Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Description

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as "liquid biopsy," have several potential uses for guiding therapeutic decisions in patients with cancer or being screened for cancer. This evidence review evaluates uses for liquid biopsies not addressed in a separate review. If a separate evidence review exists, then conclusions reached there supersede conclusions here.

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OBJECTIVE

The objective of this evidence review is to determine whether circulating tumor DNA or circulating tumor cell testing in patients with cancer or at risk of developing cancer improves the net health outcome compared with standard screening as well as diagnostic and management practices. See related policies for ctDNA specific statements for prostate, colorectal and non-small cell lung cancer.

POLICY STATEMENT

The use of circulating tumor DNA and/or circulating tumor cells is considered investigational for all indications reviewed herein (see Policy Guidelines).

POLICY GUIDELINES

This policy does not address the use of blood-based testing for "driver mutations" to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for use of liquid biopsy for detection or risk assessment of prostate cancer or the use of AR-V7 circulating tumor cells for metastatic prostate cancer.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

In 2004, the CellSearch® System (Janssen Diagnostics, formerly Veridex) was cleared by the Food and Drug Administration 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. Food and Drug Administration product code: NQI.

RATIONALE

Summary of Evidence

The ctDNA and CTCs in peripheral blood, referred to as "liquid biopsy," have several potential uses for guiding therapeutic decisions in patients with cancer or being screened for cancer. This evidence review evaluates uses for liquid biopsies not addressed in a separate review. If a separate evidence review exists, then conclusions reached there supersede conclusions here.

For individuals who have advanced cancer who receive testing of ctDNA to select targeted treatment, the evidence includes observational studies. The relevant outcomes are overall survival (OS), disease-specific survival, test validity, morbid events, and...
medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking, outside of the lung and colorectal cancer, which are covered in a separate review. The clinical validity of FoundationOne Liquid compared to tissue biopsy with FoundationOne comprehensive genetic testing was evaluated in four industry-sponsored observational studies. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether variant analysis of ctDNA can replace variant analysis of tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have advanced cancer who receive testing of CTCs to select targeted treatment, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbidity, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs can replace variant analysis of tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who receive testing of CTCs to monitor treatment response, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbidity, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. The available RCT found no effect on OS when patients with persistently increased CTC levels after first-line chemotherapy were switched to alternative cytotoxic therapy. Other studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to monitor treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer who receive testing of CTCs to monitor treatment response, the evidence includes a randomized control trial (RCT), observational studies, and systematic reviews of observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbidity, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to monitor treatment response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have received curative treatment for cancer who receive testing of CTCs to predict the risk of relapse, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbidity, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to predict relapse response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have received curative treatment for cancer who receive testing of CTCs to predict the risk of relapse, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbidity, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to predict relapse response. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at high-risk for cancer who receive testing of ctDNA to screen for cancer, no evidence was identified. The relevant outcomes are OS, disease-specific survival, test accuracy, and test validity. Published data on clinical validity and clinical utility are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and at high-risk for cancer who receive testing of CTCs to screen for cancer, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy, and test validity. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently.

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independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (v.1.2019) guidelines for breast cancer state that the use of circulating tumor cells in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring.\textsuperscript{36} The guidelines for melanoma (v.2.2019) reference papers on circulating tumor DNA in the discussion of molecular characteristics of metastatic disease with the statement. A number of tests have been developed for detecting BRAF and KIT mutations common in metastatic melanoma. The sensitivity and accuracy of these tests vary, and improved assays are in development.\textsuperscript{37}

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers. Palmetto GBA has issued a local noncoverage determination (L35071) for all circulating tumor cell assays.\textsuperscript{38}

REFERENCES


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### POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>September 2016</td>
<td>New policy</td>
<td>Policy updated with a literature review through March 5, 2018. References 2-14, 16, 18, 22-24, 28-34, and 37 added. Language added to Policy Guidelines that policy does not apply to the use of blood-based testing for EGFR mutations. Clarifying edit to policy statement, add ‘or’ to the following sentence: “The use of circulating tumor DNA and/or circulating tumor cells…” Policy Guidelines updated to clarify that this review does not address the use of blood-based testing for epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer or the use of AR-V7 circulating tumor cells for metastatic prostate cancer. Both of these topics are covered in separate reviews. Correct policy number from 2.01.141 to 2.04.141.</td>
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<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with a literature review through October 1, 2018, reference 15 added. Liquid biopsy for metastatic colorectal cancer was removed from 2.04.141 and will be added to 2.04.53 at the next update. Clarifying edit to policy statement, add ‘reviewed herein’ to stress that other indications are reviewed in separate policies.</td>
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<tr>
<td>March 2019</td>
<td>Replace policy</td>
<td>Policy updated with a literature review through May 29, 2019; references added, references on NCCN updated. Policy statements unchanged.</td>
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<tr>
<td>September 2019</td>
<td>Replace policy</td>
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