FEP 2.04.143 Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

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Related Policies: None

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

Description

Genetic testing of circulating tumor DNA (ctDNA) and circulating tumor cells in peripheral blood (referred to as “liquid biopsy”) potentially offers a noninvasive alternative to tissue biopsy for therapeutic decisions and prognosis in patients with cancer. For patients with non-small-cell lung cancer (NSCLC), detection of “driver mutations” or resistance variants is important for selecting patients for targeted therapy.

OBJECTIVE

The objective of this evidence review is to determine whether testing for driver or resistance variants using circulating tumor DNA or other “liquid biopsies” in peripheral blood improves the net health outcome in individuals with non-small-cell lung cancer.

POLICY STATEMENT

EGFR TESTING

Except as noted below, analysis of 2 types of somatic sensitizing variants within the epidermal growth factor receptor (*EGFR*) gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—using the cobas EGFR Mutation Test v2, Guardant360 test, or OncoBEAM test with plasma specimens to detect circulating tumor DNA (ctDNA) may be considered **medically necessary** as an alternative to tissue biopsy to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy in patients with advanced stage III or IV non-small-cell lung cancer (NSCLC). The cobas test is a companion diagnostic for erlotinib and gefitinib.

Analysis of other *EGFR*-sensitizing variants within exons 18 to 24 using ctDNA for applications related to NSCLC is considered **investigational**.

Analysis of the *EGFR* T790M resistance variant for targeted therapy with osimertinib using ctDNA or for other applications related to NSCLC is considered **investigational**.

Analysis of 2 types of somatic variants within the *EGFR* gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—using ctDNA is considered **investigational** for patients with advanced NSCLC of squamous cell type.

ALK TESTING

Analysis of somatic rearrangement variants of the *ALK* gene using plasma specimens to detect ctDNA or RNA is considered **investigational** as an alternative to tissue biopsy to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with NSCLC.

BRAF V600E TESTING

Analysis of the *BRAF* V600E variant using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar], trametinib [Mekinist]) in patients with NSCLC.

ROS1 TESTING

Analysis of somatic rearrangement variants of the *ROS1* gene using plasma specimens to detect ctDNA or RNA is considered **investigational** as an alternative to tissue biopsy to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients NSCLC.

KRAS TESTING

Analysis of somatic variants of the *KRAS* gene using plasma specimens to detect ctDNA is considered **investigational** as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC.

Other Genes

Analysis of alterations in the *HER2*, *RET*, and *MET* genes using plasma specimens to detect ctDNA for targeted therapy in patients with NSCLC is considered **investigational**.

POLICY GUIDELINES

The tests discussed herein are intended for use in patients with advanced (stage III or IV) non-small-cell lung cancer. Patients with sensitizing variants of the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene are considered good candidates for treatment with erlotinib, gefitinib, afatinib, or osimertinib. The Food and Drug Administration approval for the cobas EGFR Mutation Test v2 states that patients who are negative for *EGFR* exon 19 deletions or L858R variant based on the plasma test should be reflexed to routine biopsy and testing using formalin-fixed paraffin-embedded tissue. However, the plasma test may also be appropriate for patients who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, cannot undergo biopsy, or have indeterminate histology (in whom an adenocarcinoma component cannot be excluded).

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely

pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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

FDA REGULATORY STATUS

In June 2016, cobas® EGFR Mutation Test v2 (Roche Molecular Systems), a real-time PCR test, was approved by FDA through the premarket approval process (P150047).[2] This plasma test is a real-time PCR test approved as a companion diagnostic aid for selecting NSCLC patients who have *EGFR* exon 19 deletions, and L858R substitution variants, for treatment with erlotinib. A premarket approval supplement expanded the indication to include the test as a companion diagnostic for treatment with gefitinib in 2018 (P120019). Patients who test negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for *EGFR* variants. A previously approved version 2 of this test, which used tissue biopsy specimens, was also approved for detection of T790M variants in tissue, which are used to select patients to receive osimertinib. Approval of version 2 of the plasma test did not include detection of T790M variants.

