**Medical Policy Manual** Laboratory, Policy No. 46

# *Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers*

**Effective**: October 1, 2025

**Next Review:** August 2026
**Last Review:** September 2025

## IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

## DESCRIPTION

Liquid biopsy refers to the analysis of circulating tumor/cell-free DNA (ctDNA or cfDNA) or circulating tumor cells (CTCs) as methods of noninvasively characterizing tumors and tumor genome from the peripheral blood.

## MEDICAL POLICY CRITERIA

**Notes:**

- This policy only addresses testing for solid tumor cancers. For expanded tumor tissue panels, see Genetic Testing, Policy No. 83 in the Cross References section below (expanded panel testing is not covered for many indications).
- This policy does not address plasma-based *PIK3CA* testing for breast cancer.
- This policy does not address blood-based testing for *EGFR* variants in non-small cell lung cancer. See Genetic Testing, Policy No. 56 in the Cross References.
- This policy does not address circulating tumor HPV testing. See Laboratory, Policy No. 82 in the Cross References.

I. The use of cell-free tumor DNA testing for targeted treatment selection may be considered **medically necessary** when either of the following are met (see Policy

Guidelines):

A. The patient has advanced or metastatic breast cancer that is estrogen receptor (ER)-positive and HER2-negative, OR

B. Both of the following (1. and 2.) are met:

1. There is clinical documentation that tissue-based testing cannot be performed (e.g., insufficient sample, inaccessible tumor); and

2. The test includes one or more genes for which an FDA-approved targeted therapy is available for the cancer indication (see Policy Guidelines).

II. The use of cell-free DNA testing for targeted treatment selection is considered **investigational** when Criterion I. is not met.

III. The use of cell-free DNA or circulating tumor cell testing is considered **investigational** for all other indications related to solid tumors, including but not limited to measurable residual disease (MRD) testing and cancer screening in asymptomatic individuals.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

### TESTING FOR TARGETED TREATMENT SELECTION

Cell-free tumor DNA tests to guide targeted treatment selection may be limited to a single gene or include sequencing of many, often hundreds of genes. Tests that are commonly used for this purpose include, but are not limited to the following:

- Caris Assure™ (Caris MPI)
- CellMax-LBx (CellMax Life)
- FoundationOne® Liquid CDx (Foundation Medicine)
- Guardant360® CDx
- LiquidHALLMARK® (Lucence)
- Northstar Select™ (BillionToOne)
- OncoBEAM™ (Sysmex)
- PGDx elio plasma complete and resolve (Labcorp)
- Plasma Complete™ (Labcorp)
- Tempus xF (Tempus)

### CANCER INDICATIONS AND GENES WITH TARGETED CANCER TREATMENTS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION (FDA)

**Note**: This is not an exhaustive list of all genes with FDA-approved targeted treatments. Please consult the FDA website and/or National Cancer Institute website for more current or specific information.

| Cancer Indications with Targeted Treatments | | | |
|---|---|---|---|
| **Indication** | **Type** | **Genes** | **Medication** |
| **Any solid tumor** | Advanced or metastatic | *BRAF*<br>*NTRK(1/2/3)* | Tafinlar, Mekinist, Rozlytrek, Vitrakvi |
| **Breast cancer** | HER2-negative | *BRCA(1/2)* | Lynparza, Talzenna |
| | HR-positive, HER2-negative, advanced or metastatic | *ESR1*<br>*PIK3CA* | Orserdu, Pigray |
| | HER2-positive | *ERBB2 (HER2)* | Herceptin, Kadcyla, Perjeta |
| **Cholangiocarcinoma** | Advanced or metastatic | *FGFR2*<br>*IDH1* | Pemazyre, Tibsovo |
| **Colorectal cancer** | Metastatic | *BRAF*<br>*KRAS*<br>*NRAS* | Braftovi, Erbitux, Tukysa, Vectibix |
| **Gastrointestinal stromal tumor (GIST)** | Resected, unresectable, or metastatic | *KIT (c-KIT, CD117)* | Gleevec |
| **Melanoma, cutaneous** | Resected, unresectable, or metastatic | *BRAF* | Braftovi, Cotellic, Mekinist, Opdivo, Tafinlar, Tecentriq, Zelboraf |
| **Melanoma, uveal** | Unresectable, or metastatic | *HLA* | Kimmtrak |
| **Non-small cell lung cancer (NSCLC)** | Advanced or metastatic | *ALK*<br>*BRAF*<br>*EGFR*<br>*ERBB2 (HER2)*<br>*KRAS*<br>*ROS1* | Alcensa, Cyramza, Enhertu, Exkivity, Gavreto, Gilotrif, Iressa, Keytruda, Krazati, Lorbrena, Lumakras, Mekinist, Opdivo, Rozlytrek, Rybrevant, Tafinlar, Tagrisso, Tarceva, Tecentriq, Vizimpro, Xalkori, Zykadia |
| | Resected | *EGFR* | Tagrisso |
| **Ovarian cancer (including fallopian tube and primary peritoneal cancer)** | Advanced or recurrent | *BRCA(1/2)* | Lynparza, Rubraca |
| **Pancreatic cancer** | Metastatic | *BRCA(1/2)* | Lynparza |

