Introduction

Liquid biopsy is a when a blood sample (rather than a piece of tissue) is used to test for cancer cells or small genetic cancer pieces mixing in the blood. The blood sample is taken from the arm and is tested for cells or genetic pieces that cancers shed into the bloodstream. Identifying tumor cell material in the blood might help to diagnose cancer, track changes in a cancer over time or help select the right type of cancer treatment. However, there is not enough information from clinical studies to be certain that this works as well as a tissue biopsy in most people, because we don't yet know that this works as well as tissue biopsy. This treatment is not yet proven.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
The use of circulating tumor DNA and circulating tumor cells is considered investigational for all indications. This applies to laboratory tests including, but not limited to the following:

- Target Selector assay (Biocept Inc.)
- CancerIntercept (Pathway Genomics)
- CellSearch® System (Janssen Diagnostics)
- Circulo (Circulogene Theranostics)
- ColonSentry® (Innovative Diagnostic Laboratory)
- Oncotype SEQ™ Liquid Select Test (Genomic Heath)
- ColoVantage® (Quest Diagnostics)
- Epi proColon® (Epigenomics)
- FoundationACT® (Foundation Medicine)
- Guardant360 (Guardant Health)

<table>
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<th>Code</th>
<th>Description</th>
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<td>CPT</td>
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</tr>
<tr>
<td>81327</td>
<td>SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>86152</td>
<td>Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);</td>
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<tr>
<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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<td>86849</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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**Related Information**

N/A
Evidence Review

Background

Liquid biopsy refers to analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as a method of noninvasively characterizing tumors and tumor genome from the peripheral blood.

Circulating Tumor DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA (cfDNA). cfDNA 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 an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. ctDNA 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 detecting CTCs is prognostic, through quantification of circulating levels.

Technologies for 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 (eg, Sanger sequencing) are needed.
Highly sensitive and specific methods have been developed to detect ctDNA, for both single-nucleotide mutations (eg, BEAMing [which combines emulsion polymerase chain reaction [PCR] with magnetic beads and flow cytometry] and digital PCR) and copy-number changes. Digital genomic technologies allow for enumeration of rare mutant 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 (eg, EGFR and ALK in non-small-cell lung cancer), or untargeted without knowledge of specific mutations 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 on the basis of 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

Summary of Evidence

For individuals who have cancer who receive molecular characterization of tumor using circulating tumor DNA (ctDNA), the evidence includes case series and systematic reviews of these case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Ultrasensitive methods to detect mutations from ctDNA have been developed, but there is limited evidence on the analytic validity of these methods. There is a need for further optimization and standardization of testing methods. Clinical validity consists of case series that report correlations between mutations detected in ctDNA with mutations detected in tumor tissue. Results have shown variable results for clinical sensitivity. Although some reports have suggested that clinical sensitivity may be high, this finding has not been consistent. Published studies have consistently reported high clinical specificity; however, most study population have consisted of small and heterogeneous, and it is not known to what degree mutations detected by ctDNA are representative of the primary tumor. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether mutation analysis by ctDNA can replace mutation analysis in tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have cancer or are at high risk of developing cancer who receive identification and quantification of circulating tumor cells (CTCs), the evidence includes case series and meta-analyses of these case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and test validity. Published data on analytic validity are lacking. Most of the literature consists of reports of levels of CTCs and cancer prognosis, and have shown a correlation with survival in certain cancer types. However, the cutoff levels that should be used to signal a change in patient management are unknown, and there are no studies showing clinical utility and improved patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in the Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td></td>
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<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT01710605</td>
<td>Medico-economic interest of taking into account circulating tumor cells (CTCs) to determine the kind of first line treatment for metastatic, hormone-receptors positive breast cancer</td>
<td>Estimated Enrollment 819</td>
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<td>NCT02418234</td>
<td>T790M Mutation on ctDNA in patients with NSCLC after EGFR-TKI failure</td>
<td>314</td>
<td>Oct 2017 ongoing but not recruiting</td>
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<tr>
<td>NCT01930474</td>
<td>Analysis of plasma tumor DNA in lung cancer patients</td>
<td>200</td>
<td>Dec 2018 still recruiting</td>
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<tr>
<td>NCT02284633</td>
<td>Blood sample monitoring of patients with EGFR mutated lung cancer</td>
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<td><strong>Completed</strong></td>
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<tr>
<td>NCT02140463</td>
<td>Next generation personalized therapy with plasma DNA Trial 2 in refractory solid tumors (The NEXT-2 Trial)</td>
<td>260</td>
<td>Dec 2018</td>
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</table>

NCT: national clinical trial
Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) guidelines for colon cancer (v.2.2016), non-small-cell lung cancer (v.4.2016), and prostate cancer (v.2.2016) do not address CTCs or ctDNA. NCCN guidelines for breast cancer (v.2.2016) state that the use of CTCs in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring.44

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Information

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

Biocept Inc. offers assays that target mutations found in lung and breast cancers. Target Selector assay is one such test for metastatic lung cancer.

CancerIntercept (Pathway Genomics) is a 96-gene mutation panel designed to detect mutations in 9 driver genes involved primarily in breast, ovarian, lung, and colorectal cancers, as well as melanoma.