No other ctDNA tests have FDA approval. However, Foundation Medicine was granted FDA breakthrough device designation for FoundationACT™ in 2018.

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. Several companies market tests that detect tumor markers from peripheral blood, including TKI-sensitizing variants for NSCLC. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test. Clinical laboratories accredited through the College of American Pathologists enroll in proficiency testing programs to measure the accuracy of the test results. There are currently no College of American Pathologists proficiency testing programs available for ctDNA testing to ensure the accuracy of ctDNA laboratory-developed tests.

Foundation Medicine's FoundationACT™ 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.

Circulogene Theranostics' liquid biopsy test uses a finger stick blood sample and NGS to monitor known tumor variants (≈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.

Biocept offers blood-based assays that target variants found in lung and breast cancers. The test uses a proprietary real-time quantitative PCR and, using Sanger sequencing, sequences the amplified product to confirm variants.

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.

Resolution Bio offers ctDx-Lung™ uses NGS to detect single nucleotide variants, insertions and deletions, fusions, and copy number variants in approximately 20 genes targeted by a specific FDA-approved therapy or therapies in clinical trials.

Sysmex OncoBEAM™ offers liquid biopsies using BEAMing technology to detect variants in *EGFR*, *KRAS*, and *BRAF* for NSCLC as well as liquid biopsies for breast, melanoma, and colorectal cancer.

RATIONALE

Summary of Evidence

For individuals with advanced NSCLC who receive testing for biomarkers of EGFR TKIs sensitivity using ctDNA with the cobas EGFR Mutation Test v2 (liquid biopsy), the evidence includes numerous studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are overall survival, disease-specific survival, and test validity. Current evidence does not permit determining whether cobas or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of cobas. The cobas EGFR Mutation Test has adequate evidence of clinical validity for the *EGFR* TKI-sensitizing variants. The Food and Drug Administration has suggested that a strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the cobas test would result in an overall diagnostic performance equivalent to tissue biopsy. Several additional studies of the clinical validity of cobas have shown it to be moderately sensitive and highly specific compared with a reference standard of tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the cobas test should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with *EGFR* TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive

chemotherapy. The cobas test can identify patients for whom there is a net benefit of targeted therapy vs chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with advanced NSCLC who receive testing for biomarkers of EGFR TKI sensitivity using ctDNA (liquid biopsy) with the Guardant360 or OncoBEAM tests, the evidence includes several studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are overall survival, disease-specific survival, and test validity. Current evidence does not permit determining whether liquid or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of these tests. The Guardant360 and OncoBEAM tests have adequate evidence of clinical validity for the *EGFR* TKI-sensitizing variants. A strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the tests would result in an overall diagnostic performance similar to tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the Guardant360 or OncoBEAM tests should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with *EGFR* TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy vs chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with advanced NSCLC who receive testing for biomarkers of EGFR TKI sensitivity using ctDNA with tests other than the cobas EGFR Mutation Test v2, Guardant360, or OncoBEAM, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with tissue reference standard. Relevant outcomes are overall survival, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests other than the cobas, Guardant360, and OncoBEAM tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. Current evidence does not permit determining whether liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of those methods of liquid biopsy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with advanced NSCLC who receive testing for biomarkers other than EGFR using liquid biopsy to select a targeted therapy, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with the tissue biopsy reference standard. The relevant outcomes are overall survival, disease-specific survival, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision for variants other than *EGFR*. We found no RCTs providing evidence of the clinical utility of those of methods of liquid biopsy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with advanced NSCLC who progressed on EGFR TKIs who receive testing for biomarkers of EGFR TKI resistance using liquid biopsy, the evidence includes a few studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are overall survival, disease-specific survival, and test validity. For variants that indicate EGFR TKI resistance and suitability for alternative treatments with osimertinib, liquid biopsy is moderately sensitive and moderately specific compared with a reference standard of tissue biopsy. Given the moderate clinical sensitivity and specificity of liquid biopsy, using liquid biopsy alone or in combination with tissue biopsy might result in the selection of different patients testing positive for EGFR TKI resistance. It cannot be determined whether patient outcomes are improved. 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