| Cancer Indications with Targeted Treatments | | | |
|---|---|---|---|
| **Indication** | **Type** | **Genes** | **Medication** |
| **Prostate cancer** | Metastatic, castration-resistant | *BRCA(1/2)* | Lynparza, Rubraca |
| **Thyroid cancer** | Advanced or metastatic | *RET* | Gavreto |
| | Anaplastic and advanced or metastatic | *BRAF* | Mekinist, Tafinlar |
| **Urothelial carcinoma** | Advanced or metastatic | *FGFR(2/3)* | Balversa |

HR: hormone receptor

### TESTING FOR OTHER PURPOSES, INCLUDING MEASURABLE RESIDUAL DISEASE (MRD) AND CANCER SCREENING

Some cell-free tumor DNA and circulating tumor cell tests are not intended to identify genetic variants to guide targeted treatment selection but instead are used to screen for the presence of cancer or for disease recurrence. Tests that are commonly used for this purpose include, but are not limited to the following:

- Avantect Pancreatic Cancer Test and Ovarian Cancer Test (ClearNote Health)
- BTG Early Detection of Pancreatic Cancer (Breakthrough Genomics)
- CellMax-PanCa Monitoring Test (CellMax Life)
- CellMax-Prostate Cancer Test (CellMax Life)
- CELLSEARCH® Circulating Tumor Cell (CTC) tests (Cellsearch)
- Colvera® (Clinical Genomics)
- FirstSight™ (CellMax Life)
- Galleri® (Grail)
- Guardant360® Response (Guardant Health)
- Guardant360® Reveal (Guardant Health)
- HelioLiver™ (Helio Genomics®/Fulgent Therapeutics)
- Northstar Response™ (BillionToOne)
- Signatera™ (Natera)
- Velox™ (IV Diagnostics)

## LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test and the performing laboratory
2. The exact gene(s) and/or variant(s) being tested, if applicable
3. Relevant billing codes
4. Brief description of why tumor tissue testing is not possible

5. Name of medication(s) under consideration that requires genetic testing
6. Medical records related to the indication for testing:
    - Cancer type
    - Treatments received

## CROSS REFERENCES

1. Gene-Based Tests for Screening, Detection, and Management of Prostate or Bladder Cancer, Genetic Testing, Policy No. 17
2. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
3. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer, Genetic Testing, Policy No. 42
4. Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer (NSCLC), Genetic Testing, Policy No. 56
5. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83
6. Analysis of Proteomic and Metabolomic Patterns for Cancer Detection, Risk, Prognosis, or Treatment Selection, Laboratory, Policy No. 41
7. Circulating Tumor-Tissue Modified Viral DNA Testing for Cancer Management, Laboratory, Policy No. 82

## BACKGROUND

### CIRCULATING TUMOR DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA (cfDNA). Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs.[1] Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

### CIRCULATING TUMOR CELLS

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs.[1] Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for in detecting CTCs is prognostic, through quantification of circulating levels.

### DETECTING CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (e.g. BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver

mutations, which can impact therapy decisions or untargeted without knowledge of specific variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.[1]

## TARGETED TREATMENTS FOR SOLID TUMORS

There are many targeted treatments available for various solid tumor cancers. A list of some that have been approved by the FDA can be found in at their website listing the tests and associated companion diagnostics.

## BLOOD-BASED MULTI-CANCER SCREENING

Cancer is the second leading cause of death in the US following heart disease. Many cancers appear to have a better prognosis if diagnosed early in their natural history. This has led to efforts to detect preclinical cancers in asymptomatic persons through screening. However, screening tests have associated benefits and harms that must be considered when evaluating whether a test should be used in a population.

Cancer screening tests such as ‘liquid biopsies’ that are minimally invasive and can simultaneously detect multiple types of cancer have been called multicancer early detection (MCED) tests. The primary benefit of screening for cancer is the potential to diagnose cancer at an earlier stage or detect precursor lesions that can be treated with less aggressive or more effective treatment, thereby theoretically improving the length or quality of life. Thus, cancer-specific mortality and quality of life are the primary outcomes of interest for assessing benefit. However, mortality is a demanding outcome that requires long follow-up times and a large number of participants in order to produce reliable and precise estimates.

Longitudinal examination of the population-based, age-standardized stage distribution of all cancers may give early information on the likelihood of a survival benefit. However, it is possible for screening to increase the proportion of early-stage cancers that are detected without reducing the absolute incidence of advanced cancer because of overdiagnosis.

Population-based screening is applied to asymptomatic people without signs of disease. The prevalence of any given cancer is generally low. Therefore, the majority of those screened for a particular cancer are not destined to develop clinically significant cancer that needs treatment and therefore do not benefit from screening. However, all persons screened are at risk of harm from either the screening test or the cascade of events following from a positive screening test.

