding the clinical utility of CTC's in patients with metastatic breast cancer:[23]

" For HR-positive/HER2-negative breast cancer, assess for *PIK3CA* mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. *PIK3CA* mutation testing can be done

on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended." [23]

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.[24] 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.[11]

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.[25]

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.[26] 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."[26]

Esophageal and Esophagogastric Junction Cancers

The 2.2022 NCCN guidelines address esophageal and esophagogastric junction cancers stated the following regarding the clinical utility of circulating tumor cells:

> "The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced esophageal/esophagogastric cancers who may be unable to undergo a traditional biopsy or for disease progression monitoring, testing using a validated NGS-based

comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications."[27]

Gastric Cancers

The 2.2022 NCCN guidelines addressing gastric cancers stated the following regarding the clinical utility of circulating tumor cells:

> "The detection of mutations/alterations in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced gastric cancer who may be unable to undergo a traditional biopsy, or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications."[28]

Pancreatic Adenocarcinoma

The 1.2022 NCCN guidelines addressing pancreatic adenocarcinoma stated the following regarding the clinical utility of circulating tumor cells:

> "Tumor/somatic molecular profiling is recommended for patients with locally advanced/metstatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, RET) mutations (BRAF, BRCA ½, KRAS, PALB2), amplifications (HER2), microsatellite instability (MSI), and/or mismatch repair (MMR) deficiency. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible."[29]

POLICY SUMMARY

Low-level, but consistent evidence supports the clinical usefulness of measuring circulating tumor cells (CTCs) and/or circulating tumor/cell-free DNA (ctDNA or cfDNA) for certain indications. There is a lack of studies demonstrating how testing might improve diagnosis, improve patient management, change treatment decisions or improve health outcomes. Evidence-based clinical practice guidelines from the NCCN recommends the use of CTCs or ctDNA to test for PIK3CA mutations in the management of advanced or metastatic breast cancer, esophageal/esophagogastric junction cancers, gastric cancer and pancreatic adenocarcinoma. The use of CTCs for the management of other kinds of cancer, however, lacks support in the evidence base and among clinical practice guidelines (including, among others, the American Society of Clinical Oncology, the American Society of Clinical Pathology and the College of American Pathologists (CAP).

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.

MEDICAL POLICY CROSS-REFERENCES

- Circulating Tumor Cell and DNA Assays for Cancer Management (All Lines of Business Except Medicare)
- Genetic Testing: Pharmacogenetic Testing (Medicare Only)
- Non-Small Cell Lung Cancer: Molecular Testing for Targeted Therapy (All Lines of Business Except Medicare)
- Non-Small Cell Lung Cancer: Molecular Testing for Targeted Therapy (Medicare Only)
- Prostate: Protein Biomarkers and Genetic Testing (All Lines of Business Except Medicare)
- Prostate: Protein Biomarkers and Genetic Testing (Medicare Only)

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