Medical Policy Manual Laboratory, Policy No. 46

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

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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 section below.

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 measurable residual disease (MRD) testing and cancer screening.

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:

- CellMax-LBx (CellMax Life)
- FoundationOne® Liquid CDx (Foundation Medicine)
- Guardant360® CDx
- LiquidHALLMARK® (Lucence)
- OncoBEAM™ (Sysmex)
- PGDx elio plasma complete and resolve (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* *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* *PIK3CA*	Orserdu, Piqray
	HER2-positive	*ERBB2 (HER2)*	Herceptin, Kadcyla, Perjeta
Cholangiocarcinoma	Advanced or metastatic	*FGFR2* *IDH1*	Pemazyre, Tibsovo
Colorectal cancer	Metastatic	*BRAF* *KRAS* *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* *BRAF* *EGFR* *ERBB2 (HER2)* *KRAS* *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 (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) (Cellsearch)
- Colvera® (Clinical Genomics)
- FirstSight™ (CellMax Life)
- Galleri® (Grail)
- Guardant360® Response (Guardant Health)
- Guardant360® Reveal (Guardant Health)
- HelioLiver™ (Fulgent Therapeutics)
- 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
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/or Management of Prostate 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. Molecular Analysis for Targeted Therapy of 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 Patterns for Early Detection or Assessing Risk of Cancer, Laboratory, Policy No. 41

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.

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.

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 RCTs 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 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.

Since the Merker publication, 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.[30] 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.[31] 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.

Murray (2018) enrolled 172 patients with invasive colorectal cancer with plasma samples collected within 12 months after surgery.[32] 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.[33] 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.[34] 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 these studies showed an association between 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 ctDNA test results. There are no controlled studies of management changes made in response to ctDNA test results compared to other risk factors, and no studies showing whether testing improved outcomes.

SCREENING FOR CANCER IN ASYMPTOMATIC INDIVIDUALS

It has also been proposed that liquid biopsies 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.

CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS

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.[35, 36] 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

Based on a review of the recent evidence, the American Society of Clinical Oncology (2016) recommends clinicians not use circulating tumor cells to guide decisions on adjuvant systemic therapy in the clinical practice guideline on appropriate use of breast tumor biomarker assay to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer.[37]

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.2.2023) does not include circulating tumor cells or circulating tumor DNA in the treatment algorithms and states that “there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results.”[38]

The NCCN guidelines for breast cancer (v.4.2023) state that the use of circulating tumor cells or ctDNA in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring.[39] According to the guidelines, “Patients with persistently increased CTC after 3 weeks of first-line chemotherapy have a poor PFS and OS. In spite of its prognostic ability, CTC count has failed to show a predictive value.”

For non-small cell lung cancer (v.3.2023), the guidelines state that cell-free/circulating tumor DNA testing should not be used in lieu of a histological tissue diagnosis.[40] The guidelines explain that studies have demonstrated cell-free tumor DNA testing generally has high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate, and that no guidelines exist regarding the recommended performance characteristics of liquid biopsy. In specific clinical circumstances (e.g., patient is unfit for tumor tissue sampling), cell-free/circulating tumor DNA testing may be considered.

NATIONAL ACADEMY OF CLINICAL BIOCHEMISTRY

In 2008, the National Academy of Clinical Biochemistry (NACB) issued a guideline on the use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancer.[41] Circulating tumor cells were discussed in the future developments section related to prostate cancer. The

panel concluded that the measurement of circulating prostate cancer cells was not sufficiently validated to recommend testing for CTCs in routine clinical practice.

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 people with solid tumors. 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 is considered investigational.