The majority of harms from cancer screening come from downstream cascading events. The harms may arise from the diagnostic work-up of false positive screens, from diagnosis and treatment of overdiagnosed cancers, and from false negative screens for those cancers where screens are already part of standard care.

The harms from the diagnostic work-up of false positives depends on the false positive rate and on the nature of the work-up. The false positive rate per screening test may be low, but given that many screening strategies include repeated screening tests over many years or a

lifetime, the absolute number of people with complications as a result of a false-positive diagnostic work-up can be considerable. In addition, in the context of a test for multiple cancers, false positives can occur across several diseases.

Additionally, overdiagnosis of cancer that would not have become burdensome during an individual's lifetime leads to unnecessary treatments along with their associated risks.

There is also the potential for false-negative test results to cause harm. For example, for those cancers that already have established screening recommendations as part of standard care (e.g., breast, prostate), the new cancer screening test might alter individuals' adherence to existing recommendations which could lead to missed early diagnoses.

### REGULATORY STATUS

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

Signatera® (Natera) is a laboratory developed test regulated under CLIA. The test has not been cleared or approved by the US Food and Drug Administration (FDA), but has received 3 Breakthrough Device Designations from FDA.

No blood-based multi-cancer screening tests have been approved or cleared by the U.S. Food and Drug Administration (FDA). Several tests, including Galleri® (GRAIL), CanScan™ (Geneseeq), OverC™ Multi-Cancer Detection Blood Test (Burning Rock) have been granted breakthrough device designation by the FDA.

## EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on three main principles:

1. Analytic validity of the test;
2. Clinical validity of the test (i.e., sensitivity, specificity, and positive and negative predictive values in relevant populations of patients and compared to the gold standard); and
3. Clinical utility of the test (i.e., how the results of the diagnostic test will be used to improve the management of the patient).

The context of this literature search focuses on treatment selection, monitoring treatment response, risk prediction, and screening in asymptomatic individuals. Validation studies are limited; therefore, this review is predominately focused on studies that correlate survival and risk of disease progression.

## SELECTING TREATMENT IN ADVANCED CANCER

Treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of liquid biopsy testing of patients who have

advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

Liquid biopsies are easier to obtain and less invasive than tissue biopsies. True-positive liquid biopsy test results lead to the initiation of appropriate treatment (e.g., targeted therapy) without tissue biopsy. False-positive liquid biopsy test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival.

In patients able to undergo tissue biopsy, negative liquid biopsies reflex to tissue testing. In patients unable to undergo tissue biopsy, a negative liquid biopsy result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between liquid biopsy and tissue biopsy.

## CIRCULATING TUMOR DNA

The American Society of Clinical Oncology and College of American Pathologists jointly convened an expert panel to review the current evidence on the use of ctDNA assays.[2] The literature review included a search for publications on the use of ctDNA assays for solid tumors in March 2017 and covers several different indications for the use of liquid biopsy. The search identified 1,338 references to which an additional 31 references were supplied by the expert panel. Seventy-seven articles were selected for inclusion. The summary findings are discussed in the following sections, by indication.

Merker (2018) concluded that while a wide range of ctDNA assays have been developed to detect driver mutations, there is limited evidence of the clinical validity of ctDNA analysis in tumor types outside of lung cancer and colorectal cancer (CRC). Preliminary clinical studies of ctDNA assays for detection of potentially targetable variants in other cancers such as *BRAF* variants in melanoma[3] and *PIK3CA* and *ESR1* variants in breast cancer were identified.[4, 5]

Since the end date of the searches conducted by Merker (2018), a number of observational studies have been published for various ctDNA tests. For example, two observational studies of the clinical validity of FoundationOne® Liquid (formerly FoundationACT®) in patients with various cancers compared liquid biopsy to tissue biopsy with FoundationOne® comprehensive genomic testing.[6, 7] Additional studies have assessed the validity of other tests, including the Guardant360 test[8, 9] and OncoBEAM™ CRC assay[10-13]. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. Multiple high-quality studies are needed to establish the clinical validity of a test.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. Merker (2018) concluded that no such trials have been reported for ctDNA tests.[2]

## CIRCULATING TUMOR CELLS

In breast cancer, observations that estrogen receptor–positive tumors can harbor estrogen receptor–negative CTCs,[14, 15] that overt distant metastases and CTCs can have discrepant human epidermal growth factor receptor 2 (HER2) status compared with the primary tumor,[16-18] and that the programmed death-ligand 1 is frequently expressed on CTCs in patients with

hormone receptor–positive, *HER2*-negative breast cancer[19] have suggested that trials investigating whether CTCs can be used to select targeted treatment are needed.

The clinical validity of each commercially available CTC test must be established independently. Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility.

