

(204141)

Medical Benefit		Effective Date: 10/01/19	Next Review Date: 07/21
Preauthorization	No	Review Dates: 07/16, 07/17, 07/18, 07/19, 07/20	

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.

RELATED PROTOCOLS

Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

KRAS, NRAS, and BRAF Variant Analysis (Including Liquid Biopsy) in Metastatic Colorectal Cancer

Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced cancer	Interventions of interest are: • Testing of circulating tumor DNA to select targeted treatment	Comparators of interest are: • Using tissue biopsy to select treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With advanced cancer	Interventions of interest are: • Testing of circulating tumor cells to select targeted treatment	Comparators of interest are: • Using tissue biopsy to select treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With cancer	Interventions of interest are: • Testing of circulating tumor DNA to monitor treatment response	Comparators of interest are: • Standard methods for monitoring treatment response	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • With cancer	Interventions of interest are: • Testing of circulating tumor cells to monitor treatment response	Comparators of interest are: • Standard methods for monitoring treatment response	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use

Populations	Interventions	Comparators	Outcomes
Individuals: • Who have received curative treatment for cancer	Interventions of interest are: • Testing of circulating tumor DNA to predict risk of relapse	Comparators of interest are: • Standard methods for predicting relapse	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • Who have received curative treatment for cancer	Interventions of interest are: • Testing of circulating tumor cells to predict risk of relapse	Comparators of interest are: • Standard methods for predicting relapse	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use
Individuals: • Who are asymptomatic and at high risk of developing cancer	Interventions of interest are: • Testing of circulating tumor DNA to screen for cancer	Comparators of interest are: • Standard screening methods	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity
Individuals: • Who are asymptomatic and at high risk of developing cancer	Interventions of interest are: • Testing of circulating tumor cells to screen for cancer	Comparators of interest are: • Standard screening methods	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity

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.

SUMMARY OF EVIDENCE

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 profiling 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, morbid events, 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 ctDNA to monitor treatment response, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy and 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. 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 ctDNA 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 controlled trial, observational studies, and systematic reviews of observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, 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 randomized controlled trial 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 received curative treatment for cancer who receive testing of ctDNA to predict the risk of relapse, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test accuracy and 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. 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 ctDNA 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, morbid events, 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, 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.

POLICY

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 protocol 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.

BACKGROUND

Liquid biopsy refers to the analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as methods 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. 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 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 (less than 1%) of total cell-free DNA. 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

Note that targeted therapy in non-small-cell lung cancer and metastatic colorectal cancer, use of liquid biopsy for detection or risk assessment of prostate cancer, and use of AR-V7 CTC liquid biopsy for metastatic prostate cancer are addressed in separate protocols.

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.

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