Circulating Tumor Cell and DNA Assays for Cancer Management

MEDICAL POLICY NUMBER: 122

Effective Date: 10/1/2025

Last Review Date: 9/2025

Next Annual Review: 7/2026

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 Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. 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. 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.

SCOPE: Providence Health Plan, Providence Health Assurance and Providence Plan Partners as applicable (referred to individually as "Company" and collectively as "Companies").

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP 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.

PHA members must also the testing criteria governed by the Oregon Health Plan (OHP) - OHP Diagnostic Procedure Codes / Procedure Group 1119. Diagnostic services needed to establish a diagnosis are covered regardless of where the ultimate diagnosis appears. Once the diagnosis is determined, coverage of further treatment is reimbursed if the service appears funded by the OHA for that condition. Medicaid members must also meet the genetic testing criteria governed by the Oregon Health Plan (OHP) Prioritized List Guideline Notes D1 and D17.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Notes:

- 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: "Protein Biomarkers and Genetic Testing for the Prostate (Company)"
- This policy addresses the panel FoundationOne **Liquid** CDx, which is distinct from FoundationOne CDx. FoundationOne CDx is addressed in the medical policy, "Next Generation Sequencing for Cancer (Company)".

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** (e.g. CPT code 0177U or 81309).

II. The use of circulating tumor cells (CTCs) or circulating tumor/cell-free DNA (ctDNA or cfDNA) via comprehensive molecular profiling panel (see Policy Guidelines for examples) 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.-11.):
    1. Metastatic or advanced esophageal or esophagogastric junction cancer; **or**
    2. Advanced gastric cancer; **or**
    3. Locally advanced or metastatic pancreatic adenocarcinoma; **or**
    4. Non-small cell lung cancer; **or**
    5. Advanced or recurrent breast cancer; **or**
    6. Metastatic cervical cancer; **or**
    7. Ovarian Cancer; **or**
    8. Fallopian tube cancer; **or**
    9. Primary peritoneal cancer; **or**
    10. Occult primary cancer (i.e. cancer is metastatic at time of diagnosis but primary site is unknown); **or**
    11. Hepatobiliary cancer.

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

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. Cell Search PDL1 Circulating Tumor Cell
G. Cell Search Circulating Melanoma Cell
H. Cell Search Circulating Multiple Myeloma Cell (CMMC) Test
I. Cell Search HER2 Circulating Tumor Cell (CTC-HER2) Test
J. Circulogene
K. ClearID Biomarker Expression Assays
L. ClearID Breast Cancer
M. ClearID Lung Cancer
N. ClearID Solid Tumor Panel
O. ColonAiQ, Breakthrough Genomics (Singlera Genomics)
P. ColoScape Colorectal Cancer Detection
Q. Colvera
R. CtDNA Metastatic Breast Cancer Panel, Epic Sciences
S. IVDiagnostics
T. HelioLiver Test
U. IMMray PanCan-d

V. LiquidGx
W. LungLB by LungLife AI
X. OncoBEAM for Colorectal Cancer
Y. OncoBEAM for Melanoma
Z. OncobiotaLUNG, Micronoma™
AA. PlasmaSelect64
BB. Plasma Complete™
CC. RadTox cfDNA
DD. DiviTum®TKa, Biovica Inc
EE. BTG Early Detection of Pancreatic Cancer, Breakthrough Genomics

Link to Evidence Summary

POLICY CROSS REFERENCES

- Gene Expression Profile Testing for Breast Cancer, MP47
- Tumor Testing for Targeted Therapy for Non-Small Cell Lung Cancer, MP194
- Protein Biomarkers and Genetic Testing for the Prostate, MP96
- Next Generation Sequencing for Cancer, MP352

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

Examples of comprehensive molecular profiling panels for CTC and cfDNA:

- FoundationOne Liquid CDx
- Guardant360 CDx
- LiquidHALLMARK
- Tempus xF

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:
  - Reason (indication) for performing test
  - 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

BACKGROUND

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.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

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 June 2025.