## MONITORING TREATMENT RESPONSE IN CANCER

Monitoring of treatment response in cancer may be performed using tissue biopsy or imaging methods. Another proposed purpose of liquid biopsy testing in patients who have advanced cancer is to monitor treatment response, which could allow for changing therapy before clinical progression and potentially improve outcomes. Standard monitoring methods for assessing treatment response are tissue biopsy or imaging methods.

### CIRCULATING TUMOR DNA

Merker (2018) identified several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes as well as studies demonstrating that ctDNA can identify the emergence of resistance variants.[2] However, authors reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and concluded that clinical validity had not been established. Additionally, the authors concluded that there is no evidence that changing treatment before clinical progression, at the time of ctDNA progression, improves patient outcomes. Therefore, no inferences can be made about clinical utility.

### CIRCULATING TUMOR CELLS

Two randomized controlled trials have evaluated the clinical utility of using CTC to guide treatment decisions in patients with metastatic breast cancer.

Bidard (2021) reported on a noninferiority trial comparing CTC-driven and clinician-driven first-line therapy choice in patients with metastatic breast cancer.[20] Median PFS was 15.5 months (95% confidence interval [CI] 12.7 to 17.3) in the CTC arm and 13.9 months (95% CI 12.2 to 16.3) in the standard arm. The primary end point was met, with a hazard ratio (HR) of 0.94 (90% CI 0.81 to 1.09).

Smerage (2014) reported on the results of a randomized controlled trial of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after one cycle of first-line therapy could improve overall survival (OS; the primary study outcome).[21] Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median OS between arms C1 (10.7 months) and C2 (12.5 months, p=0.98). CTC levels were strongly prognostic, with a median OS for arms A, B, and C (C1 and C2 combined) of 35

months, 23 months, and 13 months, respectively (p<0.001). This trial showed the prognostic significance of CTCs in patients with metastatic breast cancer receiving first-line chemotherapy, but also that there was no effect on overall survival if patients with persistently increased CTC levels after 21 days of first-line chemotherapy were switched to alternative cytotoxic therapy.

Trials demonstrating that use of CTCs to monitor treatment for the purpose of making treatment changes are needed to demonstrate clinical utility. Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility through a chain of evidence.

## PREDICTING RISK OF RELAPSE

Monitoring for relapse after curative therapy in patients with cancer may be performed using imaging methods and clinical examination. Another proposed purpose of liquid biopsy testing in patients who have cancer is to detect and monitor for residual tumor, which could lead to early treatment that would eradicate residual disease and potentially improve outcomes. Standard monitoring methods for detecting relapse are imaging methods and clinical examination.

### CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS

Chidambaram (2022) conducted a systematic review and meta-analysis of the clinical utility of circulating tumor DNA testing in esophageal cancer.[22] Four retrospective studies (n=233, range 35 to 97) provided data to assess ctDNA for monitoring for recurrence after treatment. The pooled sensitivity was 48.9% (range 29.4% to 68.8%) and specificity was 95.5% (range 90.6% to 97.9%).

Merker (2018) identified several proof-of-principle studies demonstrating an association between persistent detection of ctDNA after local therapy and high risk of relapse.[2] However, current studies are retrospective and have not systematically confirmed that ctDNA is being detected before the metastatic disease has developed. They concluded that the performance characteristics had not been established for any assays.

Rack (2014) published results of a large multicenter study in which CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy using the CellSearch System.[23] After chemotherapy, 22% of patients were CTC-positive, and CTC positivity was negatively associated with prognosis.

Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer,[24] CRC,[25] bladder cancer,[26, 27] liver cancer,[28] and esophageal cancer.[29]

Merker (2018) concluded that there is no evidence that early treatment before relapse, based on changes in ctDNA, improves patient outcomes.[2] Similarly, no trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes.

### Signatera®

Colorectal Cancer

Chidharla (2023) published a systematic review and meta-analysis of 23 studies (n=3,568) investigating the use of ctDNA as a biomarker for minimal residual disease in patients with CRC after curative-intent surgery; only three of the included studies used the Signatera® ctDNA assay.[30] Loupakis (2021) evaluated the association of Signatera® on survival outcomes in 112 individuals who had undergone resection for metastatic CRC, and the sensitivity of Signatera testing was compared to digital droplet polymerase chain reaction (PCR) testing, but not to standard methods to identify recurrence, such as CEA and imaging.[31] Henriksen (2022) assessed the added benefit of serial ctDNA analysis; with samples taken at diagnosis, following surgery, during adjuvant therapy, and at follow up.[32] Kotani (2023) analyzed presurgical and postsurgical ctDNA levels in a large (n=1,039) prospective study that included patients with stage II to IV resectable CRC, and found that postsurgical ctDNA positivity at four weeks after surgery was associated with a significantly higher risk of recurrence (HR 10.0, 95% CI 7.7 to 14, p<0.0001), and identified patients who derived a benefit from adjuvant chemotherapy.[33] The results of the meta-analysis demonstrated that ctDNA positivity (including all tests, not just Signatera®) after surgery was associated with a significantly higher risk of recurrence, with a pooled HR of 7.27 for all stages of CRC. Furthermore, post-adjuvant chemotherapy ctDNA positivity was associated with an even higher risk of recurrence (pooled HR 10.59).

