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.
- This policy does not address blood-based testing for epidermal growth factor receptor variants in non-small-cell lung cancer. See Genetic Testing, Policy No. 56 in the Cross References section below.

The use of circulating tumor/cell-free DNA (ctDNA or cfDNA) and/or circulating tumor cells is considered investigational for all indications.
NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

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 56
5. 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. 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. 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 CTDNA AND CTCS

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 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]

Examples of liquid biopsy tests related to indications covered in this review are shown in Table 1.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Test</th>
<th>Type of Liquid Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocept</td>
<td>Liquid Biopsies for breast, colorectal, gastric, prostate, and melanoma</td>
<td>ctDNA</td>
</tr>
<tr>
<td>CellMax Life</td>
<td>CellMax-LBx Liquid Biopsy</td>
<td>CTC plus ctDNA</td>
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<tr>
<td></td>
<td>CellMax-CRC Colorectal Cancer Early Detection Test</td>
<td>CTC</td>
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<tr>
<td></td>
<td>CellMax-PanCa Monitoring Test</td>
<td>CTC</td>
</tr>
<tr>
<td></td>
<td>CellMax-Prostate Cancer Test</td>
<td>CTC</td>
</tr>
<tr>
<td>Cynvenio</td>
<td>ClearID® Solid Tumor Panel</td>
<td>ctDNA</td>
</tr>
<tr>
<td></td>
<td>ClearID® HER2 Expression LiquidBiopsy</td>
<td>CTC</td>
</tr>
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<td>Foundation Medicine</td>
<td>FoundationACT®</td>
<td>ctDNA</td>
</tr>
<tr>
<td>Guardant Health</td>
<td>Guardant360®</td>
<td>ctDNA</td>
</tr>
<tr>
<td>IVDiagnostics</td>
<td>Velox™</td>
<td>CTC</td>
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<tr>
<td>Pathway Genomics</td>
<td>CancerIntercept® Detect</td>
<td></td>
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<td>PlasmaSELECT™</td>
<td>ctDNA</td>
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<tr>
<td>Sysmex Inostics</td>
<td>OncoBEAM™</td>
<td>ctDNA</td>
</tr>
<tr>
<td>Circulogene</td>
<td>Theranostics</td>
<td>ctDNA</td>
</tr>
</tbody>
</table>

CTC: circulating tumor cell; ctDNA: circulating tumor DNA.

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 1338 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]

The clinical validity of the OncoBEAM RAS CRC assay has been evaluated in 115 patients with metastatic CRC.[6] 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\(^7,8\) that overt distant metastases and CTCs can have discrepant human epidermal growth factor receptor 2 status compared with the primary tumor\(^9-11\) and that the programmed death-ligand 1 is frequently expressed on CTCs in patients with hormone receptor–positive, \(HER2\)-negative breast cancer\(^12\) 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**

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).\(^13\) 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 OS 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**

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.[14] 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,[15] CRC,[16] bladder cancer,[17,18] liver cancer,[19] and esophageal cancer.[20]

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

**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.[21,22] 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.[23]

NATIONAL COMPREHENSIVE CARE NETWORK

The National Comprehensive Care Network (NCCN) Clinical Practice Guidelines for colon (v.3.2018) and prostate cancer (v.4.2018) do not address circulating tumor cells or circulating tumor DNA.[24,25] The guidelines for breast cancer (v.1.2018) state that the use of circulating tumor cells in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring.[26]

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.[27] 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

There is not enough research to know if measurement for circulating tumor/cell-free DNA (ctDNA or cfDNA) or circulating tumor cells (CTCs) improves overall health outcomes for people with solid tumor cancer. Levels may be associated with the presence of metastatic disease and prognosis, however, the prospective use of this information to impact care (i.e., clinical utility) has not been demonstrated. In addition, no clinical practice guidelines based on research recommended the use of CTCs in patient management. Therefore, detection and quantification of circulating tumor cells and/or circulating tumor DNA is considered investigational in the management of patients with cancer.


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<th>Description</th>
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<td>Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);</td>
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<td></td>
<td>86153</td>
<td>Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required</td>
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**Date of Origin:** July 2005