REFERENCES

1. Alix-Panabieres C, Pantel K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. *Cancer discovery.* 2016;6(5):479-91. PMID: 26969689
2. 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. *J Clin Oncol.* 2018:Jco2017768671. PMID: 29504847
3. Ascierto PA, Minor D, Ribas A, et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. *J Clin Oncol.* 2013;31(26):3205-11. PMID: 23918947
4. Baselga J, Im SA, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology.* 2017;18(7):904-16. PMID: 28576675

5. Schiavon G, Hrebien S, Garcia-Murillas I, et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. *Science translational medicine.* 2015;7(313):313ra182. PMID: 26560360
6. Zhou C, Yuan Z, Ma W, et al. Clinical utility of tumor genomic profiling in patients with high plasma circulating tumor DNA burden or metabolically active tumors. *J Hematol Oncol.* 2018;11(1):129. PMID: 30400986
7. Clark TA, Chung JH, Kennedy M, et al. Analytical Validation of a Hybrid Capture-Based Next-Generation Sequencing Clinical Assay for Genomic Profiling of Cell-Free Circulating Tumor DNA. *J Mol Diagn.* 2018;20(5):686-702. PMID: 29936259
8. Palmero R, Taus A, Viteri S, et al. Biomarker Discovery and Outcomes for Comprehensive Cell-Free Circulating Tumor DNA Versus Standard-of-Care Tissue Testing in Advanced Non–Small-Cell Lung Cancer. *JCO Precision Oncology.* 2021(5):93-102. PMID:
9. Bustamante Alvarez JG, Janse S, Owen DH, et al. Treatment of Non-Small-Cell Lung Cancer Based on Circulating Cell-Free DNA and Impact of Variation Allele Frequency. *Clin Lung Cancer.* 2021;22(4):e519-e27. PMID: 33414052
10. Grasselli J, Elez E, Caratù G, et al. Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer. *Ann Oncol.* 2017;28(6):1294-301. PMID: 28368441
11. Vidal J, Muinelo L, Dalmases A, et al. Plasma ctDNA RAS mutation analysis for the diagnosis and treatment monitoring of metastatic colorectal cancer patients. *Ann Oncol.* 2017;28(6):1325-32. PMID: 28419195
12. García-Foncillas J, Tabernero J, Élez E, et al. Prospective multicenter real-world RAS mutation comparison between OncoBEAM-based liquid biopsy and tissue analysis in metastatic colorectal cancer. *British journal of cancer.* 2018;119(12):1464-70. PMID: 30467411
13. Normanno N, Esposito Abate R, Lambiase M, et al. RAS testing of liquid biopsy correlates with the outcome of metastatic colorectal cancer patients treated with first-line FOLFIRI plus cetuximab in the CAPRI-GOIM trial. *Ann Oncol.* 2018;29(1):112-18. PMID: 28950295
14. Babayan A, Hannemann J, Spotter J, et al. Heterogeneity of estrogen receptor expression in circulating tumor cells from metastatic breast cancer patients. *PLoS One.* 2013;8(9):e75038. PMID: 24058649
15. Liu Y, Liu Q, Wang T, et al. Circulating tumor cells in HER2-positive metastatic breast cancer patients: a valuable prognostic and predictive biomarker. *BMC Cancer.* 2013;13:202. PMID: 23617715
16. Fehm T, Muller V, Aktas B, et al. HER2 status of circulating tumor cells in patients with metastatic breast cancer: a prospective, multicenter trial. *Breast cancer research and treatment.* 2010;124(2):403-12. PMID: 20859679
17. Riethdorf S, Muller V, Zhang L, et al. Detection and HER2 expression of circulating tumor cells: prospective monitoring in breast cancer patients treated in the neoadjuvant GeparQuattro trial. *Clin Cancer Res.* 2010;16(9):2634-45. PMID: 20406831
18. Ignatiadis M, Rothe F, Chaboteaux C, et al. HER2-positive circulating tumor cells in breast cancer. *PLoS One.* 2011;6(1):e15624. PMID: 21264346
19. Mazel M, Jacot W, Pantel K, et al. Frequent expression of PD-L1 on circulating breast cancer cells. *Molecular oncology.* 2015;9(9):1773-82. PMID: 26093818
20. Bidard FC, Jacot W, Kiavue N, et al. Efficacy of Circulating Tumor Cell Count-Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor-Positive, ERBB2-