Several additional non-randomized studies have evaluated CTC tests for colon cancer recurrence. For example, Reinert (2019) enrolled 125 patients with stage I to III colon cancer in a validation study of the Signatera® assay.[34] Plasma samples were collected before surgery, at 30 days following surgery, and every three months for up to three years. The recurrence rate at three years was 70% in patients with a positive ctDNA test (7 of 10) compared to 11.9% (10 of 84) of those with a negative ctDNA test. In multivariate analyses, ctDNA status was associated with recurrence after adjusting for clinicopathological risk factors including stage, lymphovascular invasion, and microradical resection status.

Fakih (2022) directly compared Signatera® testing to other surveillance strategies in individuals with resected colorectal cancer in a retrospective observational study.[35] This study was unique in that it used NCCN recommended guidelines for surveillance and ctDNA testing was performed at the same interval as standard surveillance with CEA and imaging. Test characteristics for Signatera® were not significantly different from standard imaging techniques. Estimates were imprecise, with wide confidence intervals.

Altogether, five nonrandomized studies, for of which were noncomparative, examined the association of Signatera® testing to prognosis in individuals with CRC. They differed in their study designs, populations (e.g., stage of disease), frequency and timing of standard care, outcome measures, and timing of follow up. Three studies evaluated the association between positive ctDNA results and prognosis in CRC. These studies did not provide comparisons of ctDNA testing to standard methods of risk stratification for therapy selection, monitoring response to therapy, or early relapse detection. One retrospective study compared Signatera® testing to other surveillance strategies in individuals with resected colorectal cancer. There are no randomized controlled trials, and no studies in which Signatera® testing was used to guide treatment decisions.

Signatera® for Breast Cancer

Two noncomparative studies reported the association of Signatera® testing with survival outcomes in breast cancer. There are no randomized controlled trials, and no studies in which Signatera® testing was used to guide treatment decisions. Coombes (2019) evaluated Signatera® for disease surveillance in 49 individuals who had received surgery and adjuvant therapy for stage I to III breast cancer of various subtypes.[36] In this study, the test detected ctDNA in 16 of 18 individuals who subsequently relapsed, and the presence of ctDNA test was associated with poorer prognosis. Magbanua (2021) evaluated the test as a predictor of response to neoadjuvant chemotherapy in 84 individuals with nonmetastatic breast cancer who were enrolled in the I-SPY2 trial.[37] In this population, ctDNA positivity decreased during the course of neoadjuvant chemotherapy, from 73% before treatment, to 35% at three weeks, to 14% at the inter-regimen time point, and down to 9% after chemotherapy. HRs for recurrence indicate that positive predictive value increased over time. Major limitations of both studies include a lack of comparison to standard methods of monitoring, and heterogeneity in the study populations.

Signatera® for Bladder Cancer

Two nonrandomized studies have reported an association between Signatera® testing and prognosis in bladder cancer.

Christensen (2019) assessed the association of ctDNA with prognosis in 68 individuals with localized advanced bladder cancer.[38] The presence of ctDNA at diagnosis, after chemotherapy but before cystectomy, and after cystectomy were significantly associated with recurrence (HR 29.1, p=0.001; HR 12.0, p<0.001, and HR 129.6, p<0.001, respectively). Data from a 68-month follow-up of this cohort were reported by Lindskrog (2023), who additionally reported on the association of ctDNA with prognosis in a separate cohort of 102 patients who did not receive neoadjuvant chemotherapy and had ctDNA testing before and after cystectomy (median follow-up of 72 months).[39] Results demonstrated that ctDNA was prognostic regardless of whether or not patients received neoadjuvant chemotherapy before cystectomy.

Powles (2021) reported the association of a positive Signatera® test with treatment response in 581 individuals who had undergone surgery for urothelial cancer and were enrolled in a trial of atezolizumab versus observation.[40] Study participants who were positive for ctDNA had improved disease-free survival (DFS) and overall survival in the atezolizumab arm versus the observation arm (DFS HR 0.58, 95% CI 0.43 to 0.79, p=0.0024; overall survival HR, 0.59, 95% CI 0.41 to 0.86). No difference in DFS or overall survival between treatment arms was noted for patients who were negative for ctDNA. At two-year follow up, ctDNA status remained prognostic and no relapses were observed in the ctDNA-negative patients at baseline and after neoadjuvant therapy.

Study limitations, including a lack of comparison to tests used for the same purpose preclude drawing conclusions about clinical validity and usefulness. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity.

Signatera® for Additional Indications

The evidence for the use of Signatera® to detect relapse in non-small cell lung cancer (NSCLC) following surgery is limited to a subgroup analysis of 24 individuals enrolled in TRACERx, a longitudinal cohort study of tumor sampling and genetic analysis in individuals

with NSCLC.[41] Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test (defined as at least two single-nucleotide variants detected). Of 10 individuals with no relapse after a median follow up of 775 days (range 688 to 945 days), one had a positive ctDNA test (10%). Major limitations include no comparison to standard surveillance methods and imprecise estimates due to the small sample size. Additionally, the commercially available Signatera® has been updated since this publication.