National Comprehensive Cancer Network guidelines (v.6.2018) on the management of non-small-cell lung cancer state that "if repeat biopsy is not feasible, plasma biopsy should be considered," but it is not stated to which biomarkers this statement applies.[25] In the text discussion of osimertinib, the guidelines state that "Data suggest that plasma genotyping (also known as liquid biopsy or plasmas biopsy) may be considered instead of tissue biopsy to detect whether patients have T790M; however, if the plasma biopsy is negative, then tissue biopsy is recommended if feasible."

International Association for the Study of Lung Cancer

The International Association for the Study of Lung Cancer (2018) published a statement paper on liquid biopsy for advanced non-small-cell lung cancer.[26] The work preparing the statement was supported by unrestricted grants from Guardant Health, Astra Zeneca, Biocept, and Roche. The statement made the following recommendations:

> "The criteria used to select treatment-naive patients for molecular testing of ctDNA [circulating tumor DNA] is the same used for molecular testing using DNA isolated from tissue."
> "Liquid biopsy can be considered at the time of initial diagnosis in all patients who need tumor molecular profiling, but it is particularly recommended when tumor tissue is scarce, unavailable, or a significant delay potentially greater than 2 weeks is expected in obtaining tumor tissue."

The following tests are acceptable to detect epidermal growth factor receptor (*EGFR*)–sensitizing variants and results are sufficient to start a first-line treatment with an EGFR tyrosine kinase inhibitor:

> Cobas EGFR Mutation Test v2.
> droplet digital polymerase chain reaction next-generation sequencing panels
> Multiplex panels using next-generation sequencing platforms could be considered to detect *EGFR*, *ALK*, *ROS1*, or *BRAF* variants and a positive result would be adequate to initiate first-line therapy.
> A next-generation sequencing multiplex panel was preferred to detect T790M and other common resistance alterations. A positive result for *EGFR* T790M should be considered adequate to initiate osimertinib in the second-line setting.

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. Several MolDX contractors have issued local coverage determinations or future local coverage determinations for Guardant360 (local coverage determinations ID: L37649, L37651, L37671, L37699) providing limited coverage: (1) at diagnosis when results for *EGFR*, *ALK*, *ROS1*, and *BRAF* variants are not available and tissue-based genomic profiling is infeasible, or (2) at progression for patients who have never been tested for *EGFR*, *ALK*, *ROS1*, and *BRAF* variants, or for whom tissue-based genomic profiling is infeasible, or for patients progressing on any tyrosine kinase inhibitors. The analysis of evidence concluded that the quality of evidence was moderate, strength of evidence was limited, and weight of evidence was limited.

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POLICY HISTORY

Date	Action	Description
March 2018	New Policy	Policy created with a literature review through September 11, 2017 based on review presented to BCBSA Medical Advisory Panel in September 2017 (See Appendix 1). Policy statement that the use of cobas circulating tumor DNA for detection of EGFR variants for selection of treatment with EGFK TKI is medically necessary; all other circulating tumor DNA tests are considered not medically necessary; all other NSCLC indications considered not medically necessary.
December 2018	Update Policy	Policy updated with literature review through Aug 8, 2018. References 4-6, 8, 10, 14, 16, 17, 19, and 26 added; reference 25 was updated. Policy statements regarding testing for *ALK*, *ROS1*, *BRAF*, and other variants were added as investigational. Policy statement regarding medically necessary of testing for *EGFR*-sensitizing variants was expanded to include Guardant360 and OncoBEAM as well as cobas® EGFR Mutation Test v2 (Roche Molecular Systems). All other circulating tumor DNA tests and NSCLC indication policy statements revised from not medically necessary to investigational as a correction to align with FDA regulatory status.