

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

**Effective Date:** April 15, 2018

**Related Policies:**

2.04.125 Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer  
2.04.141 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

## 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), biomarkers are associated with sensitivity to tyrosine kinase inhibitors (TKIs) and are used to identify patients likely to benefit from TKIs. Other biomarkers associated with acquired resistance to TKIs are used to select patients to receive alternative therapy.

### FDA 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). Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test. There currently are no College of American Pathologists proficiency testing programs available for ctDNA testing to ensure the accuracy of ctDNA laboratory-developed tests.

Genomic Health (Redwood City, CA) markets the Oncotype SEQ™ Liquid select. The test uses NGS to identify actionable genomic alterations for late-stage lung, breast, colon, melanoma, ovarian, and gastrointestinal cancers.

Guardant Health (Redwood City, CA) markets the Guardant360® test. This test uses NGS to identify variants in 73 genes associated with several different cancers.

Circulogene Theranostics' (Birmingham, AL) 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.

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CancerIntercept® (Pathway Genomics, San Diego, CA) is a 96-gene panel designed to detect variants in 9 driver genes involved primarily in breast, ovarian, lung, and colorectal cancers, as well as melanoma. The test uses PCR amplification of both the wild-type and variant DNA followed by enrichment of the variant and removal of the wild-type DNA using a proprietary technology after which variant DNA is sequenced using NGS.

Biocept (San Diego, CA) 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.

Foundation Medicine's (Cambridge, MA) FoundationACT™ uses hybrid capture-based NGS to detect variants in over 60 genes for targeted therapy in metastatic cancer.

Biodesix's (Boulder, CO) 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.

In June 2016, cobas® EGFR Mutation Test v2 (Roche Molecular Systems, Pleasanton, CA), a real-time PCR test, was approved by the U.S. Food and Drug Administration through the premarket approval process (P150047).<sup>2</sup> This plasma test was 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. Patients who test negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for *EGFR* variants. The 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.

### 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 variant in exon 21 (L858R)—using the cobas® EGFR Mutation Test v2 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 non-small-cell lung cancer (NSCLC). The cobas® test is a companion diagnostic for erlotinib (Tarceva®; OSI Pharmaceuticals, Melville NY).

Analysis of other *EGFR* sensitizing variants within exons 18 to 24 using ctDNA for applications related to NSCLC, is considered **not medically necessary**.

Analysis of *EGFR* T790M resistance variant for targeted therapy with osimertinib using ctDNA or for other applications related to NSCLC, is considered **not medically necessary**.

Analysis of 2 types of somatic mutations variants within the *EGFR* gene—small deletions in exon 19 and a point mutation variant in exon 21 (L858R)—using ctDNA is considered **not medically necessary** for patients with advanced NSCLC of squamous cell type.

### POLICY GUIDELINES

These tests are intended for use in patients with advanced non-small-cell lung cancer. Patients with either small deletions in exon 19 or a point variant in exon 21 (L858R) of the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene are considered good candidates for treatment with

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erlotinib, gefitinib or afatinib. The Food and Drug Administration approval for the cobas® EGFR Mutation Test v2 states that patients who are negative for epidermal growth factor receptor (*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

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.

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### 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).

### RATIONALE

#### Summary of Evidence

For individuals with newly diagnosed NSCLC who are able to undergo tissue biopsy who receive testing for biomarkers of *EGFR* TKI 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 accuracy and validity. 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. Current evidence does not permit determining whether cobas or tissue biopsy is more strongly associated with patient outcomes or treatment response. We identified no randomized controlled trials providing evidence of the clinical utility of cobas. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with newly diagnosed NSCLC who are able to undergo tissue biopsy who receive testing for biomarkers of *EGFR* TKI sensitivity using ctDNA with tests other than the cobas *EGFR* Mutation Test v2, 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 accuracy and 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 test 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. 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 newly diagnosed NSCLC who are not able to undergo tissue biopsy who receive testing for biomarkers of *EGFR* TKI 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 accuracy and validity. The cobas *EGFR* Mutation Test has adequate evidence of clinical validity for the

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*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 versus 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 newly diagnosed NSCLC who are not able to undergo tissue biopsy who receive testing for biomarkers of *EGFR* TKI sensitivity using ctDNA with tests other than the cobas *EGFR* Mutation Test v2, 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 accuracy and 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 test have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with NSCLC who progressed on *EGFR* TKI who receive testing for biomarkers of *EGFR* TKI resistance using ctDNA, the evidence includes a few studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and 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

Current National Comprehensive Cancer Network guidelines (v.4.2107) on the management of non-small-cell lung cancer discuss liquid biopsy in a few instances.<sup>71</sup> One statement reads: “if repeat biopsy is not feasible, plasma biopsy should be considered,” but it is not stated to which biomarkers this statement apply. In the text discussion of osimertinib, a study is cited supporting the use of plasma biopsy if tissue biopsy is not feasible.

#### U.S. Preventive Services Task Force Recommendations

Not applicable.

#### 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.

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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 EGFR TKI is medically necessary; all other circulating tumor DNA tests are considered not medically necessary; all other NSCLC indications considered not medically necessary.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

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### Appendix 1

#### Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross Blue Shield Association Medical Advisory Panel made the following judgments about whether assessment of biomarkers from circulating tumor DNA (ctDNA) meets the Blue Cross and Blue Shield Association TEC criteria.