One noncomparative retrospective study reported the association of Signatera® testing measured before and after surgery with relapse and recurrence in 17 individuals with esophageal adenocarcinoma.[42] Patients who were ctDNA-positive before surgery had significantly poorer DFS (p=0.042), with a median DFS of 32.0 months vs. 63.0 months in ctDNA-negative preoperative patients. This study was limited by the very small number sample size, and its retrospective design.

Bratman (2020) evaluated the use of Signatera® to predict treatment response in 106 individuals receiving pembrolizumab for solid tumors, including squamous cell cancer of head and neck, triple negative breast cancer, high-grade serous ovarian cancer, malignant melanoma, and mixed solid tumors.[43] Lower-than-median ctDNA levels at baseline were associated with improved overall survival (adjusted HR 0.49, 95% CI 0.29 to 0.83) and PFS (adjusted HR 0.54; 95% CI, 0.34 to 0.85). Among participants with at least two ctDNA measurements, any rise in ctDNA levels during surveillance above baseline was associated with rapid disease progression and poor survival (median overall survival of 13.7 months), whereas among 12 patients whose ctDNA cleared during treatment, overall survival was 100% at a median follow up of 25.4 months (range 10.8 to 29.5 months) following the first clearance. This single-center study is limited by its small sample size and variability in results across different tumor types. The study did not include a comparison of monitoring with ctDNA to standard methods of monitoring response such as repeat imaging.

**Colvera®**

Murray (2018) enrolled 172 patients with invasive colorectal cancer with plasma samples collected within 12 months after surgery.[44] In this study, multivariate analysis found that risk of recurrence was increased among patients who had positive Colvera® tests following surgery. Risk of colorectal cancer-related death was also increased among patients who had a positive ctDNA test following surgery, but multivariate analysis could not be performed for this outcome due to the low number of events.

Symonds (2020) examined the association between a positive Colvera® test result and recurrence of colorectal cancer in 144 patients who had no evidence of residual disease after surgical resection and/or neoadjuvant chemotherapy.[45] Blood samples were also tested for carcinoembryonic antigen (CEA), and the association between a positive CEA test and recurrent colorectal cancer was assessed. A positive Colvera® test was an independent predictor of recurrence, while a positive CEA test was not found to be a significant predictor of recurrence after adjusting for other predictors of recurrence (e.g., stage at primary diagnosis). Sensitivity of the Colvera® assay for detecting recurrence was significantly greater than the sensitivity of CEA (66% vs. 31.9%, p=0.001), but specificity was not significantly different (97.9% vs. 96.4%, p=1.00). The positive predictive value was not significantly different for Colvera® and CEA (94.3% vs. 83.3%, p=0.262), but the negative predictive value was significantly greater for Colvera® (84.4% vs. 71.7%, p<0.001).

Musher (2020) conducted an additional prospective cross-sectional observational study in patients undergoing surveillance after definitive therapy for stage II or III colorectal cancer.[46] Samples were collected within six months of planned radiologic surveillance imaging and tested using the Colvera® assay and a CEA assay. A total of 322 patients were included, with 27 experiencing recurrence and 295 not experiencing recurrence. The sensitivities of Colvera® and CEA for detecting colorectal cancer recurrence using a single time-point blood test were 63% (17/27) and 48.1% (13/27), respectively (p=0.046). The specificities of single time-point Colvera® and CEA were 91.5% and 96.3%, respectively (p=0.012).

While several non-randomized studies have shown an association between Colvera® ctDNA results and risk of recurrence, they are limited by their observational design and relatively small numbers of patients. Management decisions were not based on test results. There are no controlled studies of management changes made in response to Colvera® test results compared to other risk factors, and no studies showing whether testing improved outcomes.

## SCREENING FOR CANCER IN ASYMPTOMATIC INDIVIDUALS

It has been proposed that liquid biopsy tests, such as the Galleri® test (Grail), could be used to screen asymptomatic patients for early detection of cancer, which could allow for initiating treatment at an early stage, potentially improving outcomes. The outcome of primary interest is progression-free survival. Diagnosis of cancer that is not present or would not have become clinically important (false-positives and overdiagnosis) would lead to unnecessary treatment and treatment-related morbidity.