Systematic Reviews

- In 2024, Hayes conducted an evidence review assessing the clinical validity and utility of FoundationOne Liquid CDx.[5] In total 5 clinical validity studies and 5 clinical utility studies were included for review. One study reported that FoundationOne Liquid CDx identified actionable variants in 62% of patients while tissue-based comprehensive molecular profiling (CMP) identified 88%; the authors did not report a statistical comparison. One study reported that 11% of patients received matched treatment following FoundationOne Liquid CDx and 7% received treatment after tissue-based CMP testing; statistical comparisons were not reported. Four studies reported clinical outcomes (i.e., tumor response, progression-free survival [PFS], and/or overall survival [OS]) for a limited set of patients. One found no statistical difference between matched and nonmatched treatment for overall response rate, disease control, PFS, or OS. Authors concluded that evidence from 7 very poor-quality studies was insufficient to draw conclusions. Studies suggest that FoundationOne Liquid CDx may determine eligibility of patients for various therapies, including on-label treatment, tissue agnostic therapy, off-label treatment, and treatment within a clinical trial. This has potential to be particularly beneficial for patients with advanced cancers. However, whether comprehensive testing leads to improved patient outcomes over more limited testing is unknown. Also, further clarity is needed regarding when cfDNA testing can be used in preference to tissue biopsy comprehensive testing. Some guidelines suggest using cfDNA only when tumor tissue is unavailable or unfeasible. Substantial uncertainty exists due to the quality of studies and limited comparisons with other methods of determining treatment eligibility.

- In 2024, Hayes published a review of the Guardant360 and Guardant 360 CDx test and its ability to identify actionable alterations across all solid tumor sites.[6] 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 2024, ECRI conducted a genetic test assessment evaluating the clinical validity and utility of Guardant360 in informing management of advanced solid tumor cancers.[7] 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 2022, Hayes published a molecular test assessment evaluating the clinical validity and utility of the Colvera test (Clinical Genomics Pathology Inc.).[8] Initially, 3 studies were included for review, evaluating men and women with primary colorectal cancer (CRC). Sample sizes ranged from 122 to 172 patients. In the annual review, an additional 9 new abstracts were identified with 5 newly published studies that met inclusion criteria. Collectively, these "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. Investigators assigned a "D2" rating (insufficient evidence) for the Colvera test stating there was insufficient evidence to support the analytical validity, clinical validity, and clinical utility to accurately identify residual disease or recurrence in patients with previously treated stage I through IV primary colorectal cancer.

- 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.[9] 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,[10] multiple myeloma,[11] esophageal cancer,[12] and others.[13-20] 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.[21] 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.[22,23] 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

Biiliary Tract Cancers

The 1.2025 NCCN guidelines addressing biliary tract cancers stated that a cell-free DNA (cfDNA) test may be considered for identifying gene mutations.[24]

Breast Cancer

National Comprehensive Cancer Network (NCCN)

The 4.2025 NCCN breast cancer guidelines indicated the following regarding the clinical utility of CTC's in patients with metastatic breast cancer:[25]

> " 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." [25]

For patients with stage IV or recurrent breast cancer, the guidelines also recommend tissue or plasma-based ctDNA assays as part of comprehensive germline and somatic profiling to identify candidates for additional targeted therapies.

For patients with ER-/HER2- cancer, the guidelines support CTC testing with a 2B recommendation (based on lower-level evidence).

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.[26] 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.[12]

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.[27]

Cervical Cancer

National Comprehensive Cancer Network (NCCN)

The 4.2025 NCCN cervical cancer guidelines wrote that comprehensive genomic profiling via a validated plasma circulating tumor DNA (ctDNA) assay can be considered if tissue biopsy of metastatic site is not feasible or tissue is not available.[28]

Colorectal Cancer

National Comprehensive Cancer Network (NCCN)

The 3.2025 NCCN colon cancer guidelines wrote that "circulating tumor (ctDNA) is emerging as a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial."[29]

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.[30] 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."[30]

Esophageal and Esophagogastric Junction Cancers

The 3.2025 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."[31]

Gastric Cancers

The 2.2024 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."[32]

Occult Primary Cancer

The 2.2025 NCCN guidelines addressing occult primary cancer state that cell-free DNA testing can be considered if tumor tissue testing is not feasible.[33]

Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

The 2.2025 NCCN guidelines addressing ovarian cancer/fallopian tube cancer/primary peritoneal cancer state that molecular analyses may be performed on circulating tumor DNA (ctDNA or liquid biopsy) when tissue-based analysis is not clinically feasible.[34]

Pancreatic Adenocarcinoma

The 2.2025 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."[35]

EVIDENCE 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 National Comprehensive Cancer Network recommends the use of CTCs or ctDNA to test for PIK3CA mutations in the management of advanced or metastatic breast cancer, biliary tract cancers, esophageal/esophagogastric junction cancers, gastric cancer, pancreatic adenocarcinoma, cervical cancer, occult primary cancer, and ovarian, fallopian tube and primary peritoneal cancers. 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).