CellSearch® System (Janssen Diagnostics, formerly Veridex) is the only FDA-approved device for monitoring patients with metastatic disease and circulating tumor cells. In January 2004, the CellSearch® System was cleared by FDA for marketing through the 510(k) process for monitoring metastatic breast cancer, in November 2007 for monitoring metastatic colorectal cancer, and in February 2008 for monitoring metastatic prostate cancer. The system uses automated instruments manufactured by Immunicon Corp. 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.

Circulogene’s (Theranostics) liquid biopsy uses a finger stick volume of blood and NGS to monitor known tumor mutations (~3000) in 50 cancer-associated genes for targeted therapy.
The test uses a proprietary method to recover necrotic and apoptotic cell-death-associated cell-free DNA.

**ColonSentry® (GeneNews, Ontario, Canada; Innovative Diagnostic Laboratory, Richmond, VA)**

ColonSentry® is a PCR assay that uses a blood sample to detect expression of 7 genes found to be differentially expressed in CRC patients compared with controls\(^5\): ANXA3, CLEC4D, TNFAIP6, LMNB1, PRRG4, VNN1, and IL2RB. Per the company website, these genes are early warning signs of colon cancer, and test results can indicate the odds of having CRC compared with an average-risk person. An average-risk person is defined as one who is “at least 50 years old, is asymptomatic for CRC, has no personal history of benign colorectal polyps, colorectal adenomas, CRC, or inflammatory bowel disease, and does not have a first degree relative with CRC.”\(^5\) The test is intended for use in adults who are averse to colonoscopy and/or fecal occult blood testing. “Because of its narrow focus, the test is not expected to alter clinical practice for patients who comply with recommended screening schedules.”\(^5\)

Foundation ACT (Foundation Medicine) detects mutations in over 60 genes for targeted therapy in metastatic cancer.

Guardant360 (Guardant Health) is a circulating cell-free tumor-specific DNA genotyping test that includes four major types of genomic alterations, specifically EGFR single nucleotide variants (SNVs) and indels; ERBB2 SNVs, indels and copy number amplification (CNA); BRAF SNV; MET CNA and exon 14 skipping indel; KRAS and HRAS SNV; KIT SNV and indel; PDGFRA SNV and indel; ALK translocation; RET translocation; and ROS1 translocation.

Oncotype SEQ™ is the first liquid biopsy test from Genomic Heath and it is planned to launch in mid-2016. The test uses next-generation sequencing (NGS) to identify actionable genomic alterations for late-stage lung, breast, colon, melanoma, ovarian, and gastrointestinal cancers.

**SEPT9 Methylation DNA (ColoVantage, Various Manufacturers; Epi proColon, Epigenomics, Berlin)**

Serum biomarkers that are shed from colorectal tumors have been identified and include Septin 9 hypermethylated DNA (SEPT9). Septin 9 protein is involved in cell division, migration, and apoptosis, and acts as a tumor suppressor; when hypermethylated, expression of SEPT9 is
reduced. ColoVantage blood tests for serum *SEPT9* methylated DNA are offered by several laboratories.

**ARUP® Laboratories, Quest Diagnostics®, Clinical Genomics.** Epi proColon® (Epigenomics, Berlin) received FDA approval in the US in May 2016. Epigenomics has licensed its Septin 9 biomarker technology to ARUP and Quest. ColoVantage and Epi proColon® are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (e.g., DNA preparation, PCR primers, probes). Serum *SEPT9* methylated DNA testing is intended for individuals 50 years of age or older who have an average risk of colorectal cancer.46

**References**


50. Shirts B, von Roon AC, Tebo AE. The entire predictive value of the prometheus IBD sgi diagnostic product may be due to the three least expensive and most available components. Am J Gastroenterol. Nov 2012;107(11):1760-1761. PMID 23160303


54. Weng WK, Levy R. Immunoglobulin G Fc receptor polymorphisms do not correlate with response to chemotherapy or clinical course in patients with follicular lymphoma. Leuk Lymphoma. Sep 2009;50(9):1494-1500. PMID 19672774


<table>
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<th>Date</th>
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<td>New policy, approved July 12, 2016; add to Pathology/Laboratory section. Policy created with a literature review through March 10, 2016. Policy statement that the use of circulating tumor DNA and circulating tumor cells is considered investigational for all indications. Policy incorporates policy statement and other information from 2.04.37 Circulating Tumor Cells, which is now deleted.</td>
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<td>10/01/16</td>
<td>Interim Update, approved September 13, 2016. Information regarding screening/diagnostic tests ColoVantage, ColoSentry and Epi proColon extracted from medical policy 12.04.121 and added as examples of ctDNA tests. Title revised to include “Diagnosis”, reflecting the expanded scope of the policy. CPT code 88399 added with supporting information for Target Selector Test. Policy moved into new format and renumbered/moved to Genetic Testing section; previously 2.04.141 and now 12.04.141 – previous version is now deleted.</td>
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<td>01/01/17</td>
<td>Coding update; added new CPT code 81327 effective 1/1/17.</td>
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<td>12/01/17</td>
<td>Annual Review, approved November 9, 2017. Policy updated with literature review through October 2017; no references added. No change to policy statement.</td>
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<tr>
<td>02/09/18</td>
<td>Minor updated. Added test names, FoundationACT and Guardant360, to the policy statement as they were noted only under the Regulatory Information.</td>
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Email AppealsDepartmentInquiries@Premera.com

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