### GALLERI®

Schrag (2023) reported results of the PATHFINDER prospective study of the Galleri® test. PATHFINDER enrolled 6,662 adults aged 50 years or older without signs or symptoms of cancer from oncology and primary care outpatient clinics at seven U.S. health networks between 2019 and 2020.[47] A total of 6,621 participants had analyzable results and were included in the analysis; 64% of participants were women and 92% were White. The reference standard was a cancer diagnosis established by pathological, laboratory, or radiographic confirmation. Diagnostic assessments were coordinated by, and at the discretion of, the participant's doctor. Participants were followed for 12 months. A cancer signal was detected by the Galleri® test in 92 (1.4%) participants. In two of those participants, diagnostic assessments began before Galleri test results were reported. Thirty-five of the participants with a positive Galleri® test were diagnosed with cancer; 57 of the participants with a positive Galleri® test had no cancer diagnosis. The median time to diagnostic resolution was 79 days (interquartile range [IQR] 37 to 219). A total of 76 of the 90 participants with positive Galleri® test results had laboratory tests, 83 (92%) had at least one imaging test, 44 (53%) had more than one imaging study, and 44 (49%) had at least one procedure. Within 12 months of enrollment, 122 cancers were diagnosed in 121 participants: 35 (29%) detected by Galleri®; 38 (31%) detected through other screening tests; 48 (40%) clinically detected. Overall positive predictive value (PPV) was 35/92 (38%, 95% CI 29 to 48). Negative predictive value (NPV) was 6,235/6,321(99%, 95% CI 98 to 99). Specificity was 6,235/6,290 (99%, 95% CI 99 to 99). Sensitivity was not reported in the publication but is 35/121 (29%, 95% CI 21 to 38) based on the values provided. A correct first or second prediction of tissue of origin was returned for 33 (97%) of 34 true positives.

There are no studies demonstrating clinical utility of the Galleri test. A randomized controlled trial is underway in the United Kingdom, conducted within the National Health Service, to test

whether Galleri® can reduce the number of late-stage cancers.[48] The trial has enrolled over 140,000 people from the general population of England ages 50 to 77 years who did not have or were not being investigated for cancer. Participants were randomized to have their blood tested using Galleri® or to the control group who will have their blood stored. Blood is being collected up to three times annually. Follow-up is underway. The study registration indicates that the estimated study completion date is in 2026.

A systematic review by Wade (2025) evaluated the evidence for blood-based multi-cancer early detection testing as screening tests.[49] Thirty-six studies met the inclusion criteria, including one ongoing randomized controlled trial; other studies were cohort or case-control studies. According to the authors, “None of the studies were of good quality, mainly because they did not properly check whether the test result might have been incorrect and whether participants with a negative test result actually had cancer.” Additional limitations were noted regarding study populations and lack of patient-relevant outcomes such as mortality, harms, or health-related quality of life.

The review by Merker (2018) reported that there is no evidence of clinical validity for the use of ctDNA in asymptomatic individuals.[2]

Systematic reviews with meta-analyses have evaluated the diagnostic accuracy of CTCs in patients with gastric and bladder/urothelial cancer.[50, 51] Reported sensitivity was low in both cancers (42% and 35%) overall. Sensitivity was lower in patients with early-stage cancer, suggesting that the test would not be useful as an initial screen.

The evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests as a screening test for cancer; therefore, no inferences can be made about clinical utility through a chain of evidence.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The American Society of Clinical Oncology (ASCO) 2022 guideline update on biomarkers for systemic therapy in metastatic breast cancer (MBC) does not recommend the use of ctDNA as a biomarker to monitor the response to therapy (Type of recommendation: informal consensus-based; Quality of evidence: low; Strength of recommendation: moderate).[52] The guidelines also provide the following recommendations:

- Patients with locally recurrent unresectable or metastatic hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase inhibitor and hormonal therapy should undergo testing for PIK3CA mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine their eligibility for treatment with the phosphatidylinositol 3-kinase inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with PIK3CA mutations (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- There are insufficient data at present to recommend routine testing for *ESR1* mutations to guide therapy for hormone receptor-positive, HER2-negative MBC. Existing data suggest reduced efficacy of aromatase inhibitors (AIs) compared with the selective

estrogen receptor degrader fulvestrant in patients who have tumor or ctDNA with ESR1 mutations (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
- There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

## NATIONAL COMPREHENSIVE CARE NETWORK

There is no general National Comprehensive Cancer Network (NCCN) guideline on the use of liquid biopsy. Refer to treatment recommendations by cancer type (see examples below).

The National Comprehensive Care Network (NCCN) Clinical Practice Guidelines for colon cancer (v.4.2025) does not include circulating tumor cells or circulating tumor DNA in the treatment algorithms and states that "Circulating tumor (ctDNA) is a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care and treatment decision-making are not recommended based on ctDNA results."[53]

The NCCN guidelines for breast cancer (v.4.2025) state that "tumor tissue or plasma-based circulating tumor DNA (ctDNA) assays may be used and each of these have benefits and limitations for diagnosis and disease progression. Tissue-based assays have greater sensitivity for some alterations, but ctDNA may reflect tumor heterogeneity more accurately." They also state that the "clinical use of circulating tumor cells or ctDNA in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring. Patients with persistently increased CTC after 3 weeks of first-line chemotherapy have a poor PFS and OS."[54]