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

CODES*		
CPT	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
	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 *For the Therascreen PIK3CA test by QIAGEN Sciences using tumor tissue [0155U], see the Company medical policy for Genetic Testing: Gene Expression Profile Testing for Breast Cancer (Company)*
	0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
	0229U	BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
	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
	0285U	Oncology, disease progression and response monitoring to radiation, chemotherapy, or other systematic cancer treatments, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported in ng/mL
	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
	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
	0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
	0337U	Oncology (plasma cell disorders and myeloma), circulating plasma cell immunologic selection, identification, morphological characterization, and enumeration of plasma cells based on differential CD138, CD38, CD19, and CD45 protein biomarker expression, peripheral blood
	0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood

	0342U	Oncology (pancreatic cancer), multiplex immunoassay of C5, C4, cystatin C, factor B, osteoprotegerin (OPG), gelsolin, IGFBP3, CA125 and multiplex electrochemiluminescent immunoassay (ECLIA) for CA19-9, serum, diagnostic algorithm reported qualitatively as positive, negative, or borderline
	0356U	Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
	0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer
	0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection
	0395U	Oncology (lung), multi-omics (microbial DNA by shotgun next-generation sequencing and carcinoembryonic antigen and osteopontin by immunoassay), plasma, algorithm reported as malignancy risk for lung nodules in early-stage disease
	0404U	Oncology (breast), semiquantitative measurement of thymidine kinase activity by immunoassay, serum, results reported as risk of disease progression
	0405U	Oncology (pancreatic), 59 methylation haplotype block markers, next-generation sequencing, plasma, reported as cancer signal detected or not detected
	0409U	Oncology (breast), semiquantitative measurement of thymidine kinase activity by immunoassay, serum, results reported as risk of disease progression
	0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate
	~~0428U~~	**Termed 12/31/2024** ~~Oncology (breast), targeted hybrid-capture genomic sequence analysis panel, circulating tumor DNA (ctDNA) analysis of 56 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutation burden~~
	0453U	Oncology (colorectal cancer), cell free DNA (cfDNA), methylation based quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA)
	0485U	Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden
	0486U	Oncology (pan-solid tumor), next-generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm

		reported as quantitative measurement of methylation as a correlate of tumor fraction
	0487U	Oncology (solid tumor), cell-free circulating DNA, targeted genomic sequence analysis panel of 84 genes, interrogation for sequence variants, aneuploidy corrected gene copy number amplifications and losses, gene rearrangements, and microsatellite instability
	0490U	Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular–weight melanoma associated antigen, CD34 and CD45 protein biomarkers, peripheral blood
	0491U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker–expressing cells, peripheral blood
	0492U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker expressing cells, peripheral blood
	0496U	Oncology (colorectal), cell-free DNA, 8 genes for mutations, 7 genes for methylation by real-time RT-PCR, and 4 proteins by enzyme-linked immunosorbent assay, blood, reported positive or negative for colorectal cancer or advanced adenoma risk
	0501U	Oncology (colorectal), blood, quantitative measurement of cell-free DNA (cfDNA)
	0530U	Oncology (pan-solid tumor), ctDNA, utilizing plasma, next-generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation burden, interpretative report for single-nucleotide variants, copy number alterations, with therapy association
	0539U	Oncology (solid tumor), cell-free circulating tumor DNA (ctDNA), 152 genes, next-generation sequencing, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, copy number alterations, and microsatellite instability, using whole-blood samples, mutations with clinical actionability reported as actionable variant
	0562U	Oncology (solid tumor), targeted genomic sequence analysis, 33 genes, detection of single-nucleotide variants (SNVs), insertions and deletions, copy-number amplifications, and translocations in human genomic circulating cell-free DNA, plasma, reported as presence of actionable variants
	0566U	Oncology (lung), qPCRbased analysis of 13 differentially methylated regions (CCDC181, HOXA7, LRRC8A, MARCHF11, MIR129-2, NCOR2, PANTR1, PRKCB, SLC9A3, TBR1_2, TRAP1, VWC2, ZNF781), pleural fluid, algorithm reported as a qualitative result
	0571U	Oncology (solid tumor), DNA (80 genes) and RNA (10 genes), by next-generation sequencing, plasma, including single-nucleotide variants, insertions/deletions, copy-number alterations, microsatellite instability, and fusions, reported as clinically actionable variants
	0585U	Targeted genomic sequence analysis panel, solid organ neoplasm, circulating cell-free DNA (cfDNA) analysis from plasma of 521 genes, interrogation for sequence

