MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**CIRCULATING TUMOR DNA for MANAGEMENT of CANCER (Liquid Biopsy)**
Policy Number	**7.01.102**
Category	**Laboratory Tests**
Effective Date	**08/15/19**
Revised Date	
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

I. Based upon our criteria and review of the peer-reviewed literature, cell-free/circulating tumor DNA (ctDNA or liquid biopsy) (e.g., Guardant 360® test, Foundation One Liquid ™, Cobas, Genestrat, OncoBEAM) analysis for ***EGFR TKI-sensitizing variants*** (small deletions in exon 19 or a point mutation in exon 21 (L858R)) may be considered **medically necessary** for individuals with newly diagnosed advanced stage III or IV or metastatic non-small-cell lung cancer (NSCLC) including adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified when:
   A. Invasive biopsy is medically contraindicated; and
   B. There is not enough tissue for tissue-based molecular and biomarker analysis;

II. Based upon our criteria and review of the peer-reviewed literature, circulating tumor DNA (cfDNA or liquid biopsy) analysis (e.g., Guardant 360® test, Foundation One ACT ™, Cobas, Genestrat, OncoBEAM) analysis for ***EGFR TKI-sensitizing variants*** (small deletions in exon 19 or a point mutation in exon 21 (L858R))may be considered **medically necessary** for individuals with advanced stage III or IV or metastatic non-small-cell lung cancer (NSCLC) progressing on or after chemotherapy or immunotherapy *who have never been tested for molecular and biomarker analysis* when:
   A. Invasive biopsy is medically contraindicated; and
   B. There is not enough tissue for tissue-based molecular and biomarker analysis.

III. Based upon our criteria and review of the peer-reviewed literature, circulating tumor DNA (ctDNA or liquid biopsy) analysis is considered **investigational** for all other indications.

Refer to Corporate Medical Policy #2.02.35 regarding Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer.

Refer to Corporate Medical Policy #2.02.51 regarding Molecular Panel Testing of Tumor Tissue to Identify Targeted Therapies for Cancers (excluding NSCLC and CRC).

Refer to Corporate Medical Policy #11.01.03 regarding Experimental or Investigational Services.

POLICY GUIDELINES

I. A negative liquid biopsy test result for EGFR should be followed by reflex testing to a formalin-fixed paraffin-embedded tissue test.

II. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboa ratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

The standard for treatment selection in some cancers is biomarker analysis of tissue samples during biopsy or surgery. Both biopsy and surgery are invasive with slow turnaround time for obtaining results. Tumor tissue may also be heterogeneous which may result in patients receiving chemotherapy rather than targeted therapy. An alternative to tissue-based molecular testing is cell-free DNA from plasma in the blood of patients with cancer. Cell-free DNA in blood is derived from nonmalignant and malignant cell DNA. The small DNA fragments released into the blood by tumor cells are referred to as circulating tumor DNA (ctDNA). Most ctDNA is derived from apoptotic and necrotic cells, either from the primary tumor, metastases or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process, generating 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 origins. The ctDNA can be used for genomic characterization of the tumor and identification of the biomarkers of interest. Detection of ctDNA is challenging because cell-free DNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (less than 1%) of total cell-free DNA. Therefore, methods up to 500 to 1000 times more sensitive than standard sequencing approaches (e.g., Sanger) are needed. Genetic testing of ctDNA can be targeted at specific genes or at commonly found, acquired, somatic variants ("hotspots") that occur in specific cancers, which can impact therapy decisions. Panel testing for specific genetic variants that may impact therapy decision in many different cancers can also be performed.

In patients with NSCLC who cannot undergo lung biopsy, cell-free DNA tests can identify patients for whom there is a net benefit of targeted therapy versus chemotherapy.

Foundation Medicine's FoundationLiquid™ uses hybrid capture-based NGS to detect variants in over 60 genes for targeted therapy in metastatic cancer.

Guardant Health markets the Guardant360 test. This test uses NGS to identify variants in 73 genes associated with several different cancers.