For NSCLC (v.8.2025), the NCCN guidelines state that cell-free/circulating tumor DNA testing should not be used in lieu of a histological tissue diagnosis, and that "ctDNA is not routinely recommended in settings other than advanced/metastatic disease. For stages I–III, tissue-based testing is preferred. Metastatic disease confined to the thorax may have a higher yield with tissue-based testing."[55] The guidelines state that limitations of ctDNA testing include:

- Low tumor fraction/ctDNA; some assays include a measure of ctDNA fraction, which can aid in identification of situations in which low ctDNA fraction might suggest compromised sensitivity
- The presence of mutations from sites other than the target lesion, most commonly clonal hematopoiesis of indeterminate potential (CHIP) or postchemotherapy marrow clones. *KRAS* and *TP53* can be seen in either of these circumstances
- The inherent ability of the assay to detect fusions or other genomic variation of relevance

NCCN Guidelines on Genetic/Familial High-risk Assessment: Breast, Ovarian, and Pancreatic (v.1.2026) make the following statement regarding screening with ctDNA tests:[56]

"For individuals at increased hereditary risk for cancer, use of pre-symptomatic ctDNA cancer detection assays should only be offered in the setting of prospective clinical trials, because the sensitivity, false-positive rates, and positive predictive value of ctDNA tests for early-stage disease, which are needed to derive clinical utility and determine clinical validity, are not fully defined. The psychological impact of ctDNA testing remains unknown. For these reasons

ctDNA should not be used, outside of the clinical trial setting, to replace well-established methods of cancer screening (eg, mammography)"

## SUMMARY

Although there is limited evidence regarding the clinical utility of circulating tumor DNA (ctDNA) testing in patients with cancer, this testing may help to determine eligibility for FDA-approved targeted cancer treatments for advanced or metastatic breast cancer that is estrogen receptor (ER)-positive and HER2-negative, and for other solid tumors when tumor tissue is not available. Therefore, this testing may be considered medically necessary when policy criteria are met.

There is not enough research to show that testing for variants in circulating tumor DNA (ctDNA) to select targeted treatment improves health outcomes when policy criteria are not met. This includes ctDNA testing as an adjunct to, or replacement for tumor tissue testing, when tumor tissue is possible, or testing when there is no FDA-approved targeted treatment for the indication. Plasma-based ctDNA testing is generally less sensitive than tumor tissue testing and may identify changes that are not associated with the tumor. Therefore, this testing is considered investigational when medical necessity criteria are not met. Note that expanded tumor tissue panels to select targeted treatment are addressed in a separate policy and may not be covered for some indications.

There is not enough research to show that testing for circulating tumor/cell-free DNA (ctDNA or cfDNA) or circulating tumor cells (CTCs) for purposes other than targeted treatment selection can improve overall health outcomes for patients. Various ctDNA and CTC tests have been proposed to detect the presence or recurrence of solid tumor cancers. However, the impact such testing on health outcomes has not been clearly demonstrated in prospective studies. In addition, no clinical practice guidelines based on research recommended routine use of this type of testing in patient management. Therefore, CTC and ctDNA testing that is not for the purpose of selecting a targeted treatment, including but not limited to measurable residual disease (MRD) testing or cancer screening in asymptomatic individuals, is considered investigational.

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## CODES

| Codes | Number | Description |
|---|---|---|
| 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 |
| | 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) and 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 |

| Codes | Number | Description |
|---|---|---|
| | 0306U | Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient specific panel for future comparisons to evaluate for MRD |
| | 0307U | Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD |
| | 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 |
| | 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 |
| | 0340U | Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate |
| | 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 |
| | 0405U | Oncology (pancreatic), 59 methylation haplotype block markers, next-generation sequencing, plasma, reported as cancer signal detected or not detected |
| | 0409U | Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability |
| | 0410U | Oncology (pancreatic), DNA, whole genome sequencing with 5-hydroxymethylcytosine enrichment, whole blood or plasma, algorithm reported as cancer detected or not detected |
| | 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~~ | ~~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~~ (Deleted 01/01/2025) |
| | 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 |

| Codes | Number | Description |
|---|---|---|
| | | 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 |
| | 0507U | Oncology (ovarian), DNA, whole genome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected |
| | 0530U | Oncology (pan-solid tumor), ctDNA, utilizing plasma, next-generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation |
| | 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 |
| | 0560U | Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments |
| | 0561U | Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD |
| | 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 |
| | 0565U | Oncology (hepatocellular carcinoma), next-generation sequencing methylation pattern assay to detect 6626 epigenetic alterations, cell-free DNA, plasma, algorithm reported as cancer signal detected or not detected |
| | 0569U | Oncology (solid tumor), next-generation sequencing analysis of tumor methylation markers (>20000 differentially methylated regions) present in cell-free circulating tumor DNA (ctDNA), whole blood, algorithm reported as presence or absence of ctDNA with tumor fraction, if appropriate |

| Codes | Number | Description |
|---|---|---|
| | 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 |
| | 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 |
| | 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 | |

***Date of Origin:*** *July 2005*