		variants, gene copy number amplifications, gene rearrangements, and microsatellite instability, report shows identified mutations, including variants with clinical actionability
	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)
	81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements
	81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability
	81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
	81479	Unlisted Molecular Pathology
	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
HCPCS	None	

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. Zhang R, Shao F, Wu X, Ying K. Value of quantitative analysis of circulating cell free DNA as a screening tool for lung cancer: a meta-analysis. *Lung cancer.* 2010;69(2):225-231.
2. Rahbari NN, Aigner M, Thorlund K, et al. Meta-analysis shows that detection of circulating tumor cells indicates poor prognosis in patients with colorectal cancer. *Gastroenterology.* 2010;138(5):1714-1726. e1713.

3. Doyen J, Alix-Panabières C, Hofman P, et al. Circulating tumor cells in prostate cancer: a potential surrogate marker of survival. *Critical reviews in oncology/hematology.* 2012;81(3):241-256.
4. Fei F, Du Y, Di G, Wu J, Shao Z. Are changes in circulating tumor cell (CTC) count associated with the response to neoadjuvant chemotherapy in local advanced breast cancer? A meta-analysis. *Oncology research and treatment.* 2014;37(5):250-254.
5. Hayes Inc. FoundationOne Liquid CDx (Foundation Medicine Inc.). https://evidence.hayesinc.com/report/mta.foundation5564. Published 2024. Accessed 6/23/2025.
6. Hayes Inc. Guardant360 and Guardant360 CDx (Guardant Health Inc.). https://evidence.hayesinc.com/report/gte.guardant3767. Published 2024. Accessed 6/23/2025.
7. ECRI Institute. Guardant360 (Guardant Health, Inc.) Test for Informing Management of Advanced Solid Tumor Cancers. https://tinyurl.com/3cyxtmjv. Published 2024. Accessed 6/23/2025.
8. Hayes Inc. Colvera (Clinical Genomics Pathology Inc.). https://evidence.hayesinc.com/report/gte.clovera4471. Published 2022. Accessed 6/23/2025.
9. Hayes Inc. CellSearch Circulating Tumor Cell (CTC) Kit (Janssen Diagnostics LLC) For Monitoring Metastatic Breast Cancer. https://evidence.hayesinc.com/report/htb.cellsearch. Published 2017 (archived). Accessed 6/23/2025.
10. Sun C, Liao W, Deng Z, et al. The diagnostic value of assays for circulating tumor cells in hepatocellular carcinoma: a meta-analysis. *Medicine.* 2017;96(29).
11. Li J, Wang N, Tesfaluul N, Gao X, Liu S, Yue B. Prognostic value of circulating plasma cells in patients with multiple myeloma: A meta-analysis. *PloS one.* 2017;12(7):e0181447.
12. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology.* 2016;34(10):1134.
13. Xu H-T, Miao J, Liu J-W, Zhang L-G, Zhang Q-G. Prognostic value of circulating tumor cells in esophageal cancer. *World journal of gastroenterology.* 2017;23(7):1310.
14. Stephenson D, Nahm C, Chua T, et al. Circulating and disseminated tumor cells in pancreatic cancer and their role in patient prognosis: a systematic review and meta-analysis. *Oncotarget.* 2017;8(63):107223.
15. Tan Y, Wu H. The significant prognostic value of circulating tumor cells in colorectal cancer: A systematic review and meta-analysis. *Current problems in cancer.* 2018;42(1):95-106.
16. Gao Y, Xi H, Wei B, et al. Association between liquid biopsy and prognosis of gastric cancer patients: a systematic review and meta-analysis. *Frontiers in Oncology.* 2019;9:1222.
17. Mansouri S, Mokhtari-Hesari P, Naghavi-al-Hosseini F, Majidzadeh-A K, Farahmand L. The prognostic value of circulating tumor cells in primary breast cancer prior to any systematic therapy: a systematic review. *Current stem cell research & therapy.* 2019;14(6):519-529.
18. Khetrapal P, Lee MWL, Tan WS, et al. The role of circulating tumour cells and nucleic acids in blood for the detection of bladder cancer: A systematic review. *Cancer treatment reviews.* 2018;66:56-63.
19. Ye Y, Li S-L, Wang J-J, Liu B. The diagnostic value of circulating tumor cells for lung cancer: A systematic review and meta-analysis. *Medicine.* 2019;98(12):e14936.
20. Lee J-S, Rhee T-M, Pietrasz D, et al. Circulating tumor DnA as a prognostic indicator in resectable pancreatic ductal adenocarcinoma: A systematic review and meta-analysis. *Scientific reports.* 2019;9(1):1-7.

21. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *Journal of Clinical Oncology.* 2014;32(31):3483.
22. Musher BL, Melson JE, Amato G, et al. Evaluation of Circulating Tumor DNA for Methylated BCAT1 and IKZF1 to Detect Recurrence of Stage II/Stage III Colorectal Cancer (CRC). *Cancer Epidemiology and Prevention Biomarkers.* 2020;29(12):2702-2709.
23. Symonds EL, Pedersen SK, Murray D, et al. Circulating epigenetic biomarkers for detection of recurrent colorectal cancer. *Cancer.* 2020;126(7):1460-1469.
24. National Comprehensive Cancer Network (NCCN). Biliary Tract Cancers - Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf. Published 2025. Accessed 6/23/2025.
25. National Comprehensive Cancer Network (NCCN). Breast Cancer - Version 4.2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Published 2024. Accessed 6/23/2025.
26. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. *Archives of pathology & laboratory medicine.* 2018;142(10):1242-1253.
27. Van Poznak C, Somerfield MR, Bast RC, et al. Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of clinical oncology.* 2015;33(24):2695.
28. National Comprehensive Cancer Network (NCCN). Cervical Cancer -Version 4.2025. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Published 2025. Accessed 6/23/2025.
29. National Comprehensive Cancer Network (NCCN). Colon Cancer -Version 3.2025. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Published 2024. Accessed 6/23/2025.
30. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. *American journal of clinical pathology.* 2017;147(3):221-260.
31. National Comprehensive Cancer Network (NCCN). Esophageal and Esophagogastric Junction Cancers -Version 3.2025. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Published 2025. Accessed 6/23/2025.
32. National Comprehensive Cancer Network (NCCN). Gastric Cancer - Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Published 2025. Accessed 6/23/2025.
33. National Comprehensive Cancer Network (NCCN). Occult Primary Cancer -Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf. Published 2025. Accessed 6/23/2025.
34. National Comprehensive Cancer Network (NCCN). Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer - Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Published 2025. Accessed 6/23/2025.
35. National Comprehensive Cancer Network (NCCN). Pancreatic Adenocarcinoma - Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Published 2024. Accessed 6/23/2025.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
4/2023	Q2 2023 Code Set Update.
7/2023	Q3 2023 Code Set Update.
10/2023	Q4 2023 Code Set Update.
1/2024	Q1 2024 Code Set Update.
3/2024	Interim update. Liberalization to criteria to allow testing of advanced or recurrent breast cancer.
7/2024	Q3 Code Set Update.
8/2024	Annual update. Additional indications added to criteria. No changes to coding.
10/2024	Q3 2024 Code Set Update.
1/2025	Q1 2025 code set update.
4/2025	Q2 2025 code set update. New code added.
6/2025	Interim update. Added hepatobiliary tract cancers to criterion II.C
7/2025	Q3 2025 code set update. 3 new codes added and code revision.
8/2025	Annual update. No changes.
10/2025	Q4 2025 Code Set Update.