Biodesix's GeneStrat® uses droplet digital PCR to analyze cell-free DNA and RNA to identify specific driver variants for which targeted therapy is available for NSCLC.

RATIONALE

Randomized controlled trials (RCTs) comparing treatment selection based on tumor biomarkers with plasma biomarkers would potentially support evidence of clinical utlity as well as, evidence on the ability of liquid biopsy to predict treatment response similar to, or better than, tissue biopsy. If the 2 tests are highly correlated, they are likely to stratify treatment response similarly overall. To understand the implications of "false-positive: and false-negative" liquid biopsies for outcomes, patients who have discordant results on liquid biopsy and standard tissue biopsy can be assessed for response to EGFR tyrosine kinase inhibitors (TKIs). A negative liquid biopsy for EGFR-sensitizing or -resistance variants but a positive tissue-based biopsy responding to EGFR tyrosine kinase inhibitors (TKIs) would suggest the tissue biopsy was correct and the liquid biopsy results were truly false-negatives. A positive liquid biopsy and a negative tissue biopsy for EGFR variants responding to EGFR TKIs would suggest the positive liquid biopsy was correct rather than false-positive. Clinical utility might alternatively be established based on the assumption that tissue biomarkers are the standard by which treatment decisions are made, consequently agreement between liquid and tissue biopsies would infer that treatment selection based on liquid or tissue biopsies is likely to yield similar outcomes.The use of liquid biopsy rather than a tissue biopsy would reduce the number of patients undergoing invasive tissue sampling and any accompanying complications.

The Cobas test has very high accuracy (area under the receiver operating characteristic curve [AUROC], 0.96), a sensitivity of about 75%, and a specificity above 95% for detection of *EGFR* TKI-sensitizing variants using tissue biopsy as the reference standard; these estimates are consistent across several studies performed using the test. The studies were performed in Asia, Europe, Australia, and the United States, primarily in patients with advanced disease of adenocarcinoma histology. The Guardant360 test has 3 studies using tissue biopsy as the reference standard performed in the United States in the intended-use population. Estimates of specificity are consistently 90% or higher. Likewise, the OncoBEAM test has 3 studies using tissue biopsy in Asia, Europe, Australia, and the United States in the intended-use population, 2 of which provide precise estimates for specificity that are very high (>95%).

For tests other than the cobas test, Guardant360, and OncoBEAM for detecting *EGFR* TKI-sensitizing variants, few studies were identified that evaluated the clinical validity of these commercially available tests for *EGFR* variants in NSCLC.

For tests of other, less prevalent, variants, such as *ALK* and *ROS1* translocations and *BRAF* V600E variants, few studies were identified that evaluated the clinical validity of any commercially available tests, and in these studies, very few variants were detected; therefore, performance characteristics are not well-characterized.

Fewer studies have examined the performance of liquid biopsy for detection of T790M variants associated with *EGFR* TKI resistance and several different tests were used in the studies. Detection of these variants is potentially important for liquidbiopsy because this variant is of interest after the initiation of treatment, when biopsies may be more difficult to obtain.Unlike the high specificities compared with tissue biopsy demonstrated for *EGFR* variants associated with TKI sensitivity, the moderate specificity means that liquid biopsy often detects T790M variants when they are not detected in tissue biopsy. Sacher et al (2016) suggested that these false-positives might represent tumor heterogeneity in the setting of treatment resistance, such that the T790M status of the biopsied site might not represent all tumors in the patient.

The National Comprehensive Cancer Network guidelines for Non-Small Cell Lung Cancer (v3.2019) states plasma testing should be considered if repeat biopsy is not feasible in patients presenting with advanced or metastatic disease. Cell-free/circulating tumor DNA testing should not be used in lieu of tissue diagnosis. Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity but significantly compromised sensitivity with up to 30% false-negative rate. use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably if a patients is medically unfit for invasive tissue sampling and if used in the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used if follow-up tissue based analysis is planned for all patients in which an oncogenic drive is not identified.

