Protocol

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

(204141)

Medical Benefit		**Effective Date**: 10/01/16	**Next Review Date**: 07/18
Preauthorization	No	**Review Dates**: 07/16, 07/17	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With cancer	Interventions of interest are: • Molecular characterization of tumor using circulating tumor DNA	Comparators of interest are: • Molecular characterization of tumor using tissue biopsy	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Morbid events • Medication use
Individuals: • With cancer or at high risk of developing cancer	Interventions of interest are: • Identification and quantification of circulating tumor cells	Comparators of interest are: • Standard clinical and histopathologic measures of prognosis • Standard screening methods	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

Description

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as "liquid biopsy," potentially offer a noninvasive alternative to tissue biopsy for therapeutic decisions and clinical prognosis in patients with cancer.

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. Ultra-sensitive 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 been 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, 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.

If a separate protocol exists, then conclusions reached there supersede those reached herein.

Policy

The use of circulating tumor DNA and circulating tumor cells is considered **investigational** for all indications.

Policy Guidelines

This protocol does not address the use of blood-based testing for epidermal growth factor receptor mutations including testing addressed by the Circulating Tumor DNA Management of Non-Small-Cell-Lung Cancer (Liquid Biopsy) Protocol.

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.

CirculatingTumor Data

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.[1] 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 (one to two 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.

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 (less than 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 mutations (e.g., 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 (e.g., *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]

Regulatory Status

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.

Genomic Health plans to launch its first liquid biopsy test Oncotype SEQ™ 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.

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.

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

Biocept Inc. offers assays that target mutations found in lung and breast cancers.

Foundation Medicine's Foundation ACT detects mutations in over 60 genes for targeted therapy in metastatic cancer.

The 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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45. National Government Services, Inc. (Primary Geographic Jurisdiction - Illinois, New York - Entire State, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont, Wisconsin, Minnesota) Local Coverage Determination (LCD): Non-covered Services (L33629), Revision Effective Date for services performed on or after 03/16/2017.