



# Louisiana

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

**Policy #** 00597

**Original Effective Date:** 03/21/2018

**Current Effective Date:** 10/12/2020

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer is addressed separately in medical policy 00452.*

*Note: Proteomic Testing for targeted Therapy in Non-Small Cell Lung Cancer is addressed separately in medical policy 00446.*

*Note: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) is addressed separately in medical policy 00497.*

*Note: Miscellaneous Genetic and Molecular Diagnostic Tests is addressed separately in medical policy 00577.*

### **When Services May Be Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

#### **EGFR TESTING**

Based on review of available data, the Company may consider **at diagnosis**, analysis of somatic variants in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (EGFR), using the cobas<sup>®</sup> EGFR Mutation Test v2, Guardant360<sup>®</sup> test, OncoBEAM<sup>™</sup> test or InVisionFirst-Lung test with plasma specimens to detect circulating tumor DNA (ctDNA) as an alternative to tissue biopsy to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (eg, erlotinib [Tarceva<sup>®</sup>], gefitinib [Iressa<sup>®</sup>], afatinib [Gilotrif<sup>™</sup>], or osimertinib [Tagrisso<sup>®</sup>])<sup>‡</sup> in patients with advanced (stage III or IV) lung adenocarcinoma, large cell

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carcinoma, advanced squamous cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified to be **eligible for coverage**.\*\*

### Patient Selection Criteria at Diagnosis

Coverage eligibility will be considered **at diagnosis** when **ALL** of the following criteria are met:

- When tissue-based testing is not feasible, i.e. quantity not sufficient for standard molecular tissue-based testing, do not have a biopsy-amenable lesion, or cannot undergo biopsy; **AND**
- When prior results for EGFR gene variants testing is not available.

Based on review of available data, the Company may consider **at progression**, analysis of the EGFR T790M resistance variant, using the cobas EGFR Mutation Test v2, Guardant360 test, OncoBEAM test or InVisionFirst-Lung test with plasma specimens to detect circulating tumor DNA (ctDNA) as an alternative to tissue biopsy to guide treatment with osimertinib [Tagrisso®]<sup>‡</sup> in patients with advanced (stage III or IV) lung adenocarcinoma, large cell carcinoma, advanced squamous cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified to be **eligible for coverage**.\*\*

### Patient Selection Criteria at Progression

Coverage eligibility will be considered **at progression** when **ALL** the following criteria are met:

- When new tissue-based testing is not feasible, i.e. not enough tissue for standard molecular tissue-based testing, do not have a biopsy-amenable lesion, or cannot undergo biopsy; **AND**
- When prior results for this EGFR gene variant testing is not available.

### *Note:*

*The cobas test is a companion diagnostic for erlotinib (Tarceva; OSI Pharmaceuticals, Melville NY). Patients who are negative for EGFR variant based on the plasma test should be reflexed to routine biopsy and tissue-based testing when feasible.*

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### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

#### **EGFR TESTING**

Based on review of available data, the Company considers analysis of other *EGFR* sensitizing variants within exons 22 to 24, or other applications related to NSCLC to be **investigational**.\*

#### **ALK TESTING**

Based on review of available data, the Company considers analysis of somatic rearrangement variants of the *ALK* gene using plasma specimens to detect ctDNA or RNA 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 to be **investigational**.\*

#### **BRAF V600E TESTING**

Based on review of available data, the Company considers analysis of the *BRAF* V600E variant using plasma specimens to detect ctDNA 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 to be **investigational**.\*

#### **ROS1 TESTING**

Based on review of available data, the Company considers analysis of somatic rearrangement variants of the *ROS1* gene using plasma specimens to detect ctDNA or RNA as an alternative to tissue biopsy to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients NSCLC to be **investigational**.\*

#### **KRAS TESTING**

Based on review of available data, the Company considers analysis of somatic variants of the *KRAS* gene using plasma specimens to detect ctDNA 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 to be **investigational**.\*

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### **OTHER GENES**

Based on review of available data, the Company considers analysis of alterations in the *HER2*, *RET*, and *MET* genes using plasma specimens to detect ctDNA for targeted therapy in patients with NSCLC to be **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.