Negative Metastatic Breast Cancer: The STIC CTC Randomized Clinical Trial. *JAMA Oncol.* 2021;7(1):34-41. PMID: 33151266
21. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol.* 2014;32:3483-9. PMID: 24888818
22. Chidambaram S, Markar SR. Clinical utility and applicability of circulating tumor DNA testing in esophageal cancer: a systematic review and meta-analysis. *Dis Esophagus.* 2022;35(2). PMID: 34286823
23. Rack B, Schindlbeck C, Juckstock J, et al. Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. *Journal of the National Cancer Institute.* 2014;106(5). PMID: 24832787
24. Thalgott M, Rack B, Horn T, et al. Detection of circulating tumor cells in locally advanced high-risk prostate cancer during neoadjuvant chemotherapy and radical prostatectomy. *Anticancer research.* 2015;35(10):5679-85. PMID: 26408743
25. Deneve E, Riethdorf S, Ramos J, et al. Capture of viable circulating tumor cells in the liver of colorectal cancer patients. *Clinical chemistry.* 2013;59(9):1384-92. PMID: 23695297
26. Rink M, Chun FK, Dahlem R, et al. Prognostic role and HER2 expression of circulating tumor cells in peripheral blood of patients prior to radical cystectomy: a prospective study. *European urology.* 2012;61(4):810-7. PMID: 22277196
27. Gazzaniga P, de Berardinis E, Raimondi C, et al. Circulating tumor cells detection has independent prognostic impact in high-risk non-muscle invasive bladder cancer. *International journal of cancer Journal international du cancer.* 2014;135(8):1978-82. PMID: 24599551
28. Schulze K, Gasch C, Staufer K, et al. Presence of EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. *International journal of cancer Journal international du cancer.* 2013;133(9):2165-71. PMID: 23616258
29. Vashist YK, Effenberger KE, Vettorazzi E, et al. Disseminated tumor cells in bone marrow and the natural course of resected esophageal cancer. *Annals of surgery.* 2012;255(6):1105-12. PMID: 22580852
30. Reinert T, Henriksen TV, Christensen E, et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer. *JAMA Oncol.* 2019;5(8):1124-31. PMID: 31070691
31. Fakih M, Sandhu J, Wang C, et al. Evaluation of Comparative Surveillance Strategies of Circulating Tumor DNA, Imaging, and Carcinoembryonic Antigen Levels in Patients With Resected Colorectal Cancer. *JAMA Netw Open.* 2022;5(3):e221093. PMID: 35258578
32. Murray DH, Symonds EL, Young GP, et al. Relationship between post-surgery detection of methylated circulating tumor DNA with risk of residual disease and recurrence-free survival. *J Cancer Res Clin Oncol.* 2018;144(9):1741-50. PMID: 29992492
33. Symonds EL, Pedersen SK, Murray D, et al. Circulating epigenetic biomarkers for detection of recurrent colorectal cancer. *Cancer.* 2020;126(7):1460-69. PMID: 31909823
34. 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 Epidemiol Biomarkers Prev.* 2020;29(12):2702-09. PMID: 32958500

35. Msaouel P, Koutsilieris M. Diagnostic value of circulating tumor cell detection in bladder and urothelial cancer: systematic review and meta-analysis. *BMC Cancer.* 2011;11:336. PMID: 21816094
36. Tang L, Zhao S, Liu W, et al. Diagnostic accuracy of circulating tumor cells detection in gastric cancer: systematic review and meta-analysis. *BMC Cancer.* 2013;13:314. PMID: 23806209
37. 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. *J Clin Oncol.* 2016;34(10):1134-50. PMID: 26858339
38. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Colon Cancer. [cited 08/14/2023]. 'Available from:' http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
39. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Breast Cancer. [cited 08/14/2023]. 'Available from:' http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
40. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer. [cited 8/14/2023]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
41. Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. *Clinical chemistry.* 2008;54:e11-79. PMID: 19042984

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, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
	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

Codes	Number	Description
		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 highrisk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gammacarboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
	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
	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
	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
	~~0397U~~	~~Oncology (non-small cell lung cancer), cell-free DNA from plasma, targeted sequence analysis of at least 109 genes, including sequence variants, substitutions, insertions, deletions, select rearrangements, and copy number variations~~ (Deleted 10/01/2023)
	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

Codes	Number	Description
	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*