**1. The technology must have final approval from the appropriate governmental regulatory bodies.**

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 tyrosine kinase inhibitor (TKI)-sensitizing variants for non-small-cell lung cancer. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments 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.

In June 2016, cobas® EGFR Mutation Test v2 (Roche Molecular Systems), a real-time polymerase chain reaction test, was approved by FDA through the premarket approval process. This plasma test is approved as a companion diagnostic aid for selecting non-small-cell lung cancer patients who have *EGFR* exon 19 deletions and L858R substitution variants for treatment with erlotinib. Patients who test negative for the *EGFR* variants detected should be referred for (or “reflexed” to) routine biopsy with tissue testing for *EGFR* variants. The 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.

**2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

Numerous studies of patients in whom liquid biopsy and tissue biopsy results are available have demonstrated the diagnostic characteristics of liquid biopsy using a tissue biopsy as the reference standard. There is insufficient evidence on the association between liquid biopsy results and patient outcomes. Given this evidence and the pattern of diagnostic characteristics of liquid biopsy, separate conclusions on the effect of the technology on health outcomes were reached for different tests and biomarkers.

For detection of biomarkers of *EGFR* TKI sensitization, such as exon 19 deletion and L858R variants, the cobas EGFR Mutation Test v2 using real-time polymerase chain reaction technology is the only ctDNA test with demonstrated clinical validity compared with tissue biopsy. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of additional molecular methods must be established independently. Several meta-analyses and individual studies have demonstrated that the cobas liquid biopsy is moderately sensitive for *EGFR* variants associated with TKI sensitivity (range, 60%-80%), with high specificity (range, >90% to 100%) using tissue samples as the reference standard. The evidence is sufficient to reach a conclusion on the cobas EGFR Mutation Test v2.

The evidence demonstrating the clinical validity of other marketed tests that detect TKI-sensitizing variants using ctDNA is insufficient to reach a conclusion.

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For detection of the T790M biomarker associated with *EGFR* TKI treatment resistance, the evidence demonstrating the clinical validity is insufficient to reach a conclusion.

### 3. The technology must improve the net health outcome.

For detection of *EGFR* TKI-sensitizing biomarkers, such as exon 19 deletion and L858R variants, a strategy of liquid biopsy using a test with proven clinical validity followed by reflex tissue testing will attain the same sensitivity as tissue testing and high specificity. This strategy will permit selection of patients appropriately for *EGFR* TKI treatment (ie, erlotinib, gefitinib, afatinib) with a low false-positive rate. Depending on the prevalence of *EGFR* TKI-sensitizing biomarkers, a variable number of patients would avoid tissue testing. Use of the cobas *EGFR* Mutation Test v2 for detection of *EGFR* TKI-sensitizing biomarkers should improve the net health outcome.

It cannot be determined whether liquid biopsy using other ctDNA tests for detection of TKI-sensitizing biomarkers improves the net health outcome.

For detection of the T790M biomarker associated with *EGFR* TKI treatment resistance, liquid biopsy test characteristics of moderate sensitivity and specificity compared with tissue biopsy and uncertainty about outcomes for patients with discordant liquid and tissue biopsy do not translate into an osimertinib treatment selection strategy that will improve outcomes. It cannot be determined whether liquid biopsy for detection of TKI-resistance biomarkers improves the net health outcome.

### 4. The technology must be as beneficial as any established alternatives.

For detection of *EGFR* TKI-sensitizing biomarkers, a strategy of liquid biopsy using the cobas *EGFR* Mutation Test v2, which has proven clinical validity, followed by reflex tissue testing of negatives and appropriate selection of *EGFR* TKI therapy for patients testing positive, should attain patient outcomes as beneficial as a strategy of tissue biopsy testing alone.

For detection of TKI-sensitizing biomarkers using other marketed ctDNA tests for detection of TKI-sensitizing biomarkers, it is uncertain whether liquid biopsy alone or in combination with tissue biopsy testing will attain patient outcomes as beneficial as a strategy of tissue testing alone.

For detection of the T790M biomarker associated with *EGFR* TKI treatment resistance and for selection of treatment with osimertinib, it is uncertain whether liquid biopsy alone or in combination with tissue biopsy testing will attain patient outcomes as beneficial as a strategy of tissue testing alone.

### 5. The improvement must be attainable outside the investigational settings.

The cobas *EGFR* Mutation Test v2 is an FDA-approved companion diagnostic intended to be performed at a lab certified by CLIA and the College of American Pathologists. Therefore, conclusions concerning the clinical validity and clinical utility would be expected to apply outside the investigational setting for the detection of *EGFR* TKI-sensitizing variants.

Because there is insufficient evidence supporting the clinical validity of other methods of assessing ctDNA TKI-sensitizing variants, conclusions concerning improved health outcomes outside the investigational setting cannot be made.

Because there is insufficient evidence supporting the clinical validity of methods of assessing ctDNA TKI-resistance variants, conclusions concerning improved health outcomes outside the investigational setting cannot be made.

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Based on the above, liquid biopsy for detection of *EGFR* TKI-sensitive biomarkers using the cobas EGFR Mutation Test v2 meets the Blue Cross Blue Shield Association TEC criteria.

Based on the above, liquid biopsy for detection of TKI-sensitive biomarkers using other methods does not meet the Blue Cross Blue Shield Association TEC criteria.

Based on the above, liquid biopsy for detection of biomarkers associated with TKI resistance with any method does not meet the Blue Cross Blue Shield Association TEC criteria.