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**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	

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

### **Background/Overview**

#### **Predictive BIOMARKERS IN NON-SMALL-CELL LUNG CANCER**

Several predictive genetic biomarkers have been identified for NSCLC. Somatic genome alterations known as "driver mutations" are usually transformative variants arising in cancer cells in genes encoding for proteins important in cell growth and survival. Randomized controlled trials have demonstrated improved efficacy, often in conjunction with decreased toxicity, of matching targeted therapies to patients with specific driver mutations. Several such targeted therapies are approved by the Food and Drug Administration (FDA) for NSCLC. Guidelines generally suggest the analysis of either the primary NSCLC tumor or of metastasis for the presence of a set of driver mutations to select an appropriate treatment.

#### **Genetic Biomarkers With FDA-Approved Targeted Therapies**

The list of targeted therapies approved for NSCLC is evolving. Currently, there are FDA-approved targeted therapies for epidermal growth factor receptor (*EGFR*) variants, anaplastic lymphoma kinase (*ALK*) translocations, *ROS1* translocations, and *BRAF* variants for NSCLC. Companion diagnostics using tissue samples have also been FDA-approved to identify the associated driver mutations for the targeted therapies. The evaluation of molecular analysis of tissue samples for targeted therapy of NSCLC is found in medical policy 00452.

#### **EGFR Variants**

Specific *EGFR* variants confer sensitivity to treatment with tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, afatinib, and osimertinib; the most common variants are deletions in exons 19 and an exon 21 substitution variant (L858R). These variants are referred to as TKI-sensitizing variants and are found in approximately 10% of white patients and up to 50% of Asian patients. The prevalence of *EGFR* variants is not well characterized in other ethnic or racial groups but is estimated to be 10% to 15% in studies including general U.S. populations. TKIs are indicated as first-line treatment for patients with sensitizing variants; progression-free survival is improved with the use of TKIs. Patients receiving TKIs have fewer treatment-related adverse events than patients receiving cytotoxic chemotherapy.

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### **ALK and ROS1 Translocations**

*ALK* rearrangements confer resistance to TKIs. Approximately 4% of patients have *ALK* rearrangements. The TKI crizotinib, an inhibitor of *ALK*, *ROS1*, and mesenchymal-epithelial transition (*MET*) tyrosine kinases, is indicated in patients with *ALK*-positive tumors. In randomized trials comparing crizotinib with standard chemotherapy in *ALK*-positive patients, crizotinib has been associated with improved progression-free survival, response rates, lung cancer symptoms, and quality of life. *ROS1* rearrangements develop in 1% to 2% of patients. For such patients, crizotinib has been shown to be effective, with response rates of about 70%.

### **BRAF Variants**

*RAF* proteins are serine/threonine kinases that are downstream of *RAS* in the *RAS*-*RAF*-*ERK*-*MAPK* pathway. In this pathway, the *BRAF* gene is the most frequently mutated in NSCLC, in 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. *BRAF* or *MEK* inhibition with TKIs (eg, vemurafenib/dabrafenib or trametinib) was originally approved by the FDA for treatment of unresectable or metastatic melanoma with *BRAF* V600 variants but the combination of dabrafenib and trametinib was expanded to include treatment of metastatic NSCLC in 2017.

### **Genetic Biomarkers With Off-Label Targeted Therapies**

Proposed targeted therapies may be used off-label for genetic alterations in human epidermal growth factor receptor 2 (trastuzumab, afatinib), *MET* (crizotinib), and *RET* (cabozantinib). Human epidermal growth factor receptor 2 is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. Human epidermal growth factor receptor 2 is expressed in approximately 25% of NSCLC. *RET* (rearranged during transfection) is a proto-oncogene that encodes a receptor tyrosine kinase growth factor. *RET* fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas. *MET* amplification is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs. *MET* amplification occurs in 2% to 4% of treatment-naïve NSCLC and *MET* and *EGFR* commutations occur in 5% to 20% of NSCLC tumors with acquired resistance to EGFR TKIs.