The American Society of Clinical Oncology and College of American Pathologists Joint Review of Circulating Tumor DNA Analysis in Patients With Cancer (2018) key findings include current evidence suggests that the optimal specimen type for analysis of circulating tumor DNA (ctDNA) in blood is plasma. Analytical validity must be established for any clinical ctDNA test and different ctDNA assays may not give the same results because of different assay performance characteristics, such as differing limits of detection. Most assays have insufficient evidence to demonstrate clinical validity, and most have no evidence of clinical utility. Well-designed clinical trials or equivalence studies are needed to demonstrate clinical utility for most assays. Evidence shows discordance in results between ctDNA assays and tumor tissue genotyping and supports value of tumor tissue genotyping to confirm undetected ctDNA findings. For advanced cancer, the evidence indicates that more reliable test results occur when the ctDNA assay is performed at the time of disease progression and not when responding to prior therapy. There is evidence that positive findings from well-validated ctDNA assays may support initiation of a targeted therapy option where an assay for the relevant genomic marker has demonstrated clinical utility when performed in tissue. For monitoring therapy effectiveness, evidence of clinical validity is still emerging, and there is currently no evidence of clinical utility to suggest that ctDNA assays are useful in this context, outside of a clinical trial. For early-stage cancer, evidence of clinical validity is still emerging, and there is currently no evidence of clinical utility to suggest that ctDNA assays are useful at diagnosis or in the adjuvant setting after completing treatment, outside of a clinical trial. For cancer screening, there is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful in this context, outside of a clinical trial. Given the rapid pace of research, re-evaluation of the literature will shortly be required, along with the development of tools and guidance for clinical practice.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of heterozygosity variants for chromosomal abnormalities (effective 1/1/2020)
81401	Molecular Pathology Procedure Level 2
81402	Molecular Pathology Procedure Level 3
81403	Molecular Pathology Procedure Level 4
81404	Molecular Pathology Procedure Level 5
81405	Molecular Pathology Procedure Level 6
81406	Molecular Pathology Procedure Level 7
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81479	Unlisted molecular pathology procedure
86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required

HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
C18.0-C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum, and anus and anal canal (code range)
C25.0-C25.9	Malignant neoplasm of pancreas (code range)
C34.10 - C34.12	Malignant neoplasm of upper lobe, bronchus or lung (code range)
C34.30-C34.32	Malignant neoplasm of lower lobe, bronchus or lung (code range)
C34.80-C34.82	Malignant neoplasm of overlapping sites of bronchus and lung (code range)
C34.90-C34.92	Malignant neoplasm of unspecified part of bronchus or lung (code range)
C50.011-C50.929	Malignant neoplasm of breast (code range)
C56.1-C56.9	Malignant neoplasm of ovary (code range)
C61	Malignant neoplasm of prostate
C78.5	Secondary malignant neoplasm of large intestine and rectum
C79.60-C79.62	Secondary malignant neoplasm of ovary (code range)
C79.81	Secondary malignant neoplasm of breast
D05.00-D05.02	Lobular carcinoma in situ of breast (code range)
D05.10-D05.12	Intraductal carcinoma in situ of breast (code range)
D05.80-D05.92	Carcinoma in situ of breast, specified, unspecified (code range)
D07.30-D07.39	Carcinoma in situ of other and unspecified female genital organs (code range)
D40.0	Neoplasm of uncertain behavior of prostate
C18.0-C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum, and anus and anal canal (code range)

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*Key Article

KEY WORDS

Circulating tumor cells, CTC, ctDNA, cell-free DNA, cfDNA, Guardant 360®, FoundationACT™, liquid biopsy.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Guardant 360® plasma based comprehensive genomic profiling in NonSmall Cell Lung Cancer. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37649&ver=11&CntrctrSelected=360*1&Cntrctr=360&s=6&DocType=1&bc=AAgAAAQBAAAA&