### **Genetic Biomarkers Without Targeted Therapies**

The most common predictive variant in North American populations is *KRAS*, occurring in 20% to 25% of NSCLC. Patients with *KRAS* variants have shorter survival than those without *KRAS* variants, and thus *KRAS* is a prognostic marker. It also predicts a lack of TKI efficacy. Because

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*KRAS* variants are generally not found with other tumor biomarkers, *KRAS* testing might identify patients who would not benefit from further molecular testing. Targeted therapies are under investigation for *KRAS*-variant NSCLC.

### **Tyrosine Kinase Inhibitor-Resistance Variants**

#### **EGFR Variants**

The *EGFR* variant T790M has been associated with acquired resistance to TKI therapy. When the T790M variant is detected in tissue biopsies from patients with suspected resistance to TKI therapy, osimertinib is recommended as second-line therapy. However, the use of osimertinib as first-line therapy for patients who have *EGFR*-sensitizing variants is emerging and may prevent the development of T790M resistance.

### **Treatment Selection**

#### **Tissue Biopsy as a Reference Standard**

The standard for treatment selection in NSCLC is biomarker analysis of tissue samples obtained by biopsy or surgery. However, a lung biopsy is invasive with a slow turnaround time for obtaining results. Tissue biopsy may also be an imperfect reference standard due to inadequate sampling, tumor heterogeneity, or other factors.

#### **Technologies for Detecting Circulating Tumor DNA**

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 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 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 (<1%) of total cell-free DNA. Therefore, methods up to 500 to 1000 times more sensitive than standard sequencing approaches (eg, Sanger) are needed.

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Sensitive and specific methods are available to detect ctDNA and identify single nucleotide variants, duplications, insertions, deletions, and structural variants. Examples of methods are as follows:

- Denaturing high-performance liquid chromatography involves polymerase chain reaction (PCR) followed by denaturing plus hybridization and then separation.
- Peptide nucleic acid-locked nucleic acid PCR suppresses wild-type *EGFR* followed by enrichment for mutated *EGFR*.
- Amplification refractory mutation system PCR generates different-sized PCR products based on the allele followed by separation of PCR fragments to determine the presence of variants.
- BEAMing combines emulsion PCR with magnetic beads and flow cytometry.
- Digital genomic technologies, such as droplet digital PCR, allow for the enumeration of rare variants in complex mixtures of DNA.

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 (eg, *EGFR* and *ALK* in NSCLC); such testing can also be untargeted and may include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing. Panel testing for specific genetic variants that may impact therapy decisions in many different cancers can also be performed.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

In June 2016, cobas<sup>®</sup> EGFR Mutation Test v2 (Roche Molecular Systems), a real-time PCR test, was approved by the FDA through the premarket approval process (P150047). 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 the 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.

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The U.S. Food and Drug Administration approved in August 2020 the Guardant360 CDx assay, liquid biopsy companion diagnostic that also uses next-generation sequencing (NGS) technology, to identify patients with specific types of mutations of the epidermal growth factor receptor (EGFR) gene in patients with metastatic non-small cell lung cancer (NSCLC).

FDA notes that the test (Guardant360 CDx) is intended to be used as a companion diagnostic to identify non-small cell lung cancer (NSCLC) patients who may benefit from treatment with the targeted therapy Tagrisso (osimertinib) in accordance with the approved therapeutic product labeling. Companion Diagnostic Indication: Non-small cell lung cancer (NSCLC); Biomarker: EGFR exon 19 deletions, L858R, and T790M\*; Therapy: TAGRISSO<sup>®‡</sup> (osimertinib). A negative result from a plasma specimen does not assure that the patient's tumor is negative for genomic findings. NSCLC patients who are negative for these biomarkers should be reflexed to tissue biopsy testing using an FDA-approved tumor tissue test, if feasible.

Additionally, the test is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms. The test is for use with patients previously diagnosed with cancer and in conjunction with other laboratory and clinical findings. Genomic findings other than those listed are not prescriptive or conclusive for labeled use of any specific therapeutic product.

No other ctDNA tests have FDA approval. Foundation Medicine (FoundationACT<sup>™‡</sup>) was granted Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions in 2018. FoundationACT<sup>™‡</sup> is currently marketed as FoundationOne Liquid.

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, the 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

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College of American Pathologists proficiency testing programs available for ctDNA testing to ensure the accuracy of ctDNA laboratory-developed tests.

### **Rationale/Source**

For individuals with advanced non-small-cell lung cancer (NSCLC) who receive testing for biomarkers of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) sensitivity using circulating tumor DNA (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. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), 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 randomized controlled trials (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, OncoBEAM or InVision tests, the evidence includes several studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. The relevant outcomes are OS, DSS, 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, OncoBEAM, and InVision tests have adequate evidence of clinical validity for the *EGFR* TKI-sensitizing variants. A strategy of liquid biopsy followed by referral (reflex)

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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, OncoBEAM or InVision 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, OncoBEAM or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with a tissue reference standard. The relevant outcomes are OS, DSS, 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, OncoBEAM, and InVision tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. Current evidence does not permit determining whether a 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 a 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 OS, DSS, 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.

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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 studies assessing the diagnostic characteristics of liquid biopsy. The relevant outcomes are OS, DSS, 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. However, although there is higher discordance in the liquid vs tissue results for the resistance variant, retrospective analyses have suggested that patients positive for T790M in liquid biopsy have outcomes with osimertinib that appear to be similar overall to patients positive by a tissue-based assay. The evidence is insufficient to determine the effects of the technology on health outcomes. Although the evidence is limited, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published joint guidelines endorsed by American Society of Clinical Oncology with an expert consensus opinion that physicians may use liquid biopsy (cell-free DNA) to identify EGFR T790M variants in patients with progression or resistance to EGFR targeted TKIs and that testing of the tumor sample is recommended if the liquid biopsy result is negative. Similarly, the National Comprehensive Cancer Network guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when testing for the T790M resistance variant, liquid biopsy should be considered and when a liquid biopsy is negative tissue-based testing is strongly recommended.

## **Supplemental Information**

### **Practice Guidelines and Position Statements**

#### **National Comprehensive Cancer Network**

National Comprehensive Cancer Network guidelines (v.3.2019) discuss the role of liquid biopsy in the management of non-small-cell lung cancer. The guidelines state that cell-free/circulating tumor DNA testing should not be used in lieu of tissue diagnosis. They also state that cfDNA testing can be used if the patient is not medically fit for tissue sample or there is insufficient tissue for molecular analysis and follow-up with tissue-based analysis will be done if plasma-based analysis is negative. The guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when

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testing for T790M, plasma-based testing should be considered and when plasma-based testing is negative tissue-based testing is strongly recommended.

### **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. 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* MutationTest 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.

### **College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology**

The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (2018) published a guideline on molecular testing for

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the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. The American Society of Clinical Oncology also endorsed the joint College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guidelines with minor modifications.

The guidelines noted the following recommendation regarding liquid biopsy for activating EGFR mutations and a consensus opinion regarding liquid biopsy for the T790M resistance mutation.

- Recommendation: "In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify [activating] EGFR mutations."
- Expert Consensus Opinion: "Physicians may use plasma cfDNA methods to identify EGFR T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative."
- No recommendation: "There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of EGFR or other mutations, or the identification of EGFR T790M mutations at the time of EGFR TKI resistance."

### **National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence (2018) issued an innovation briefing on plasma EGFR mutation tests for adults with locally advanced or metastatic NSCLC. The briefing reviewed seven ctDNA tests available in Europe and concluded:

- "The intended place in therapy would be as an alternative to tissue EGFR testing or before tumour testing to inform decisions about prescribing EGFR-TKIs. Plasma testing may be particularly useful for people whose disease has developed resistance to an EGFR-TKI and who could be offered second-line EGFR-TKIs, if appropriate, without having further tissue testing."
- "The main points from the evidence summarized in this briefing are from 7 non-UK-based prospective studies with 2,106 adults. They show that the diagnostic accuracy of plasma EGFR mutation testing has a similar specificity, but lower sensitivity, compared with tissue EGFR mutation testing in adults with locally advanced or metastatic NSCLC."

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- "Key uncertainties around the evidence or technology are that tests for identifying EGFR-TK mutations are rapidly evolving and there is no established gold-standard test against which to evaluate them."

### 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.

### Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT03116633 <sup>a</sup>	An Observational Multicenter Study to Evaluate the Performance and Utility of Inivata Liquid Biopsy Analysis Compared With Tissue Biopsy Analysis for Detection of Genomic Alterations in Patients With Lung Cancer	260	Oct 2018 (last updated Apr 2018)
NCT02906852 <sup>a</sup>	Prospective Observational Study to Evaluate	530	Nov 2018

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NCT No.	Trial Name	Planned Enrollment	Completion Date
	the Performance of Inivata Liquid Biopsy Analysis Compared With Standard Tissue Biopsy Analysis for Detection of Genomic Alterations in Patients With Advanced Non-small Cell Lung Cancer		(last updated Apr 2018)
NCT01930474	Analysis of plasma tumor DNA in lung cancer patients	200	Dec 2018 (unknown)
NCT02140463	Next generation personalized therapy with plasma DNA Trial 2 in refractory solid tumors (The NEXT-2 Trial)	260	Dec 2018 (last updated Jan 2018)
NCT02894853 <sup>a</sup>	Lung Cancer Early Molecular Assessment Trial	1297	Dec 2019
NCT02160366	Profile Related Evidence to Determine Individualized Cancer Therapy (PREDICT) Program in Advanced Cancer Patients	2000	Sep 2019
<i>Unpublished</i>			

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02620527 <sup>a</sup>	Study of Concordance Between Circulating Tumor DNA Assay and Foundation One Tissue Analysis For Genomic Alterations	1400	Dec 2017 (completed)
NCT02418234	T790M Mutation on ctDNA in patients with NSCLC after EGFR-TKI failure	314	Nov 2017 (completed)
NCT02284633 <sup>a</sup>	Blood sample monitoring of patients with EGFR mutated lung cancer	250	Dec 2018

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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### **Policy History**

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03/01/2018 Medical Policy Committee review

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- 03/21/2018 Medical Policy Implementation Committee approval. New policy.
  - 12/06/2018 Medical Policy Committee review
  - 12/19/2018 Medical Policy Implementation Committee approval. Eligibility for coverage statement of testing for *EGFR*-sensitizing variants was expanded to include Guardant360 and OncoBEAM and added advanced stage III or IV to specify non-small cell lung cancer. Added criteria for diagnosis and progression and a “*Note*” to the eligible for coverage section. Added investigational statements regarding testing for *ALK*, *ROS1*, *BRAF*, and other variants.
  - 12/05/2019 Medical Policy Committee review
  - 12/11/2019 Medical Policy Implementation Committee approval. Revised the coverage section of the policy to mostly track BCBSA.
  - 05/07/2020 Medical Policy Committee review
  - 05/13/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
  - 06/10/2020 Coding update
  - 09/03/2020 Medical Policy Committee review
  - 09/09/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
  - 12/11/2020 Coding update
- Next Scheduled Review Date: 09/2021

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